Blood values of minerals (e.g., calcium, phosphorus), vitamin D metabolites, alkaline phosphatase, and parathyroid hormone are usually normal. Evaluation of bone mineral content and areal bone density by DXA is the clinical gold standard for measuring BMD. DXA evaluation in patients 15 years of age or younger includes total body less head and lumbar spine, and in those 16 years and older includes lumbar spine and hip. In certain clinical scenarios, it may be useful to obtain alternative sites, such as the distal femur or forearm scan. Additional research modalities allow for the assessment of bone microarchitecture (e.g., trabecular versus cortical bone), quality, and strength, such as peripheral quantitative CT and trabecular bone score.

In the pediatric age group, osteoporosis may be primary or secondary (Table 749.1, Fig. 749.1). The primary osteoporoses can be divided into heritable disorders of connective tissue, including osteogenesis imperfecta (see Chapter 742), Bruck syndrome, osteoporosis-pseudoglioma syndrome, Ehlers-Danlos syndrome (see Chapter 744), Marfan syndrome (see Chapter 743), homocystinuria, and idiopathic juvenile osteoporosis. Secondary forms of osteoporosis include various neuromuscular disorders, chronic illness, endocrine disorders, and drug-induced and inborn errors of metabolism, including lysinuric protein intolerance and Gaucher disease.

When no obvious primary or secondary cause can be detected, **idiopathic juvenile osteoporosis** should be considered, especially if the following clinical features are evident: onset before puberty, long bone and lower back pain, vertebral fractures, long bone and metatarsal fractures, a washed-out appearance of the spine and appendicular skeleton on standard radiographs, and improvement of bone density after puberty. Trabecular bones such as the spine and metatarsals are particularly affected by atraumatic fractures. Several modes of therapy (including oral calcium supplements, calcitriol, bisphosphonates, and calcitonin) have been used with some success in individual conditions, but the effect of these treatments is difficult to gauge because spontaneous recovery occurs after the onset of puberty in more than 75% of cases.

Osteoporosis-pseudoglioma syndrome is an autosomal recessive disorder manifested by variable age at onset, low bone mass, fractures in childhood, and abnormal eye development. It is caused by pathogenic loss of function variants in *LRP5*, which encodes the low-density lipoprotein receptor-related protein 5. Interestingly, gain-of-function pathogenic variants to this gene result in increased bone density.

The life-cycle implications of either significant demineralization or osteoporosis in childhood need to be stressed. Events in childhood influence peak bone mass, and late adolescence is a period of rapid bone mineral accretion. Peak bone mass is typically achieved by 20-25 years of age (depending on the bone measured), and the contribution during childhood is considerable. A number of measures influence bone mass including adequate calcium intake, vitamin D sufficiency, weight-bearing physical activity, and body mass index (BMI) within a healthy range. General recommendations include achieving the recommended daily allowance (RDA) of calcium for age. Excellent and convenient sources of dietary calcium include dairy products, but also bony fish, green vegetables, and calcium-supplemented drinks (e.g., orange juice). Yogurt and hard cheeses can be used in many lactase-deficient children. Also, a serum 25-hydroxyvitamin D level between 30-50 ng/mL in those with known threats to bone health can be beneficial to maximize calcium absorption and ensure normal range parathyroid hormone. Weight-bearing exercise

Table 749.1 Diagnoses That Confer Increased Risk for Osteoporosis

ENDOCRINE DISORDERS
Female Hypogonadism
Turner syndrome
Hypothalamic amenorrhea (female athletic triad)
Anorexia nervosa
Premature ovarian insufficiency
Depot medroxyprogesterone acetate therapy
Estrogen receptor α (ESR1) pathogenic variants
Hyperprolactinemia
Male Hypogonadism
Primary gonadal failure (Klinefelter syndrome)
Secondary gonadal failure (idiopathic hypogonadotropic hypogonadism)
Delayed puberty
Hyperthyroidism
Hyperparathyroidism
Hypercortisolism (therapeutic or Cushing disease)
Growth hormone deficiency
Thyrotoxicosis
INFLAMMATORY DISORDERS
Dermatomyositis
Chronic hepatitis
Juvenile idiopathic arthritis
Systemic lupus erythematosus
GASTROINTESTINAL DISORDERS
Malabsorption syndromes (cystic fibrosis, celiac disease, biliary atresia)
True or perceived lactose intolerance
Inflammatory bowel disease
Chronic obstructive jaundice
Primary biliary cirrhosis and other cirrhoses
Alactasia
Subtotal gastrectomy
BONE MARROW DISORDERS
Bone marrow transplant
Lymphoma
Leukemia
Hemolytic anemias (sickle cell anemia, thalassemia)
Systemic mastocytosis
CONNECTIVE TISSUE/BONE DISORDERS
Idiopathic juvenile osteoporosis
Osteogenesis imperfecta
Ehlers-Danlos syndrome
Marfan syndrome
Homocystinuria
Fibrous dysplasia
Previous or recurrent low impact fractures
Early-onset osteoporosis with *WNT1* pathogenic variants
X-linked osteoporosis with fractures with *PLS3* pathogenic variants
DRUGS
Alcohol
Heparin
Glucocorticoids
Thyroxine
Anticonvulsants
Gonadotropin-releasing hormone agonists
Cyclosporine
Chemotherapy
Tobacco cigarettes
MISCELLANEOUS DISORDERS
Immobilization (cerebral palsy, spinal muscular atrophy, Duchenne muscular dystrophy)
Chronic renal disease
Glycogen storage disease type 1
Chronic hepatitis
Hypophosphatasia
Low calcium dietary intake
Gaucher disease
Severe congenital neutropenia

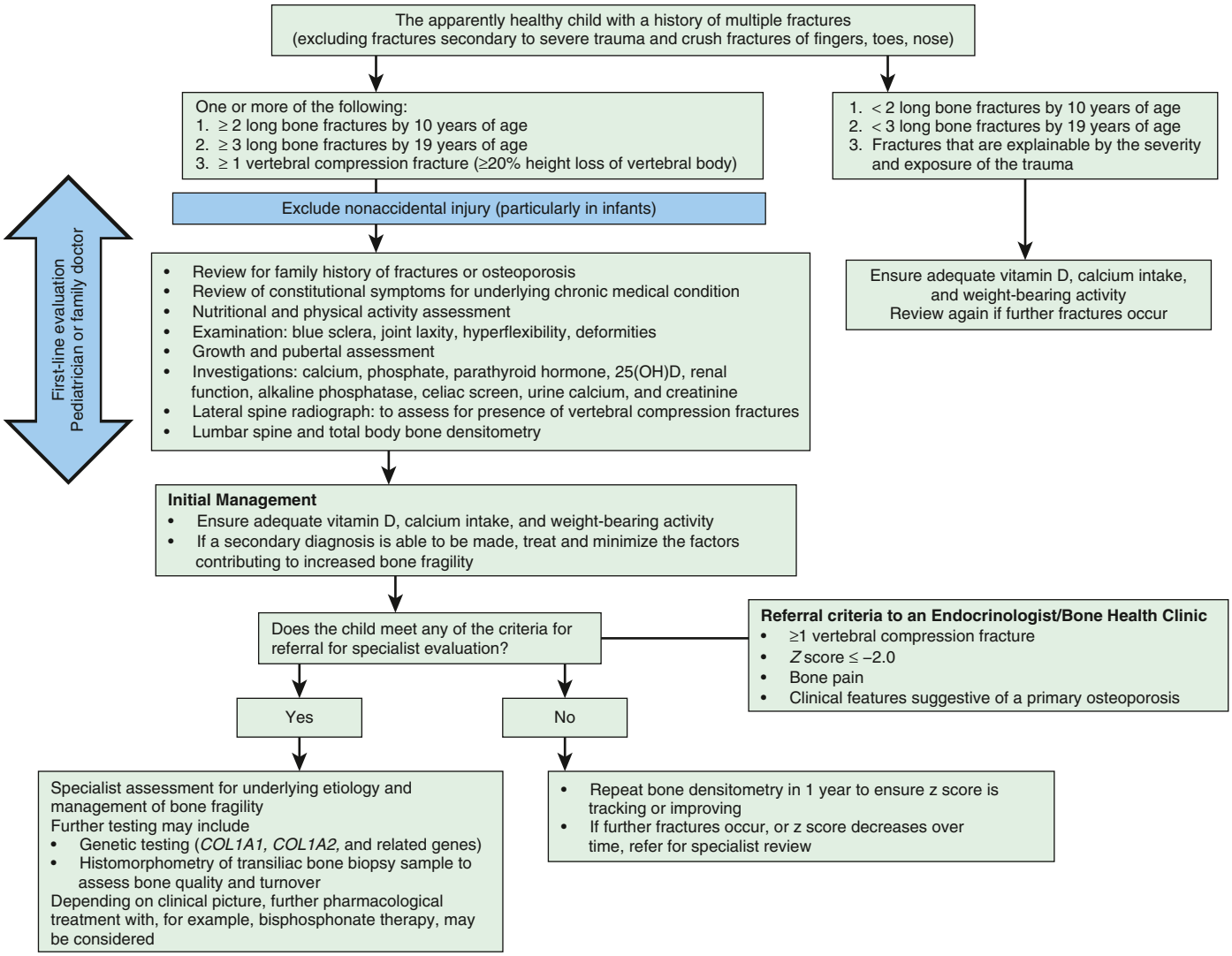

Fig. 749.1 An algorithm for the management of a child presenting with a clinically significant fracture history. The algorithm outlines the initial evaluation, management, and when to consider referral for specialist review. *(Data from Mayranpaa MK, Viljakainen HT, Toiviainen-Salo S, et al. Impaired bone health and asymptomatic vertebral compressions in fracture-prone children: a case-control study. J Bone Miner Res. 2012;27:1413–1424; and Bishop N, Arundel P, Clark E, et al. Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2013 pediatric official positions. J Clin Densitom. 2014;17:275–280.)*

enhances bone formation and reduces bone resorption. Factors that can prevent acquisition of peak bone mass include the use of alcohol and tobacco. Because it appears that adult-onset osteoporosis stems primarily from genetic factors, representing a complex trait interaction, specific interventions during childhood to augment bone mass are not available.

The treatment of secondary osteoporosis is best achieved by treating the underlying disorder when feasible (see Fig. 749.1). Hypogonadism should be treated with hormone replacement therapy, but in adolescent girls, nutritional issues should first be addressed and, ultimately, prescription of transdermal over oral estrogen (see Chapter 732). Calcium intake should be increased to 1,500-2,000 mg/day. In glucocorticoid-induced osteoporosis, an emphasis is placed on the lowest possible dose to prevent disease activity (e.g., in children with inflammatory bowel disease) with alternate-day dosing or, when appropriate, topical (e.g., eczema) or inhaled (e.g., asthma) glucocorticoids. Special diets for inborn errors of metabolism are also appropriate, as well as enzymatic replacement for diseases such as hypophosphatasia, a genetic disorder leading to deficient endogenous alkaline phosphatase production and defective bone mineralization. Screening for celiac disease should be carried out in unexplained cases of low bone mass, as adherence to a gluten-free diet can significantly enhance bone health in these patients (see Chapter 384).

Treatment with bisphosphonates that inhibit bone resorption in certain secondary (e.g., glucocorticoid-induced) and adult-onset osteoporosis has been successful. Bisphosphonate therapy can also be beneficial for children and adolescents and has historically been used with osteogenesis imperfecta and cerebral palsy. The use of bisphosphonates has expanded to additional patient populations with secondary osteoporosis, such as recurrent fractures and low bone mineral density, and high risk for skeletal fragility because of their underlying medical conditions. In consultation with a metabolic bone expert, bisphosphonate treatment should be considered in the following patient populations: Duchenne muscular dystrophy, spinal muscular atrophy, and other nonambulatory patients (i.e., cerebral palsy, metabolic disorders). All modifiable risk factors should be addressed, including adequate calcium intake; sufficient vitamin D; weight-bearing physical activity, such as time within a stander and physical therapy; healthy range BMI; and evaluation of overall heath (i.e., regular menstrual periods in adolescent girls, no other endocrinopathies, and optimizing the treatment status of the underlying medical condition).

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Rehabilitation Medicine

PART XXXI

Chapter 750

Rehabilitation for Traumatic Brain Injury

Chong-Tae Kim and J. Michael King

Traumatic brain injury (TBI) is a major cause of pediatric disability in children older than 1 year old in the United States (see Chapter 82). According to data from the Centers for Disease Control and Prevention (2006–2010), TBI due to falls (72.8%) is most common in the 0-4 age range. **Nonaccidental TBI** remains a significant cause of TBI at this age (20-30 cases/100,000) (see Chapter 17). Falls (35.1%) and being struck by or against an object (34.9%) are most common in those 5-14 years of age. Assaults, falls, and motor vehicle injuries make up to 85% of the TBI experienced in those 15-24 years of age. TBI is more common in males than females at all ages.

PATHOPHYSIOLOGY

TBI is the consequence of primary and secondary injury (see Chapter 82). Primary injury results from direct physical impact. Secondary injury is the consequence of aberrant neurochemical homeostasis after primary injury (Fig. 750.1). This injury mechanism helps explain why individuals may experience global dysfunction of the brain despite relatively small or focal brain lesions on imaging studies. Minimizing secondary injury is critical to preventing further brain insult after the primary injury.

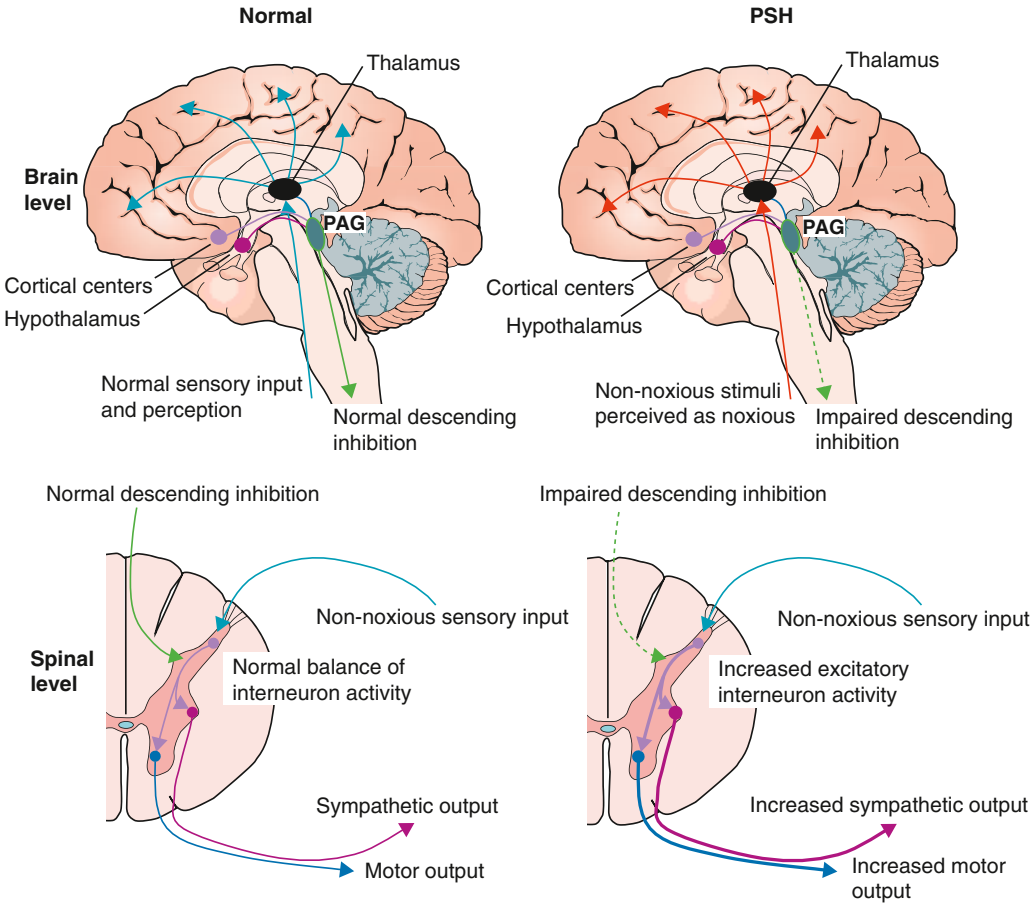

Fig. 750.1 Excitatory:inhibitory ratio model of the pathogenesis of PSH. In normal circumstances, various cortical, hypothalamic, thalamic, and other subcortical inputs modulate activity within brainstem centers—the PAG is shown here as one of the key brainstem hubs in this process. These brainstem nuclei provide inhibitory drive to spinal-reflex arcs, thereby maintaining balance between inhibitory and excitatory interneuron influences on motor and sympathetic efferents, allowing normal sensory stimuli to be perceived as nonnoxious. In the excitatory:inhibitory ratio model of PSH, disconnection of descending inhibition produces maladaptive dendritic arborization and spinal-circuit excitation, with nonnoxious stimuli triggering increased motor and sympathetic output (spinally) and potentially becoming perceived as noxious (centrally). PAG, Periaqueductal grey. PSH, paroxysmal sympathetic hyperactivity. *(From Meyfroidt G, Baguley IJ, Menon DK. Paroxysmal sympathetic hyperactivity: the storm after acute brain injury. Lancet. 16:721–729, 2017 [Fig. 2].)*

Very young children who have not yet closed their cranial sutures accommodate some increase in intracranial pressure that may result from TBI. However, young children have a relatively large head size compared with their body, higher brain water content, and less myelination, all of which may contribute to greater brain distortion and injury than from a comparable injury experienced by an adult.

SEVERITY

The acute severity of TBI is typically classified with the **Pediatric Glasgow Coma Scale** (GCS) (see Chapter 82). GCS scores of 13-15 are considered mild TBI, 9-12 moderate TBI, and 3-8 severe TBI. Additional parameters may be helpful in classifying severity. The longer the duration of loss of consciousness (i.e., <30 min, <24 hr, or >24 hr), the more severe the TBI. Longer duration of posttraumatic amnesia (<1 day, 1-7 days, or >7 days) is also reflective of a more severe TBI. Biomarkers (chemicals sensitive to nerve tissues) are being investigated as potential indicators of severity.

MEDICAL COMPLICATIONS

Disorders of Consciousness

Children with severe TBI manifest various levels of altered consciousness (Table 750.1). They may progress from coma to unresponsive wakefulness syndrome (formerly vegetative state) and/or minimally conscious state. The longer the period of impaired consciousness, the poorer the functional recovery. Rapid transition from coma/unresponsive wakefulness syndrome to a minimally conscious state increases the possibility of better recovery. As patients recover from impaired consciousness, they may have altered circadian sleep–wake patterns. In this phase, it is particularly important to **avoid overstimulation at night**, such as with procedures, and to avoid sedative medications during the day. **A sleep diary** over a period of several days to a week is a useful measure to monitor sleep patterns and determine the effectiveness of medications. **Neurostimulators** (e.g., amantadine, bromocriptine, methylphenidate, or L-dopa) may be used to improve arousal during the day. Trazodone or melatonin may help facilitate sleep onset or maintenance at night, respectively. Modafinil or donepezil can be tried if the above neurostimulators are ineffective. Paradoxically zolpidem has been reported to improve alertness in several cases.

Cognitive-Behavioral Disorders

The management and outcome of mild TBI (concussion) are discussed in Chapter 729. As patients with severe TBI recover from initial low levels of consciousness, they may demonstrate significant cognitive-behavioral disorders, such as agitation, aggression, decreased frustration tolerance, impulsivity, inattention, emotional lability, perseveration, impaired working memory, and poor safety awareness and judgement. Agitation is common in the early stages of recovery. The first line of management for agitation is to decrease excessive environmental, visual, auditory, and tactile stimulation. Physical constraint is typically implemented as a last resort to prevent harm to the patient and others, and it should be removed as soon as the danger has resolved. The **Rancho Los Amigo scale** (RLAS) (Table 750.2) may be used to evaluate the level of this impairment. It is important to exclude potential exacerbating factors or medical causes of impaired mental status and behavior, including electrolyte abnormalities, infection, and concomitant injuries in patients who incur multiple traumas including severe TBI. Posttraumatic amnesia can be particularly debilitating because it may limit the acquisition and retention of new learning skills. The **Children's Orientation and Amnesia Test** may be helpful in determining when a patients' posttraumatic amnesia has ended, after which these children may be candidates for cognitive rehabilitation. This test assesses **general orientation** (name, age, birthdate, school, etc.), **temporal orientation** (current time, day of the week, year, etc.), and **memory** (verbal and nonverbal).

Most patients who have moderate or severe TBI will have varying degrees of long-term residual cognitive impairments, which can include impaired judgment, attention deficits, and impaired working memory (see Chapter 49). The most rapid recovery in cognitive skills tend to occur in the first year after the TBI. Children with more severe injuries and children from lower socioeconomic status (SES) families tend to have more significant long-term deficits after a TBI.

Table 750.1 Level of Consciousness

	COMA	UNRESPONSIVE WAKEFULNESS SYNDROME	MINIMALLY CONSCIOUS STATE (–)	MINIMALLY CONSCIOUS STATE (+)
Eye opening	None	Spontaneous or to stimulus	Spontaneous	Spontaneous
Brain stem reflexes	None	Present	Present	Present
Orientation	None	None	Inconsistent	Consistent
Purposeful response	None	None	Trivial responses with localization (visual fixation or tracking, localization to pain)	Evident reliable responses with verbal, behavioral, and/or motor

Table 750.2 Rancho Los Amino Scale

LEVEL	COGNITIVE-BEHAVIORAL CHARACTERISTICS	CLINICAL FEATURES
I	No response	Comatose state
II	Generalized response	Nonpurposeful, reflexive, stereotyped response to simulations
III	Localized response	Specifically localized (head turn, blink eye, grasp), consistent response to stimulations
IV	Confused-agitated	Confused and hyperactive or bizarre behavior
V	Confused-inappropriate	Less agitated and able to follow simple instructions consistently but difficult to follow complicated ones
VI	Confused-appropriate	Still impaired recent memory, needs assistance for unfamiliar situations
VII	Automatic-appropriate	Able to do daily routine independently but has difficulty solving problems
VIII	Purposeful-appropriate	Independent and functional in activities at home and community but may have some difficulties in stressful situations

Posttraumatic Seizure

The incidence of posttraumatic seizure (PTS) is dependent on injury severity and age. About 30–35% of children with severe TBI will experience a PTS. Very early-onset PTS may develop within 24 hours after a TBI, early-onset PTS within 7 days, and late onset more than 7 days after a TBI. Early-onset PTS is more common in children, and late-onset PTS is more common in adults. The risk of late-onset PTS is increased in particularly severe TBI, those caused by penetrating injury, the presence of subdural hematoma, in injuries occurring in children younger than 5 years, and in patients with a history of early-onset PTS. Prophylactic treatment with an antiepileptic medication for 7 days after a TBI is commonly prescribed (see Chapter 82). However, treatment with an antiepileptic medication beyond 1 week offers no further benefit as a prophylactic agent. The risk of PTS decreases to the same incidence as in the general population after 5 years from TBI.

Paroxysmal Sympathetic Hyperactivity

Paroxysmal sympathetic hyperactivity (PSH) is a constellation of symptoms manifested by hyperthermia, tachycardia, tachypnea, diaphoresis, and increased tone, including dystonic posturing. It is primarily attributable to autonomic dysregulation. The mechanism has not been clearly defined but is thought to be because of disruption of the inhibitory function of the mesencephalon on the diencephalon (see Fig. 750.1). Some drug-related symptoms may mimic the features of PSH and may require discontinuation and the use of alternative medication; for example, haloperidol and chlorpromazine may cause neuroleptic malignant syndrome, and phenytoin may precipitate a fever. The assessment measure pediatric PSH-AM is suggested to improve diagnostic sensitivity (Tables 750.3, 750.4, and 750.5). There is no current established standard of care for management of PSH, but bromocriptine, propranolol or labetalol, clonidine, amantadine, intrathecal baclofen, morphine, benzodiazepine, and gabapentin have been prescribed with variable success. Morphine, fentanyl, propofol, propranolol, and gabapentin have consistently been effective in adult patients for both prevention and treatment. Most patients require more than one class of medication (opioid, beta blockers, alpha 2 agonists, neuromodulators, benzodiazepines, sarcolemmal calcium release blockers). Oral baclofen, Dilantin, and carbamazepine are reported to be ineffective for PSH. PSH is a negative factor for short-term but not long-term functional outcomes.

Neuroendocrine Disorders

Hypothalamic-pituitary injury that occurs with TBI can cause various endocrine disorders. Growth hormone deficiency is the most common and results in growth retardation. Precocious puberty, more common in females than males, may result from loss of neural inhibition on gonadotropin release. Three different types of salt and water metabolism derangements, diabetes insipidus (DI), syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and cerebral salt wasting (CSW) can develop after a severe TBI (see Chapter 82).

Spasticity

Spasticity is a major complication that develops in children with severe TBI (see Chapter 752).

OUTCOME ASSOCIATED WITH SEVERE TRAUMATIC BRAIN INJURY

Given different mechanisms of injury, younger children who incur a severe brain injury tend to have better functional outcomes than older children. However, given the same severity of TBI, the outcome of very young children is poorer than that of older children. The age defined as "very young children" (2-5 years) is variable depending on the studies. The specific reason for this difference in outcomes has not been identified, but a plausible explanation is that although very young children demonstrate a higher potential for neuroplasticity with focal brain injuries, their immature and developing brains are more vulnerable to the diffuse effects on the brain of most forms of TBI.

The GCS score is a strong prognostic factor for mortality and functional outcome in the acute injury phase but not for functional outcome in the subacute or chronic phase for children within the severe TBI group. Duration of posttraumatic amnesia or time to follow commands are better prognostic factors for long-term functional outcomes.

Cognitive and behavioral impairments (poor memory-learning and executive skills, hyperactivity, depression, awareness deficits) are the most common and long-lasting sequelae of TBI. These deficits can inhibit successful school reentry and participation in social activities.

Given the same severity, the long-term functional outcome of children who sustain nonaccidental (inflicted) trauma is worse than that of children with other forms of TBI. Children who incur nonaccidental trauma are typically very young. If developmentally delayed before their brain injury, they are likely to have poorer long-term functional outcomes. The

Table 750.3 Pediatric PSH-AM Pediatric Clinical Feature Scale (PCFS)

	AGE (YR)	0	1	2	3
Heart rate	1-4	<110	100-124	125-139	≥140
	5-15	<100	100-119	120-139	≥140
Respiratory rate	1-4	<30	30-34	35-39	≥40
	5-15	<25	25-29	30-34	≥35
Systolic BP	1-4	<100	100-109	110-119	≥120
	5-15	<120	120-129	130-139	≥140
Diastolic BP	1-4	<65	65-72	73-79	≥80
	5-15	<75	75-82	83-89	≥90
Temperature		37	37-37.9	38-38.9	≥39
Sweating		Normal	Increased sweating	Localized diaphoresis	Generalized diaphoresis
Posturing (muscle tone) during episode		None	Mild increase	Neat increase	Generalized spasticity/opisthotonos

Severity of CF (subtotal score of PCFS): Nil =0, Mild 1-6, Moderate 7-12, Severe ≥13
BP, Blood pressure; PSH-AM, paroxysmal sympathetic hyperactivity-assessment measure.

Table 750.4 Pediatric Diagnosis Likelihood Tool (PDLT)

	PRESENT/ABSENT (1/0)
1. Clinical features occur simultaneously	
2. Episodes are paroxysmal in nature	
3. Sympathetic overactivity to normally nonpainful stimuli	
4. Features persist > 3 consecutive days	
5. Features persist > 1 week postinjury	
6. Features persist despite treatment of alternative differential diagnoses	
7. At least single episode daily	
8. Medication administered to decrease sympathetic features	
9. Absence of parasympathetic features during episodes	
10. Absence of other presumed cause of features	
11. Antecedent acquired brain injury	

Table 750.5 Pediatric PSH-AM

PSH DIAGNOSTIC LIKELIHOOD	COMBINED TOTAL (PCFS + PDLT)
Unlikely	<8
Possible	8-16
Probable	>17

PSH-AM, paroxysmal sympathetic hyperactivity assessment measure; PCFS, pediatric clinical feature scale; PDLT, pediatric diagnosis likelihood tool.

long-term functional outcome of children who sustain a TBI is better than those who sustain a nontraumatic (anoxic) brain injury.

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Chapter 751

Spinal Cord Injury and Autonomic Dysreflexia Management

Ashlee M. Jaffe and Abigail Case

See Chapter 81.

Individuals from birth to 21 years of age account for 25% of all cases of traumatic **spinal cord injury (SCI)**. Children are more susceptible to lap-belt injuries, upper cervical injuries, SCIs without radiologic abnormalities **(SCIWORA)**, and delayed onset of neurologic deficits, ranging from 30 minutes to 4 days. A population-based study found the epidemiology of pediatric spinal injury in the US varies greatly by age, ethnicity, and payor. Low-income populations are more likely to sustain spinal cord injury due to firearms than other populations.

The most accurate way to evaluate a patient who has sustained an SCI is by performing a standardized physical examination, as endorsed by the International Standards for Neurological and Functional Classification of SCI, recommended for children 6 years of age and older (Fig. 751.1). Life expectancy is related to the neurologic level of injury and the American Spinal Injury Association (ASIA) impairment scale classification.

CLINICAL MANIFESTATIONS

Immediately after an SCI, there is typically a period of **spinal shock** with low tone and absent reflexes. Eventually, signs of an **upper motor neuron** lesion may emerge, including spasticity and involuntary muscle spasms. However, if there is a substantial segment of spinal cord infarction present, patients may have persistent flaccid paralysis.

Children with neurologic levels of injury at T6 or above are at particular risk for interruption and decentralization of the autonomic nervous system. The most common manifestations include bradycardia, hypotension, temperature dysregulation, and, once spinal shock has resolved, **autonomic dysreflexia (AD)**. AD is a sustained sympathetic response as a result of a noxious stimulus *below* the level of injury. Symptoms resulting from AD typically include hypertension, bradycardia, headache, and flushing of the skin above the level of injury, although vague symptoms such as fatigue, irritability, or crying may be the presenting symptoms in younger patients. Noxious stimuli resulting from bladder or rectal distention is a common cause of AD, but there are a large number of other causes that need to be considered (Table 751.1). Children and adolescents with cervical and upper thoracic level SCI have lower baseline blood pressures (BPs) compared with the general population. Therefore caution should be used when referencing age-appropriate BPs because BP elevations of even 20-40 mm Hg above this lower baseline may be suggestive of AD. *Identification and treatment of the noxious stimulus is typically associated with resolution of symptoms without the use of antihypertensive medication.* If necessary, antihypertensive agents with a rapid onset and short duration, such as nifedipine and nitropaste, are advocated to treat elevated BP while the underlying cause is identified (Fig. 751.2). Emergent management of AD is necessary because of the risk of stroke and additional organ damage resulting from sustained hypertension. Consideration of a medical alert bracelet, education of supervising adults, and carrying of an AD emergency reference card is recommended (Fig. 751.3).

Patients with SCI are particularly vulnerable to **deep venous thrombosis** and **pulmonary embolism** because of immobilization of their affected limbs and venous stasis during the first 90 days after an injury. Deep venous thromboses are more common in postpubertal children >14 years old than in younger children. Mechanical prophylaxis (graduated compression stockings and sequential calf compression devices) are recommended for all children with acute SCI; adolescents should also start anticoagulant thromboprophylaxis, especially if additional risk factors like lower extremity fractures are present (unless contraindicated because of the risk of bleeding or prior allergic response). Late-occurring deep venous thrombosis most commonly occurs with prolonged immobilization related to illness or surgery, and prophylactic measures should be continued during these situations as well.

Consequent of SCI, patients often present with varying degrees of bowel and bladder incontinence. After an SCI, the bladder can be areflexic or hyperreflexic, and detrusor sphincter dyssynergia may occur. Clean intermittent catheterization (CIC) of the bladder is typically performed up to 4-6 times/day to prevent urinary retention and vesicoureteral reflux. Constipation can negatively impact the success of a CIC program. Anticholinergic medications may improve bladder storage capacity and prevent urinary incontinence between bladder catheterizations. *Antibiotics are only recommended for symptomatic urinary tract infections; asymptomatic bacteriuria, without vesicoureteral reflux, is generally due to colonization and typically not treated.* If intermittent catheterization is required, one can begin teaching the skills necessary for independent catheterization as early as 3 years of age with a goal of obtaining complete independence by 5-7 years old reflecting the progression toward independent bladder management of the child's able-bodied peers.

Bowel continence programs can be successfully introduced around 2-4 years old. There should be an attempt to distinguish between upper motor neuron (UMN) and lower motor neuron (LMN) bowel dysfunction because the management and bowel agents chosen may vary

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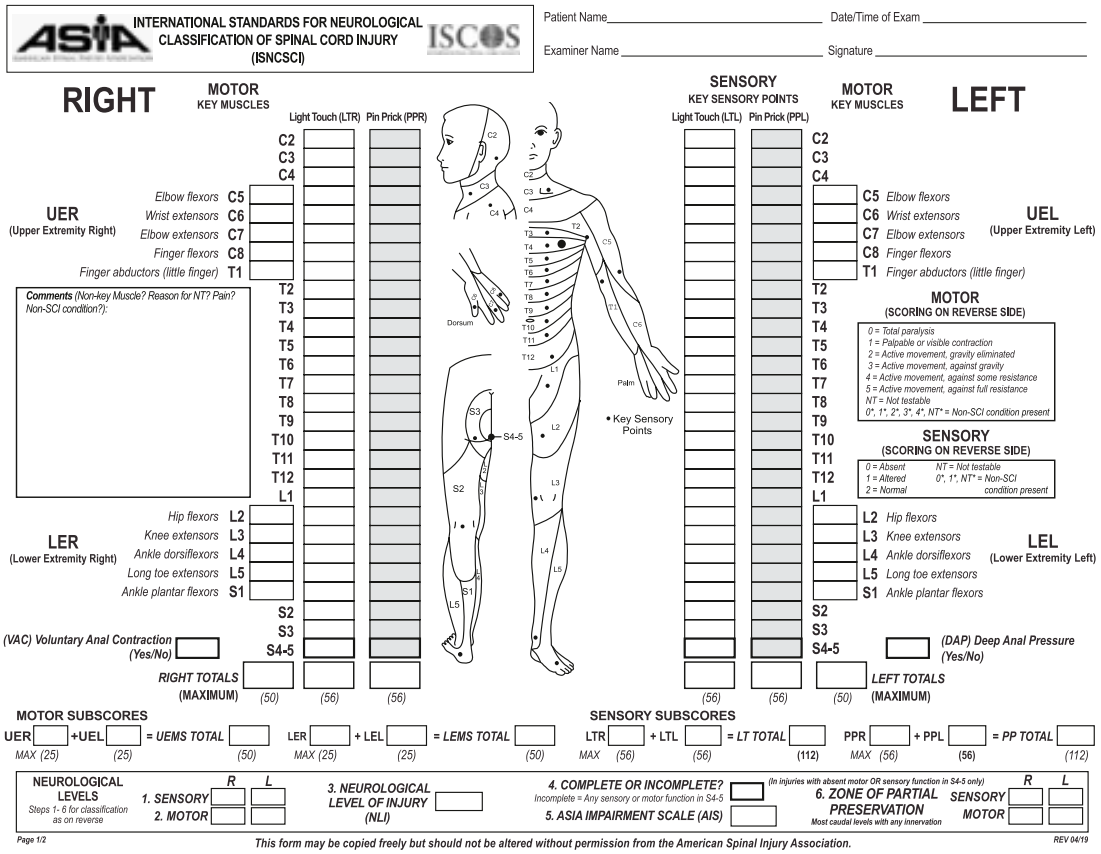
Children with neurologic levels of injury at T6 or above are at particular risk for interruption and decentralization of the autonomic nervous system. The most common manifestations include bradycardia, hypotension, temperature dysregulation, and, once spinal shock has resolved, **autonomic dysreflexia (AD)**. AD is a sustained sympathetic response as a result of a noxious stimulus *below* the level of injury. Symptoms resulting from AD typically include hypertension, bradycardia, headache, and flushing of the skin above the level of injury, although vague symptoms such as fatigue, irritability, or crying may be the presenting symptoms in younger patients. Noxious stimuli resulting from bladder or rectal distention is a common cause of AD, but there are a large number of other causes that need to be considered (Table 751.1). Children and adolescents with cervical and upper thoracic level SCI have lower baseline blood pressures (BPs) compared with the general population. Therefore caution should be used when referencing age-appropriate BPs because BP elevations of even 20-40 mm Hg above this lower baseline may be suggestive of AD. *Identification and treatment of the noxious stimulus is typically associated with resolution of symptoms without the use of antihypertensive medication.* If necessary, antihypertensive agents with a rapid onset and short duration, such as nifedipine and nitropaste, are advocated to treat elevated BP while the underlying cause is identified (Fig. 751.2). Emergent management of AD is necessary because of the risk of stroke and additional organ damage resulting from sustained hypertension. Consideration of a medical alert bracelet, education of supervising adults, and carrying of an AD emergency reference card is recommended (Fig. 751.3).

Patients with SCI are particularly vulnerable to **deep venous thrombosis** and **pulmonary embolism** because of immobilization of their affected limbs and venous stasis during the first 90 days after an injury. Deep venous thromboses are more common in postpubertal children >14 years old than in younger children. Mechanical prophylaxis (graduated compression stockings and sequential calf compression devices) are recommended for all children with acute SCI; adolescents should also start anticoagulant thromboprophylaxis, especially if additional risk factors like lower extremity fractures are present (unless contraindicated because of the risk of bleeding or prior allergic response). Late-occurring deep venous thrombosis most commonly occurs with prolonged immobilization related to illness or surgery, and prophylactic measures should be continued during these situations as well.

Consequent of SCI, patients often present with varying degrees of bowel and bladder incontinence. After an SCI, the bladder can be areflexic or hyperreflexic, and detrusor sphincter dyssynergia may occur. Clean intermittent catheterization (CIC) of the bladder is typically performed up to 4-6 times/day to prevent urinary retention and vesicoureteral reflux. Constipation can negatively impact the success of a CIC program. Anticholinergic medications may improve bladder storage capacity and prevent urinary incontinence between bladder catheterizations. *Antibiotics are only recommended for symptomatic urinary tract infections; asymptomatic bacteriuria, without vesicoureteral reflux, is generally due to colonization and typically not treated.* If intermittent catheterization is required, one can begin teaching the skills necessary for independent catheterization as early as 3 years of age with a goal of obtaining complete independence by 5-7 years old reflecting the progression toward independent bladder management of the child's able-bodied peers.

Bowel continence programs can be successfully introduced around 2-4 years old. There should be an attempt to distinguish between upper motor neuron (UMN) and lower motor neuron (LMN) bowel dysfunction because the management and bowel agents chosen may vary



Muscle Function Grading

0 = Total paralysis

1 = Palpable or visible contraction

2 = Active movement, full range of motion (ROM) with gravity eliminated

3 = Active movement, full ROM against gravity

4 = Active movement, full ROM against gravity and moderate resistance in a muscle specific position

5 = (Normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person

NT = Not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)

0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present [a]

Sensory Grading

0 = Absent **1** = Altered, either decreased/impaired sensation or hypersensitivity

2 = Normal **NT** = Not testable

0*, 1*, NT* = Non-SCI condition present [a]

[a] Note: Abnormal motor and sensory scores should be tagged with a '*' to indicate an impairment due to a non-SCI condition. The non-SCI condition should be explained in the comments box together with information about how the score is rated for classification purposes (at least normal / not normal for classification).

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, adbuction, adduction, internal and external rotation **Elbow:** Supination	C5
Elbow: Pronation **Wrist:** Flexion	C6
Finger: Flexion at proximal joint, extension **Thumb:** Flexion, extension and abduction in plane of thumb	C7
Finger: Flexion at MCP joint **Thumb:** Opposition, adduction and abduction perpendicular to palm	C8
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation **Knee:** Flexion **Ankle:** Inversion and eversion **Toe:** MP and IP extension	L4
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments S4-5 by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3.

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.

AMERICAN SPINAL INJURY ASSOCIATION

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

ISCOS

Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI).
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
*If voluntary anal contraction = **No** AND all S4-5 sensory scores = **0** AND deep anal pressure = **No**, then injury is **Complete**. Otherwise, injury is **Incomplete**.*

5. Determine ASIA Impairment Scale (AIS) Grade.
Is injury Complete? If YES, AIS=A
NO ↓
Is injury Motor Complete? If YES, AIS=B
NO ↓ (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?
NO ↓ AIS=C **YES ↓ AIS=D**

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact and the ASIA Impairment Scale does not apply.

6. Determine the zone of partial preservation (ZPP).
The ZPP is used only in injuries with absent motor (no VAC) OR sensory function (no DAP, no LT and no PP sensation) in the lowest sacral segments S4-5, and refers to those dermatomes and myotomes caudal to the sensory and motor levels that remain partially innervated. With sacral sparing of sensory function, the sensory ZPP is not applicable and therefore "NA" is recorded in the block of the worksheet. Accordingly, if VAC is present, the motor ZPP is not applicable and is noted as "NA".

Fig. 751.1 American Spinal Injury Association standards worksheet. *(From the American Spinal Injury Association: International standards for neurological and functional classification of spinal cord injury [ISNCSCI]. Richmond, Virginia, 2019, https://asia-spinalinjury.org/international-standards-neurological-classification-sci-isncsci-worksheet/.)*

Table 751.1 Potential Etiologies of Noxious Stimuli Causing Autonomic Dysreflexia

URINARY SYSTEM
• Bladder distention
• Bladder or kidney stones
• Blocked/kinked catheter
• Detrusor sphincter dyssynergia
• Urinary tract infection
• Urologic instrumentation
• Shock wave lithotripsy
GASTROINTESTINAL SYSTEM
• Bowel distention
• Bowel impaction
• Gallstones
• Appendicitis
• Gastric ulcers
• Gastritis
• Gastrointestinal instrumentation
• Hemorrhoids
INTEGUMENTARY SYSTEM
• Constrictive clothing, shoes, or orthotics
• Blisters
• Burns, sunburn, or frostbite
• Ingrown toenail
• Insect bites
• Pressure ulcers
MUSCULOSKELETAL SYSTEM
• Fractures
• Heterotopic ossification
• Functional electrical stimulation
REPRODUCTIVE SYSTEM—MALE
• Epididymitis
• Scrotal compression (sitting on scrotum)
• Sexual intercourse
• Sexually transmitted infections
REPRODUCTIVE SYSTEM—FEMALE
• Menstruation
• Pregnancy, especially labor and delivery
• Vaginitis
• Sexual intercourse
• Sexually transmitted infections
HEMATOLOGIC SYSTEM
• Deep vein thrombosis
• Pulmonary embolus
OTHER SYSTEMIC CAUSES
• Boosting (an episode of autonomic dysreflexia intentionally caused by an athlete with spinal cord injury in an attempt to enhance physical performance)
• Excessive alcohol intake
• Excessive caffeine or diuretic intake
• Over-the-counter or prescribed stimulants
• Substance abuse

From Consortium for Spinal Cord Medicine: Acute management of autonomic dysreflexia: individuals with spinal cord injury presenting to health-care facilities, Washington, DC, 2001, Paralyzed Veterans of America, 10–11.

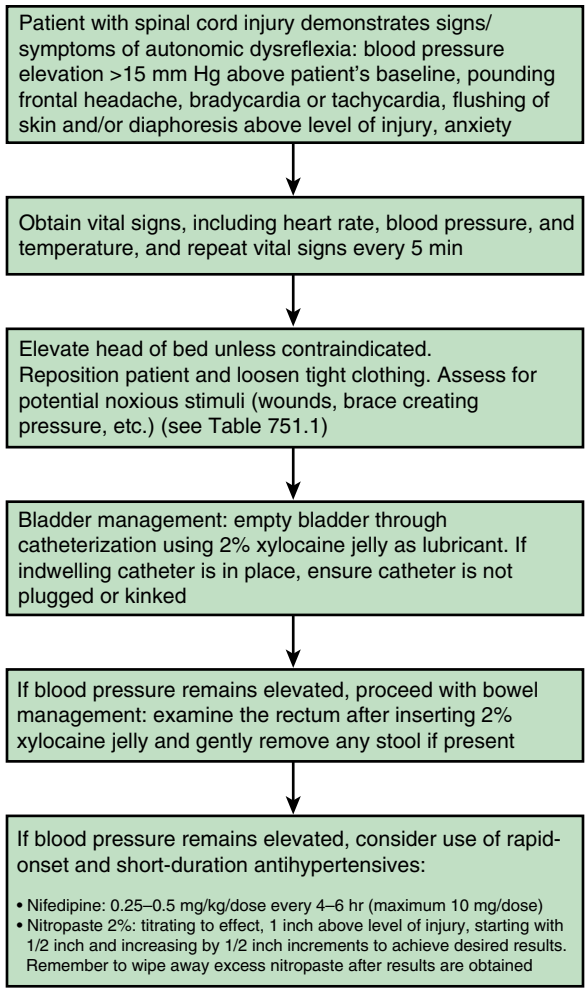


Fig. 751.2 Algorithm for the management of autonomic dysreflexia.

significantly. Lesions at or proximal to the conus medullaris typically result in UMN bowel dysfunction, whereas lesions distal to the conus typically result in LMN bowel dysfunction characterized by an areflexic bowel lacking peristalsis. Management of **bowel incontinence** requires the use of diet modifications, bowel medications, and planned evacuations. Emptying is facilitated by use of the gastrocolic reflex, digital stimulation, suppositories, and enemas in those with UMN bowel dysfunction. Individuals with LMN bowel dysfunction often require manual removal because peristalsis and reflexes are not intact.

Individuals with SCI have increased risk for dysphagia, delayed gastric emptying, ileus, gastric ulcerations, pancreatitis, and superior mesenteric artery syndrome. Presentation of an acute abdomen in SCI is challenging to identify because a patient may be incapable of feeling the pain intensity typically associated with an intraabdominal disorder. As a result, an acute abdomen may be manifested by nonspecific signs and symptoms, such as vomiting, poorly localized dull pain, restlessness, fever, and leukocytosis.

Frequent monitoring for **skin breakdown** and **pressure ulcers** is necessary, both acutely as well as lifelong. Pressure ulcers may heal more slowly in patients with SCI and can significantly impact function. Common locations include the occiput, elbows, sacrum, ischium, and heels. Devices such as halo vests and splints increase the risk of developing a pressure sore. Frequent inspection and repositioning for pressure relief when in bed and when sitting are important measures to minimize the risk of pressure ulcer development.

Depending on the level of the lesion, paralysis of the diaphragm or intercostal and abdominal muscles can result in restrictive ventilatory impairment and ineffective coughing. Respiratory muscle training, abdominal binders, and noninvasive ventilation and airway clearance devices, such as the insufflator–exsufflator cough assist device, should be considered in select patients.

Spasticity typically increases with noxious stimulation and can interfere with sleep, comfort, positioning, and care (see Chapter 752). Untreated spasticity can lead to contracture development and functional limitations. Management includes pharmacologic therapy, stretching, splinting, and positioning to reduce tone. Focal spasticity can be treated with chemodenervation by injecting botulinum toxin into select hypertonic muscles or phenol perineurally. Intrathecal baclofen may be an option for severe generalized spasticity or spasticity that is predominately in the lower extremities.

Increased bone resorption occurs as a result of prolonged immobilization. If excessive calcium is not adequately excreted by the kidneys, insidious onset of abdominal pain, nausea, vomiting, lethargy, polydipsia, polyuria, and behavior changes may occur. This **immobilization**

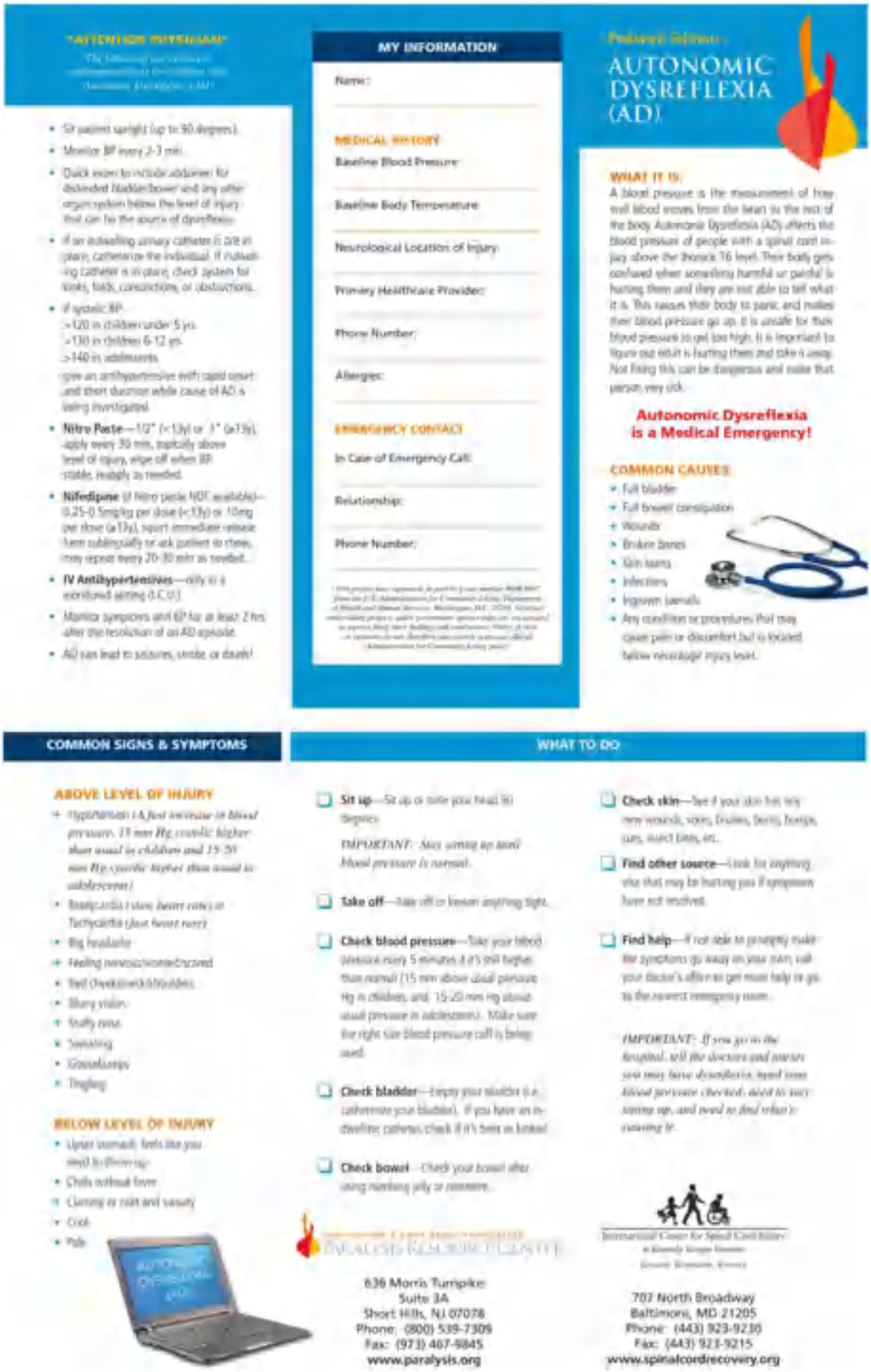


Fig. 751.3 Example of pediatric autonomic dysreflexia emergency card, which can be downloaded in multiple languages for free from the Christopher & Dana Reeve Foundation Paralysis Resource Center website (https://www.christopherreeve.org/living-with-paralysis/free-resources-and-downloads/wallet-cards).

hypercalcemia is managed with IV normal saline and the bisphosphonate pamidronate. Failure to manage the immobilization hypercalcemia may result in nephrocalcinosis, urolithiasis, or renal failure. Loss of bone mineral density begins immediately after an SCI occurs and osteopenia plateaus 6-12 months later. This may result in **pathologic fractures,** with the most common sites of fracture including the supracondylar region of the femur and the proximal tibia. Precautions are necessary because fractures may occur with minor trauma, range of motion exercises, and gait training. Treatment should include the use of removable splints or casts that are well padded over bony prominences to prevent skin breakdown, which is more likely with insensate skin under the cast. Prevention through progressive weight bearing, if feasible and safe, and calcium and vitamin D supplementation is encouraged.

The risk of development of spinal deformities and scoliosis is about 25% in patients sustaining SCI both before and during puberty, and some of these children will require surgical correction. Because of the high incidence of scoliosis in patients younger than 15 at the time of their injury, radiographs of the thoracolumbar-sacral spine should generally be obtained every 6 months before skeletal maturity and every 12 months thereafter. Children who sustain injuries before puberty are also susceptible to hip dislocation and require periodic screening for this condition. Although neurologic **heterotopic ossification** is less prevalent in children compared with adults, it may occur on average about 4 months, but up to 14 months, after the initial injury. The most common site of heterotopic ossification is the hip, but it may also occur in the knee, elbow, and shoulder.

Children and adolescents with SCI are at risk for decreased muscle mass, insulin resistance, decreased glucose transport, dyslipidemia, obesity, and decreased bone health as they age. Long term, patients with SCI have a 3-5-fold greater odds of cardiovascular disease compared with able-bodied individuals. Nutrition education and monitoring are important for decreasing long-term morbidities. Promoting exercise and physical activity and fitness are important for well-being. Youth with SCI may develop latex allergy thought to be a result of repeated, early exposure to latex products; thus a latex-free environment and degree of suspicion for allergies to bananas, kiwis, avocados, or chestnuts is advised.

Psychologic adjustment to SCI is influenced by the developmental age at the time of injury. SCI will impact the child's psychosocial development, so adjustment should be monitored closely. Long-term outcomes related to coping, depression, and anxiety are better in adults who sustained their injury during childhood, compared with those who sustained their injuries in adulthood. Positive coping strategies and strong social supports are associated with greater social participation. Education regarding sexual development and function with SCI injury should be provided.

PROGNOSIS

Prognosis for functional recovery after an SCI depends on the neurologic level of injury and the level of completeness. Examination at least 72 hours after injury has been determined to be a better indicator of the prognosis than earlier examinations. Reexamination after recovery from spinal shock provides additional prognostic information. It is prudent for those determining and communicating the diagnosis to understand the limitations of the anorectal examinations, and thus completeness of injury, unique to children. Those individuals with an initial incomplete injury have an increased likelihood of eventual neurologic recovery. The neurologic level of injury can be helpful in determining the level of independence with functional activities (Table 751.2). The use of technology in rehabilitation encourages the pediatric patient to become more engaged in their own care and advance their

Table 751.2 Projected Functional Outcomes at 1 Year After Injury and/or Diagnosis According to Neurologic Level of Injury

	C1-C4	C5	C6	C7	C8- T1
Feeding	Dependent	Independent with adaptive equipment	Independent	Independent	Independent
Dressing—Upper Body	Dependent	Independent with adaptive equipment	Independent	Independent	Independent
Dressing—Lower Body	Dependent	Independent with adaptive equipment	Independent with adaptive equipment	Independent with adaptive equipment	Independent with adaptive equipment
Bathing	Dependent	Dependent	Dependent	Some assistance to independent with equipment	Independent
Bed mobility	Dependent	Dependent	Some assistance to independent	Independent	Independent
Transfers— Level Surface	Dependent	Dependent	Some assistance to independent	Independent	Independent
Wheelchair Propulsion	Independent with power; dependent with manual	Independent with power; may be independent with manual on level surfaces	Independent	Independent	Independent
Driving	Dependent	May be independent with adaptations	Independent	Independent	Independent
	T2-T9		**T10-L2**		**L3-L5**
Activities of daily living (feeding, dressing bathing)	Independent		Independent		Independent
Transfers	Independent		Independent		Independent
Ambulation	Standing in frame, tilt table, or standing wheelchair Exercise only		Household ambulation with orthosis		Community ambulation is possible

Adapted from Hornyak J, Wernimont C: Spinal cord injuries. In: Murphy K, McMahon M, Houtrow A eds. Pediatric Rehabilitation: Principles and Practice, 6th ed. New York: Demos Medical Publishing, 2021.

independence, which is correlated with higher quality of life. Common technology includes therapeutic and functional stimulation, EMG biofeedback and EMG-triggered stimulation, assistive technology for computer access, and implanted functional electrical stimulation system including phrenic nerve stimulators.

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Chapter 752

Spasticity

Joyce L. Oleszek and Loren T. Davidson

Spasticity is a component of the upper motor neuron syndrome characterized by velocity-dependent resistance to passive range of motion, resulting in tonic stretch reflexes and accompanied by exaggerated tendon jerks. Spasticity management is determining what degree of spasticity may be tolerable and of functional benefit versus detrimental.

When devising a treatment plan, both the positive and negative effects of spasticity on function must be considered. Treatment should maximize function, independence, comfort, and quality of life while minimizing sedation and adverse effects. Management strategies including systemic medications, injections, and surgery are reviewed.

SYSTEMIC MEDICATIONS

Systemic medications are used as a treatment for generalized spasticity (Table 752.1). Although efficacy of certain antispasmodics has been demonstrated, their use should be contingent on functional benefit because adverse effects are quite common. Frequently used medications include baclofen, benzodiazepines, dantrolene sodium, tizanidine, clonidine, and trihexyphenidyl.

GABAergic Medications

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter of the central nervous system. The two most relevant GABA receptors for the purposes of pharmacologic management of spasticity are $GABA_A$ and $GABA_B$. **Benzodiazepines** exert their effect by increasing the affinity of GABA for the $GABA_A$ receptor. This results in presynaptic inhibition and a net inhibitory effect at both spinal and supraspinal levels. Of the benzodiazepines, diazepam is a commonly used medication to treat spasticity because of its long half-life and need for less frequent administration. In children younger than 2 years of age, clonazepam is a good option because of the availability of a liquid formulation and dosing guidelines. Sedation and cognitive slowing limit the usefulness of this class of medications in children. However, benzodiazepines can be helpful for dystonic storms or disturbed sleep in children with cerebral palsy (CP). The use of benzodiazepines may lead to physiologic dependence; thus abrupt discontinuation should be avoided to prevent withdrawal.

Baclofen is a $GABA_B$ agonist and a preferred agent in the treatment of spasticity of spinal origin. Baclofen exerts an inhibitory effect on both monosynaptic and polysynaptic spinal reflexes, but its supraspinal receptor sites can result in sedation as is common to all GABAergic medications. Daytime dosing of oral baclofen is often better tolerated than benzodiazepines with regard to sedation. Intrathecal administration of baclofen via an intrathecal baclofen (ITB) pump (see later) allows greater selectivity of spasticity reduction while minimizing adverse cognitive effects. Oral baclofen is considered a first-line medication for the management of dystonia in CP with common indications including pain or difficulty sleeping associated with dystonia. Abrupt cessation of oral or ITB baclofen must be avoided because of withdrawal potential.

α_2-Adrenergic Agents

Clonidine and **tizanidine** are examples of centrally acting α_2-adrenergic agonists that decrease spasticity and have an antinociceptive effect. Clonidine is used more frequently as an antihypertensive. Clonidine exerts its effect on spasticity via both presynaptic inhibition of sensory afferents as well as release of glutamate at the level of the spinal cord. In comparison to clonidine, tizanidine has less-potent hemodynamic effects, which is desirable when used primarily for spasticity reduction. However, tizanidine is extensively metabolized by the liver, so hepatic impairment may have a significant effect on its pharmacokinetics. Although clonidine and tizanidine are used widely as antispasmodics in practice, there is limited evidence for their use in reducing spasticity in children with CP. Tizanidine's antispasticity effect has been demonstrated in adults with multiple sclerosis and spinal cord injury. Clonidine has been shown to be effective for disturbed sleep associated with severe hypertonia. The adverse effect profile of these agents can limit their use.

Peripherally Acting Calcium Blockers

Dantrolene sodium works at the level of skeletal muscle to block calcium release from the sarcoplasmic reticulum. Despite its peripheral site of action, dantrolene may induce sedation, although to a lesser degree than other centrally acting agents. A few small studies have shown that dantrolene decreases clonus and spasticity but can also decrease strength. Dantrolene is often well tolerated in children, but its risk of hepatotoxicity requires monitoring of liver function tests. Hepatotoxicity risk increases with age, increasing dose, and female gender (see Table 752.1).

INJECTION MANAGEMENT

Injection management of spasticity should be considered when spasticity causes significant functional impairments that are refractory to more conservative options. Combining treatment options such as injections and systemic medications can be very effective.

Botulinum toxin (BoNT) and phenol injections are used to treat localized spasticity. OnabotulinumtoxinA (Botox) and AbobotulinumtoxinA (Dysport) have obtained U.S. Food and Drug Administration (FDA) approval for both upper and lower limb spasticity in pediatrics. RimabotulinumtoxinB (Myobloc) and IncobotulinumtoxinA (Xeomin) both have FDA approval but neither have a pediatric indication. BoNT is derived from the bacteria *Clostridium botulinum,* and there are seven immunologically distinct serotypes designated A through G. Its mechanism of action involves a light chain protein binding to synaptobrevin at the neuromuscular junction, inhibiting vesicles from anchoring to the cell membrane and preventing acetylcholine release from the presynaptic membrane. This interferes with nerve impulse transmission and results in weakness of the muscle injected. Onset of action is within 2 weeks of administration, duration is 3-6 months, and effects wane as the neuromuscular junction reestablishes its original function. Injections should be administered no more frequently than every 3 months to reduce neutralizing antibody formation, which occurs in 1–2% of treated individuals. BoNT-A is a safe and effective treatment for spasticity in the upper and lower extremities in children with CP, but the effects on long-term functional improvement with repeated injections are less well known. The combination of BoNT-A injections to the gastrocnemius muscles and serial casting has been shown to improve ankle range of motion and gait. BoNT-A can also improve ease of care and comfort in nonambulatory children with CP. The most common adverse events (AEs) include localized pain and weakness, unsteadiness and increased falls, fatigue, urinary incontinence, and dysphagia. Systemic AEs

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INJECTION MANAGEMENT

Injection management of spasticity should be considered when spasticity causes significant functional impairments that are refractory to more conservative options. Combining treatment options such as injections and systemic medications can be very effective.

Botulinum toxin (BoNT) and phenol injections are used to treat localized spasticity. OnabotulinumtoxinA (Botox) and AbobotulinumtoxinA (Dysport) have obtained U.S. Food and Drug Administration (FDA) approval for both upper and lower limb spasticity in pediatrics. RimabotulinumtoxinB (Myobloc) and IncobotulinumtoxinA (Xeomin) both have FDA approval but neither have a pediatric indication. BoNT is derived from the bacteria *Clostridium botulinum,* and there are seven immunologically distinct serotypes designated A through G. Its mechanism of action involves a light chain protein binding to synaptobrevin at the neuromuscular junction, inhibiting vesicles from anchoring to the cell membrane and preventing acetylcholine release from the presynaptic membrane. This interferes with nerve impulse transmission and results in weakness of the muscle injected. Onset of action is within 2 weeks of administration, duration is 3-6 months, and effects wane as the neuromuscular junction reestablishes its original function. Injections should be administered no more frequently than every 3 months to reduce neutralizing antibody formation, which occurs in 1–2% of treated individuals. BoNT-A is a safe and effective treatment for spasticity in the upper and lower extremities in children with CP, but the effects on long-term functional improvement with repeated injections are less well known. The combination of BoNT-A injections to the gastrocnemius muscles and serial casting has been shown to improve ankle range of motion and gait. BoNT-A can also improve ease of care and comfort in nonambulatory children with CP. The most common adverse events (AEs) include localized pain and weakness, unsteadiness and increased falls, fatigue, urinary incontinence, and dysphagia. Systemic AEs

Table 752.1 Dosing Guidelines, Pharmacologic Actions, and Adverse Event Profile of Commonly Prescribed Oral Antispasmodic Medications for Children

MEDICATION/DOSING GUIDELINES	PHARMACOLOGIC ACTIONS	ADVERSE REACTIONS/PRECAUTIONS
BACLOFEN 0.125-1 mg/kg/day *2-7 yr:* 2.5-10 mg tid-qid (10-40 mg/day) *8-12 yr:* 5 mg-15 mg tid-qid (15-60 mg/day) *12-16 yr:* 5-20 mg tid-qid (20-80 mg/day) Note: Caution advised with renal impairment; consider reducing dose.	• Centrally acting, structural analog of GABA • Binds to $GABA_B$ receptors causing presynaptic inhibition of mono/polysynaptic spinal reflexes • Rapid absorption, blood level peaks in 1 hr, half-life 5.5 hr. • Renal excretion (70–80% unchanged) • Hepatic excretion (15%)	• CNS depression (sedation, fatigue) • Nausea • Headache • Dizziness • Confusion • Euphoria • Hallucinations • Hypotonia • Ataxia • Paraesthesias Note: Abrupt withdrawal may cause seizures, hallucinations, rebound muscle spasms, and hyperpyrexia.
DIAZEPAM 0.12-0.8 mg/kg/day *6 mo-12 yr:* 0.12-0.8 mg/kg/day PO divided q 6-8h *>12 yr:* 2-10 mg PO bid-qid Note: Starting a qhs dose only or proportionately larger dose at bedtime may limit excessive daytime sedation.	• Centrally acting, binds to $GABA_A$ receptors mediating presynaptic inhibition in brainstem reticular formation and spinal polysynaptic pathways • Rapid absorption, blood level peaks in 1 hr, with half-life of 30-60 hr	• CNS depression (sedation, impaired memory, and impaired attention) • Ataxia • Dependence/potential for substance abuse/overdose • Withdrawal syndrome (including anxiety, agitation, irritability, tremor, muscle twitching, nausea, insomnia, seizures, hyperpyrexia) • Increased potential for adverse effects with low albumin levels due to being 98% protein bound
DANTROLENE SODIUM 3-12 mg/kg /day *>5 yr:* 6-8 mg/kg/d PO divided bid-qid Start 0.5 mg/kg qd-bid for 7 days, then 0.5 mg/kg tid for 7 days, then 1 mg/kg tid for 7 days, then 2 mg/kg tid to a maximum of 12 mg/kg/d or 400 mg/day.	• Peripheral action, blocking release of calcium from sarcoplasmic reticulum with uncoupling of nerve excitation and skeletal muscle contraction • Blood level peaks in 3-6 hr (active metabolite 4-8 hr), half-life of approx. 15 hr	• Malaise • Fatigue • Nausea • Vomiting • Diarrhea • Muscle weakness with high dose **Note:** Hepatotoxicity (baseline liver function tests MUST be checked before starting dantrolene, tested weekly during dose titration and regularly every 1-2 months thereafter). Drug *should be discontinued promptly* if liver enzymes become elevated.
TIZANIDINE *<10 yr:* Initiate 1 mg orally at bedtime initially, increasing to 0.3-0.5 mg/kg in 4 divided doses *>10 yr:* Commence 2 mg orally at bedtime initially, increased according to response, maximum 24 mg/day in 3-4 divided doses	• Centrally acting, $alpha_2$ adrenoceptor agonist activity at both spinal and supraspinal sites. Prevents release of excitatory amino acids, facilitating presynaptic inhibition • Good oral absorption, blood level peaks in 1-2 hr, half-life of 2.5 hr	• Dry mouth • Drowsiness • Headache • Dizziness • Insomnia • Anxiety • Aggression • Mood swings • Visual hallucinations • Risk of hypotension (although 10 times less anti-hypertensive potency than clonidine) • Nausea/vomiting • Constipation • Liver function tests should be monitored; baseline and 1 month after maintenance dose achieved.
CLONIDINE 0.025-0.1 mg/day in 2-3 divided doses.	• Centrally acting, mixed alpha adrenoceptor agonist with predominant alpha-2 activity causing membrane hyperpolarization at multiple sites in brain, brainstem, and dorsal horns of spinal cord. • Rapidly absorbed orally, blood level peaks in 1-1½ hr, half-life of 6-20 hr.	• Drowsiness • Dry mouth • Bradycardia • Orthostatic hypotension • Abrupt cessation may result in rebound hypertension.

can occur in up to 3.6% of children with CP receiving BoNT-A, and those with a history of dysphagia and/or aspiration pneumonia are at increased risk. The FDA requires black box labeling on BoNT products, cautioning of a rare but potentially life-threatening complication of BoNT effects spreading beyond the injection site. Co-administration of BoNT and other agents interfering with neuromuscular transmission, such as aminoglycosides and curare-like agents, should be performed with caution because the effect of the toxin may be potentiated.

Phenol neurolysis can be used in combination with BoNT injections to allow treatment of more affected muscles while remaining within the safe dose range of BoNT. Phenol causes nonselective denaturing of proteins upon exposure to the nerve, thereby causing nerve injury by precipitating and dehydrating the protoplasm. This, in turn, interferes with nerve conduction and impairs innervation to muscles. Phenol injections are typically used to target nerves to large proximal muscles (musculocutaneous, obturator and sciatic nerves), and the duration of clinical effect may be longer than BoNT. There is limited evidence on the use of phenol in children with CP, but a few small studies show safety and efficacy. Phenol injection of the anterior branch of the obturator nerve in children with CP has been found to be safe and effective. AEs include pain, swelling and inflammation, and dysesthesias. The low cost of phenol incurs a significant advantage over BoNT, but the need for electrical stimulation or ultrasound guidance and general anesthesia may negate this benefit.

SURGICAL MANAGEMENT

Intrathecal baclofen (ITB) is approved to treat spasticity of cerebral origin. ITB is delivered to the intrathecal space by a catheter connected to a subfascially implanted pump. This mechanism of delivery produces much higher local concentrations in the cerebrospinal fluid at a fraction of the equivalent systemic dose of baclofen, thereby minimizing the CNS depressive effects. Catheter tips are typically positioned at C5-T2 but can be placed intraventricularly for severe dystonia. ITB pumps require refills at 2-6–month intervals depending on dose rate and pump size and need to be replaced every 5-7 years for end of battery life. The frequent maintenance required can be prohibitive to some families. Before ITB pump placement, a single bolus dose of baclofen can be delivered via lumbar puncture to evaluate responsiveness and impact on functional abilities. ITB is effective in reducing spasticity and dystonia in CP and may improve the ease of care and quality of life of children with CP. Continuous ITB treatment is superior to placebo on attainment of individual treatment goals in children with Gross Motor Function Classification System (GMFCS) level IV and V CP (Fig. 752.1). Serious AEs can occur with ITB. One 14-year study of 430 patients found at least one complication in 25% of patients: infection in 9.3%, CSF leak in 4.9%, catheter problem in 15.1%, and a pump-related problem in 1%. Electromagnetic interference and MRI may cause transient operational changes to the ITB pump and changes to the flow rate; thus the pump should be interrogated by a programmer after MRI as a precaution. **ITB withdrawal** is a medical emergency and needs to be identified early and managed aggressively. Sequelae can include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity that, in rare cases, can advance to rhabdomyolysis, multiple organ–system failure, and death. Caregivers need to be educated on the early symptoms of baclofen withdrawal. Prevention of abrupt discontinuation of ITB requires careful attention to programming and monitoring of the infusion system, refill scheduling, and pump alarms.

Selective dorsal rhizotomy (SDR) is a surgical procedure that decreases muscle spasticity by sectioning hyperexcitatory sensory nerve rootlets that innervate the lower extremities. The surgical technique involves single or multilevel osteoplastic laminectomies exposing the L2-S1 nerve roots, and sensory rootlets are chosen for sectioning using intraoperative electromyography. The most ideal candidates are thought to be children 3-8 years of age with spastic diplegic CP, minimal upper limb involvement, good selective motor control and strength with the ability to rise from the floor independently, minimal contractures, and good cognitive skills.

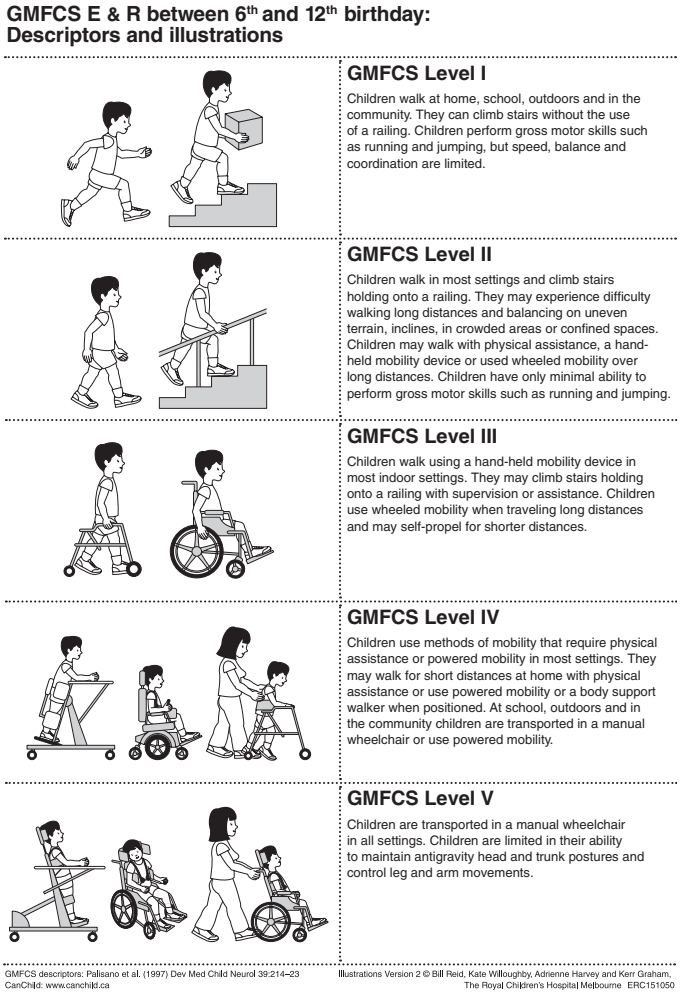

Fig. 752.1 Gross Motor Function Classification System Expanded and Revised (GMFCS E & R). *(Descriptors: ©Palisano et al, 1997 – Dev Med Child Neurol., 39:214-23 (CanChild: www.canchild.ca); Illustrations Version 2 © Bill Reid, Kate Willoughby, Adrienne Harvey and Kerr Graham, The Royal Children's Hospital Melbourne)*

Ambulatory children with CP have better function and quality of life in the 24 months after SDR. A prospective gait analysis study in adults with CP 20 years after SDR showed improved locomotor function with increased gait speed. SDRs are performed to a lesser extent in children with spastic quadriplegic CP, and goals in this population are often to decrease lower limb spasticity while improving comfort, care, and positioning. A study in nonambulatory children with severe CP showed improvements in daily care and comfort at a mean follow-up of 19 months after SDR, although unmasking of prior dystonia can occur. AEs after SDR include bladder or bowel dysfunction, sensory dysesthesias, and back pain; however, these occur infrequently and are typically transient. A systematic review of spinal deformities after SDR in children with CP found scoliosis to be the most common deformity occurring in approximately 30% of children, but this risk has never been satisfactorily shown to be higher than the risk in those children who have not undergone SDR. Studies have reported higher rates of spondylolysis and spondylolisthesis after SDR than would be expected in the general CP population. Spine radiographs should be obtained routinely after SDR to monitor for spinal deformity.

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Chapter 753

Birth Brachial Plexus Palsy

Maureen R. Nelson and Nicholas L. Fleming

Birth brachial plexus palsy (BBPP) may cause significant arm weakness and subsequent functional deficits in children. The nerves to the arm are affected with variable degrees of weakness and sensory loss. Most children will have good recovery spontaneously, but functional deficits will remain in 20–30% of children with BBPP.

The mechanism for BBPP is lateral stretch of the plexus for the vast majority of cases. Anatomic variations in bones, blood vessels, and tendons lead to a very small number of cases. The incidence of BBPP is reported as 0.5-4.6 per 1,000 live births, with variability thought to be attributable to the type of obstetric care and the size of infants around the world.

Risk factors for BBPP include prior infants with BBPP, shoulder dystocia, birthweight >4 kg, multiparous mothers, mothers with excessive weight gain, and diabetic mothers. Delivering twins or triplets, as well as cesarean sections, have been described as protective from BBPP. Factors with a higher risk of poor outcome are birthweight greater than 4 kg, Horner syndrome, cephalic presentation, and induction or augmentation of labor.

Nerve injuries include neurapraxia, neurotmesis, and axonotmesis. **Neurapraxia** is the least severe of these types and is a reversible loss of nerve conduction. This type will recover. **Neurotmesis** is the most severe and is a total and complete disruption of the nerve. An *avulsion* describes a **neurotmesis** that is a preganglionic lesion, and a *rupture* describes the same event for a postganglionic lesion. **Axonotmesis** is the intermediate form and the most difficult to delineate. There is disruption of the epineurium with variable injury to the axons creating the diagnostic and prognostic difficulties (Fig. 753.1). For these reasons, it is advisable to urgently seek out consultation from specialty clinics or specializing physicians in your geographic area for close monitoring and treatment considerations, including surgical candidacy.

Not only is there variability in the degree of nerve injury, but there is also variability in location. The brachial plexus consists of the anterior primary rami, or roots, from C5, C6, C7, C8, and T1. These roots will combine and then branch to form the trunks, divisions, and branches before separating distally to individual peripheral nerves as illustrated by Figure 753.2.

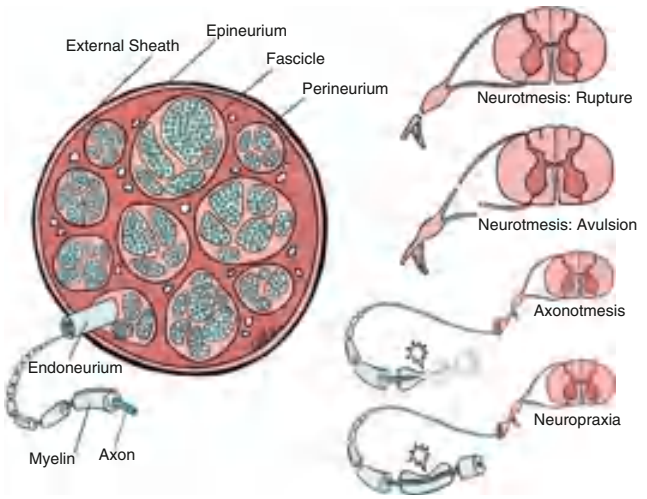

Fig. 753.1 Anatomy of peripheral nerve and injury type. *(Courtesy Kendall Hulk, DO.)*

There is variable impact on motor and sensory systems as well. The sensory fibers are relatively protected compared with the motor fibers because the sensory fibers run together until they are outside of the spinal cord into the dorsal root ganglion, where their cell bodies lie. The motor fibers have the cell bodies within the spinal cord and so are not as cohesive in their path. Therefore the sensory fibers may be spared, while motor fibers show clinical deficits.

Narakas is a commonly used classification system (Table 753.1). Erb palsy is generally described as the upper trunk or C5-C6 palsy. It is by far the most common injury seen in BBPP. When C7 is included in the injury, it may be referred to as *extended Erb palsy*. Together, these forms of Erb palsy make up 75% of all BBPP. These two groups also demonstrate the greatest recovery rate, at 80% and 60%, respectively, resulting in a functional arm. **Klumpke palsy**, C8-T1, is extremely rare in BBPP, likely not occurring except in the case of anatomic variation. If a baby presents with a C8-T1 deficit, the baby most likely originally had a complete C5-T1 BBPP and then had recovery of the upper portion of the plexus. This can happen because C4, C5, C6, and sometimes C7 are protected coming out from the spinal cord, held in a gutter along the transverse processes by connective tissue, whereas C8 and T1 are not. The phrenic nerve may also be involved with its innervation from C3, C4, and C5, with potential respiratory concerns. The differential diagnosis of an infant with a weak or less functional arm is broad, and there should be consideration for other neurologic injury (stroke, spinal cord injury, underlying congenital or metabolic diagnosis), musculoskeletal issues (fracture, muscular torticollis, anomalous rib impinging nerves), infection, tumor, and other sources of pain or pathology that could lead to developmental disregard or a learned nonuse of an extremity. **Phrenic nerve** (4th cervical and C3-C5) injury may also be present and result in ipsilateral diaphragm paralysis and respiratory distress.

PHYSICAL EXAMINATION

Motor movement evaluation is the focus of this exam. The Active Movement Scale is a reliable passive assessment of muscle strength that is widely used for infant examination of BBPP. Mallet scores, which assess shoulder abduction and external rotation deficits, are likewise useful but are more pertinent for examination of the toddler or older children. Examination for sensation, particularly sharp sensation, useful in its own right, will also frequently help with active motor evaluation in infants. Assessment of muscle stretch reflexes is important, in that infants with brachial plexus palsy will be areflexive or hyporeflexive in the involved arm. Evaluation of primitive reflexes, particularly the Moro reflex, is helpful, because most of these infants will have C5-C6 involvement, and therefore the Moro may show shoulder abduction and elbow flexion on one side but not the involved side. Range-of-motion examination is critical. Deficits are commonly seen because of the imbalance of muscles that are active and those that are not. Shoulder adduction and internal rotation is a common position, as is elbow flexion, forearm pronation, and wrist and finger flexion. Torticollis is commonly present and almost always with the face turned away from the involved arm. **Horner syndrome** (ptosis, miosis, and anhidrosis) may be present ipsilaterally and is an indicator of severity. In children with very severe deficits, the arm may be cooler because of the sympathetic nervous system outflow at T1. The size of the involved arm eventually is usually smaller, about 95% of the uninvolved arm, because of muscle atrophy and smaller diameter and length of the bone.

Among older infants and children, compensatory movements of the arm may be noted. Common examples are use of trunk momentum to move (particularly to rotate) the proximal arm, hyperlordosis of the lumbar spine to position the arm more advantageously, use of the pectoralis muscle to flex the shoulder, and use of the knee while sitting to physically flex the elbow. Examination of the back for symmetry, along with the scapulae for winging, is also relevant. Scapular winging can be problematic both socially and clinically. Having the older child manipulate buttons, snaps, or zippers, throw

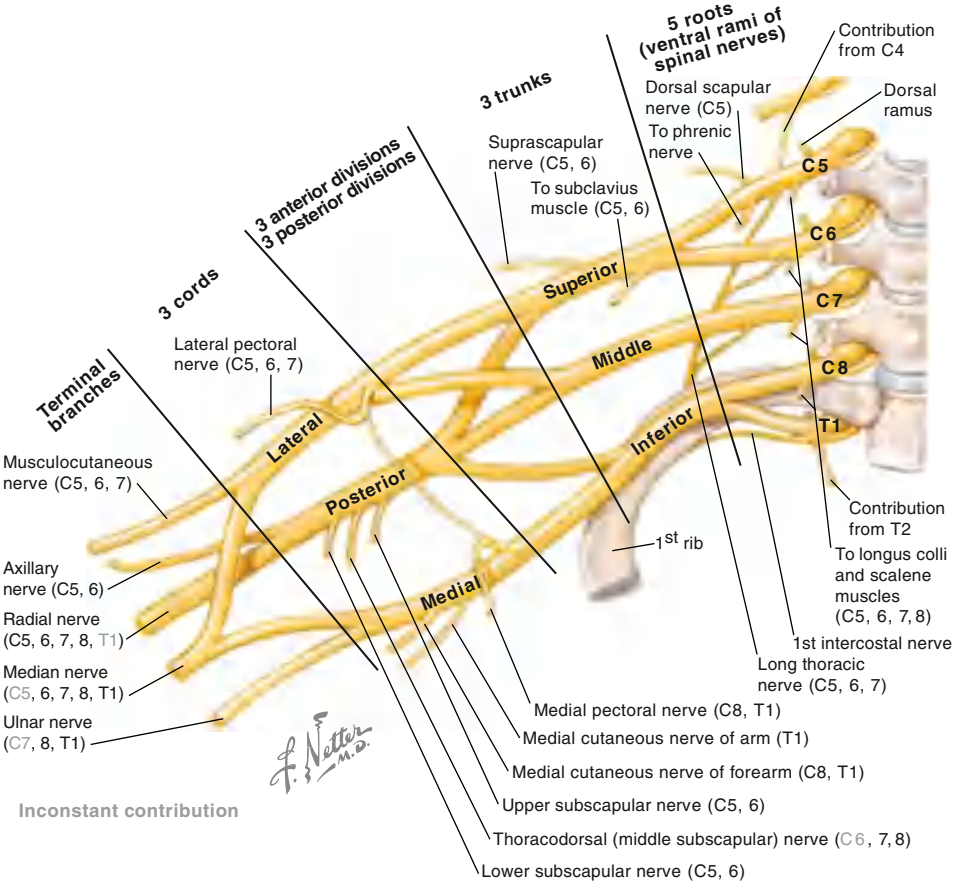

Fig. 753.2 Schematic of the brachial plexus. *(Netter illustration from www.netterimages.com. Elsevier Inc.)*

Table 753.1 Narakas Classification

GROUP	NAME	ROOTS	CLINICAL DESCRIPTION
I	Erb palsy	C5-6	Paralysis of shoulder and biceps with should abduction, external rotation, and elbow flexion
II	Extended Erb palsy	C5-7	As above with paralysis of wrist
III	Total palsy	C5-8, T1	Complete flaccid paralysis
IV	Total palsy with Horner syndrome	C5-8, T1	Complete flaccid paralysis with Horner syndrome

and catch a ball, and write, print, or color may be revealing, along with how they remove their shirt for examination.

When hand function was evaluated with testing of children with upper-plexus involvement, 80% of the children had significantly decreased performance compared with the contralateral hand. This indicates the hand function is impaired even in children who only have upper plexus involvement.

EVALUATION

Radiographic evaluation may be needed. Plain films can be viewed immediately if there is reason to consider clavicle or humerus fracture, infection, osteomyelitis, or tumor. Ultrasound (US) can be used to evaluate for shoulder dislocation. CT myelogram had been the mainstay diagnostic tool for brachial plexus evaluation despite its radiation dose and invasive lumbar puncture. However, MRI lacks these drawbacks and provides a more accurate and reliable evaluation.

US and electrodiagnostic evaluation (EDX) can also be helpful in evaluation of the brachial plexus. US is an ever-improving technology but does not yet evaluate the deeper nerve root avulsions or ruptures, making isolated US imaging inappropriate. However, US can be useful for postganglionic injury evaluation, specifically for the upper plexus. EDX may be supplemental and is especially helpful as a confirmatory test for lower plexus avulsion injuries given its strong specificity and MRI's weaker diagnostic accuracy for these lower plexus injuries.

EDX includes both nerve conduction studies (NCS) and electromyography (EMG) and should be performed by someone who is experienced in the examinations of infants and young children, both for the most precise evaluation and the most comfortable experience for the youngster. The following EDX pearls should be noted:

1. Normal electrical sensory response in areas where the child cannot feel indicates a *preganglionic neurotmesis* (avulsion).
2. Motor nerve conduction studies are useful to check for continuity of nerve fibers to muscles that are weak or paralyzed.
3. F waves are useful in evaluating proximally because these responses go from peripheral nerves to the spinal cord and back.
4. Somatosensory evoked potentials are difficult to perform on infants while awake, because of motor artifact obliterating the responses

with movement, and are imprecise because of overlapping responses to peripheral stimulation. These are useful intraoperatively because stimulation can be performed on the nerve roots themselves to determine proximal continuity.

5. EMG can show activation in muscles with paralysis or severe weakness.
6. The absence of biceps motor unit potentials at 1 month of age predicts future lack of clinical biceps recovery, although biceps EMG at 3 months has been reported to overestimate recovery potential.

TREATMENT

Early referral or consultation with a specialty clinic or specialized physician is paramount and should be completed as early as possible or by 1 month of age for close monitoring and consideration of possible microsurgery. Postoperative improvement in hand and arm function has been shown to have a negative correlation with age at time of primary surgery. Infants who do not show satisfactory improvement in muscle strength are candidates for such primary surgeries, which may include nerve transfers, in which branches from an uninvolved nerve are microsurgically transferred to the distal peripheral nerves supplied by the injured nerve roots and/or nerve grafting, in which one or more of the nonavulsed roots is attached distally to the trunk, cord, or peripheral nerve by means of an autogenous graft (commonly the sural nerve of the leg) or synthetic nerve conduits. There is general consensus that primary nerve surgeries should be performed at 3 months of age for Narakas type III and type IV. Those with upper-plexus (Narakas type I and type II) involvement are monitored closely, and there is surgical consideration for primary nerve surgery between 3 and 6 (or even 9) months of age. Classically, observed elbow flexion less than 3/5 at 6 months of age or a positive "cookie test" (child cannot bring cookie to mouth without bending neck forward more than 45 degrees) at 9 months would prompt decision to undergo primary surgery in these populations. The surgical focus for a complete palsy or "flail arm" is reinnervation of the hand, whereas the surgical goals of an upper-plexus reconstruction include, in descending priority, elbow flexion, glenohumeral abduction, shoulder stability, and shoulder external rotation. It should be noted that the goals of surgery are not to regain normal arm function but rather to have a more functional arm.

Regarding primary nerve surgeries, some have reported better outcomes with nerve transfer rather than nerve graft procedures. However, the heterogenous nature of BBPP, variable surgical techniques, and available nerve options often dictate what can be performed. Spinal accessory to suprascapular nerve transfer and radial nerve (long head of triceps branch) to axillary nerve transfer has been reported as the most common dual nerve transfer procedure. Other common nerve transfers include median or ulnar nerve to the musculocutaneous nerve (MCN), medial pectoral nerve to MCN, intercostal nerve to MCN, and contralateral or cross cervical nerve root transfers. Nerve graft procedures typically include harvesting of the sural (purely sensory) nerve or using synthetic nerve grafts. These grafts are typically used to reestablish the conduit of the suprascapular nerve, graft C5-to-posterior division, or graft C3/C4-to-upper trunk.

Regardless of whether primary surgery is pursued, treatment begins on the initial evaluation with instruction to the parents for positioning and early stretching exercises to begin at 2 weeks, or at 3-4 weeks if a humerus or clavicle fracture is present. They are also told of the critical task of maintaining infant awareness of the involved arm, initially by manually mimicking activities with the affected arm that the baby performs with the contralateral arm and by using a wrist rattle on the arm. Lack of awareness of the arm, sometimes called *developmental disregard*, in children can result in less active use of the arm, with functional loss, as a consequence. The parents also are informed of the higher risk of BBPP for future infants, and so the families are encouraged to speak with the obstetrician about optimal management in future deliveries.

The baby will start with occupational or physical therapy at approximately 2 weeks of age with focus on maintaining joint motion, maximizing strength, promoting sensory awareness, and supporting age-appropriate development. Parent education should be reinforced and a home program including daily stretching, positioning, and strengthening techniques should be constructed. Therapeutic taping may be done for supination, wrist extension, or, most commonly, for shoulder positioning to minimize an adducted, internally rotated posture. Neuromuscular electrical stimulation to the muscles minimizes atrophy and promotes increased size, and therefore strength, of muscle fibers. Ideal parameters for its use have not yet been determined, but a 20-30–minute twice-daily program is effective and has been shown to increase bone density.

The therapist or physician may consider a brace or splinting. Splints can be prescribed in conjunction with a physical or occupational therapist's guidance and are often worn the majority of the day (e.g., 22 hours/day). Common splinting strategies include supporting wrist extension with a baby with wrist-drop and/or extending the fingers and abducting the thumb as well, providing straps to assist with supination (Sup) of the forearm and even braces focused on positioning the shoulder in external rotation (ER). Protocols for splinting strategies such as the "Sup-ER orthosis" have been created and studied in small populations; however, there is currently no general consensus on implementation of such protocols. Early, close monitoring is not only important for surgical considerations, but it is also important for monitoring for secondary problems that can increase the negative impact of functional deficits in children with BBPP. Contractures of the elbow, shoulder, forearm, wrist, and fingers may occur. Although muscle imbalance and fibrosis can contribute to contracture, the evidence suggests a physiologic response related to muscle denervation leading to a failure of growth in the sarcomeres of these affected muscles. Early shoulder dislocations have been described in severe presentations. Botulinum toxin injections help balance out muscles that are overpowering weak muscles and such an intervention can minimize contractures and even prevent or help reduce a shoulder dislocation in these severe cases.

For older babies and children, muscle, tendon, and bony procedures are generally performed. These are often called *secondary surgeries*. Monitoring for shoulder deformity and dislocation is an important part of long-term follow-up. Because the shoulder joint develops as the infant and toddler grows, deficits frequently develop. Glenohumeral dysplasia, sometimes with shoulder dislocation, occurs in 60–80% of those with BBPP. Muscular imbalance across the developing shoulder results in deformity of the skeletally immature glenohumeral joint. The weakness of shoulder external rotation, combined with strong internal rotation, leads to this difficulty. The natural history of this deformity is progression if left untreated. This leads to further functional limitations, even with a strong hand. Treatment aims to minimize this progression. Treatment options include botulinum toxin injections, arthroscopic or open anterior capsule release or release of contracture, musculotendinous lengthening, tendon transfers (e.g., latissimus dorsi to increase external rotation and abduction strength), muscle transfers (e.g., gracilis muscle can be transferred to allow for elbow flexion and/or wrist extension), and, for severe deficits, a derotational humeral osteotomy.

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Chapter 754

Meningomyelocele (Spina Bifida)

Pamela E. Wilson and Tess S. Simpson

See also Chapter 631.

Meningomyelocele, or spina bifida (SB), is a congenital neural tube defect that results in the malformation of the spine and a potential dysplastic spinal cord. The severity of defect ranges from SB occulta (see Chapter 631.2) upward to anencephaly (see Chapter 631.6). SB without anencephaly is the most prevalent nonchromosomal central nervous system (CNS) defect in the United States. For unknown reasons, Hispanic women have the highest rate of SB (3.80/10,000 live births), followed by non-Hispanic White women (3.09/10,000 live births); the lowest rate is in non-Hispanic Black women (2.73/10,000 live births).

ETIOLOGY

See Chapter 631.1.

PREVENTION

See Chapter 631.1.

PRENATAL SCREENING

Prenatal screening is recommended for all pregnant women to detect neural tube defects. A blood test is done in the second trimester to evaluate alpha-fetal protein (AFP). If a neural tube defect is present, the AFP is often elevated, and further screening using high-resolution ultrasound is indicated. Ultrasound may reveal not only the spinal defect but also abnormal brain development, suggested by the "lemon and banana signs." The lemon sign is a medial indentation and scalloping of the frontal bones in the skull, whereas the banana sign is associated with hindbrain herniation of the cerebellum into the foramen magnum. The importance in early identification allows families to plan for delivery and consider fetal interventions, mainly prenatal surgical closure of the defect. Prenatal closure decreases the need for a ventricular shunt and lowers the incidence of severe Arnold-Chiari malformations, along with improved motor outcomes. However, there is an increased incidence of preterm delivery and a risk for uterine dehiscence; these risks may be reduced with fetoscopic procedures.

CLINICAL IMPLICATIONS

Meningomyelocele is a multisystem condition that includes characteristic abnormalities within the CNS. The neurologic lesion is assessed by the most caudal intact nerve segment with a motor test of grade 3. Lesions associated with SB are often grouped together as thoracic, upper lumbar (L1-L2), midlumbar (L3), lower lumbar (L4-L5), and sacral. Based on this information, a clinician can make inferences on the functional capabilities of the child and answer pertinent questions during the initial encounters (Table 754.1). The most basic question all families ask is: "Will my child walk?"

Initial surgical interventions are related to closure of the open defect. This is generally done the first day of life. Once the back is closed, the child will be monitored to see if hydrocephalus develops. Hydrocephalus is very common and related to hindbrain herniation and obstruction of the fourth ventricle. Hydrocephalus may occur at any time but most frequently within the first few months. Ventricular dilation may precede a change in head circumference or signs of increased intracranial pressure. The occurrence of hydrocephalus is approximately 77–95% and does appear to have an association with level of lesion. Treatment of ventriculomegaly, if mild, may be limited initially to clinical observation. Surgical placement of a ventricular shunt or endoscopic third ventriculostomy is indicated when occipital frontal circumference (OFC) is increasing. The risk for shunt revision in the first 2 years is 30–50%, which then decreases to 10%.

Hindbrain herniation or the **Chiari type II malformation** is seen in 80–90% of individuals with meningomyelocele. The classic manifestations include caudal displacement of the cerebellum, pons, and medulla and elongation of the fourth ventricle. The Chiari II malformation can be symptomatic (from brainstem herniation/compression) in approximately 20% of children. Respiratory symptoms associated with a Chiari malformation include stridor, vocal cord dysfunction, and central or obstructive apnea. Swallowing and feeding problems may require gastrostomy tube placement. If the child has a symptomatic Chiari II malformation, surgical

Table 754.1 Prognosticating in Meningomyelocele

MOTOR LEVEL SPINAL CORD SEGMENT	CRITICAL MOTOR FUNCTION PRESENT	MOBILITY: SCHOOL AGE	RANGE: ADULT	ACTIVITY: ADOLESCENT
T12	Totally paralyzed lower limbs	Standing brace, wheelchair	Wheelchair	Wheelchair, no ambulation
L1-L2	Hip flexor muscles	Crutches, braces, wheelchair	Wheelchair, household ambulation	Wheelchair, nonfunctional ambulation
L3-L4	Quadriceps muscles	Crutches, braces, household ambulation, wheelchair	Crutches, household ambulation, wheelchair	50% Wheelchair, household ambulation with crutches
L5	Medical hamstrings, anterior tibial muscles	Crutches, braces, community ambulation	Crutches, community ambulation	Community ambulation with crutches
S1	Lateral hamstring and peroneal muscles	Community ambulation	Community ambulation	Community ambulation 50% crutch or cane
S2-S3	Mild loss of intrinsic foot muscles possible	Normal	Normal	Limited endurance because of late foot deformities

From Braddon RL, ed. *Physical Medicine & Rehabilitation*, 4th ed. Philadelphia: Saunders; 2011: Table 54.1.

decompression is indicated. All children with SB are at risk for **tethered cord syndrome** (see Chapter 646.1). After shunt malfunction, this is the second most common cause for neurologic decline. Clinical manifestations of tethered cord syndrome include any change in gait, change in bowel or bladder function, increasing scoliosis, back pain, or orthopedic changes. Surgical detethering procedures are indicated in those with neurologic decline, but the success rate is variable.

The **orthopedic complications** of myelomeningocele are common and have predictable patterns. The spine deformities include scoliosis, lordosis, and kyphosis (see Chapter 720). The development of scoliosis has an association with the neurologic level. Children with thoracic level meningomyeloceles have an 80–100% risk, whereas those with a sacral level are at very low risk. Spine deformities tend to increase more rapidly during growth, especially puberty. Treatment of scoliosis includes both nonsurgical and surgical options. Braces, such as thoracic-lumbar-sacral orthotics (TLSO), therapy, and proper seating options may be beneficial. Surgically implanted growing rods to support the developing spine have been used in younger children. Spine surgery should be considered if the scoliotic spine curvature reaches 45 degrees; the child who is nearing skeletal maturity is a better candidate for spine surgery. Realistic expectations need to be discussed with the child and family. Correction of the spine may improve sitting, posture, and pelvic obliquity but may have a negative impact on function and ambulation.

The **development of the hip** is also influenced by neurologic level (see Chapter 719). The risk for dislocation is highest for those with lesions at the L3 level, followed by L1-L2. Unilateral hip dislocations should be fixed surgically because they may result in pelvic obliquity and problems with sitting, whereas bilateral dislocations generally do not require interventions. Contractures of soft tissues are commonly seen in children with higher lesion levels. Hip flexors and knee flexors are commonly involved.

Abnormalities in the foot occur in approximately 90% of children and adolescents. The goal of treatment is to achieve a plantar grade foot for weight bearing and to allow shoe wear. Clubfoot deformities are common in babies, and treatment includes serial casting and orthotics (see Chapter 715.3). The results are often suboptimal, and surgery may be needed. In addition, congenital vertical talus (rocker-bottom feet) is often encountered and needs to be addressed (see Chapter 715.4).

Osteoporosis (see Chapter 749) begins to develop in childhood and is more severe in higher-level meningomyelocele. Fractures of the lower extremities are most common in the femur, followed by the tibia. Preventive treatment includes nutritional approaches such as the use of supplemental calcium and vitamin D. Those with documented fractures should undergo a diagnostic evaluation (see Table 749.1), including dual-energy x-ray absorptiometry (DEXA). The use of bisphosphonates may be considered if the diagnostic evaluation does not reveal other underlying causes. The utility of early weight bearing has been advocated, but passive standing may have little impact on bone density.

Neurogenic bladder and bowel can be anticipated. The goals of treatment interventions are to protect kidney function and achieve social continence. For continence of urine, clean intermittent catheterization (CIC) is the mainstay of management. It is not atypical for newborn babies to be started on a CIC program. Urodynamics and renal ultrasounds are routinely used to monitor for hydronephrosis and track intravesicular pressures. Medications may be used to reduce bladder contractions and improve volume capacity. Surgical techniques are being used to improve continence, including bladder augmentation, urethral surgeries, and catheterizable channels. Poor CIC technique and/or urinary reflux may lead to urinary tract infection (UTI), which is diagnosed by having two findings: a urinalysis with white cell count of >10 and urinary culture >100,000 cfu/mL. A multicomponent bowel program is generally needed to achieve bowel continence. Nonsurgical interventions include adequate hydration, dietary manipulation, fiber regulation, and use of laxatives and enemas. Surgical interventions, such as the antegrade continence enema (ACE), have improved continence in many children and adolescents with SB.

Latex allergies are common. The etiology is likely multifactorial, but increased early exposure may play a role in the development of severe reactions (see Chapter 190). Care providers need to be keenly aware of products that contain latex or that have a cross reactivity, such as foods mixed with avocado, bananas, or kiwi fruit. Radioallergosorbent testing is used for identification of potential severe allergens.

People with SB show a wide range of **neuropsychologic abilities**. Many show a complex neuropsychologic profile that includes strengths in some areas and weaknesses in other areas. Common areas of strengths include vocabulary, word reading, spelling, and certain types of memory. Common weaknesses include motor skills, attention, organization, math, reading comprehension, and executive functioning skills. Overall cognitive functioning typically falls within the average range for children with SB; however, neurologic factors such as a Chiari II malformation or the presence of hydrocephalus increase the risk for neuropsychologic challenges. Neuropsychologic assessment is recommended to identify any potential gaps in cognition and social or emotional skills. This assessment can provide helpful information related to a child or adolescent's education and employment needs and assist with development of an individualized educational plan (IEP) or vocational rehabilitation plan. Appropriate early intervention and support programs should be initiated through an IEP or 504 plan if indicated (see Chapter 56). Effective interventions both at school and the home should be structured, explicit, and individualized. Parents and teachers can support learning goals by progressing in an orderly fashion from one learning target to the next and by modeling how to approach problems or tasks, often with step-by-step instructions and supervised practice.

ADOLESCENCE AND TRANSITION TO ADULTHOOD

Improved and expanded clinical care has increased the life span of individuals with SB, with the majority of individuals now living well into adulthood. Secondary conditions associated with SB (e.g., UTIs, skin breakdown, learning challenges) and more difficulty accessing healthcare services compared with their age-matched peers make adolescents and young adults with SB less likely to achieve emerging adult milestones such as leaving home, attending college, or finding employment.

The primary care clinician, in conjunction with specialty services, plays a pivotal role in developing future planning. It is important to discuss early on strategies to encourage developmentally appropriate independence and self-management skills. Individualized, comprehensive transition care that includes care coordination, decision-making support, education and employment resources, and independent living support is recommended for providers caring for children and adolescents with SB.

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Chapter 755

Upper and Lower Extremity Assistive Devices

Abigail Case and Sarah Helen Evans

Assistive devices, such as orthoses, prostheses, walkers, crutches, and wheelchairs, are key components of intervention for individuals with physical disabilities, and with the continued advancement in technology, robotic forms of these devices are also important to consider. The type of device chosen depends on the underlying diagnosis, functional abilities of the individual, prognosis for functional improvement or decline, tone abnormalities, range of motion, strength, and the overall gait pattern. Physicians, licensed independent practitioners, and physical therapists perform the evaluation of a child requiring an assistive device.

ORTHOSES

An **orthosis** is a device that is applied to the surface of the body to maintain alignment or position, to prevent or assist movement of the body part, or to provide support. Named for the body parts covered, orthoses can be static, made of rigid material, and designed to immobilize joints to inhibit movement, or they can be dynamic, allowing movement of the limb to occur. For example, **AFO** stands for *ankle-foot orthosis*, a brace worn on the foot that extends from the toes to the mid-calf position, supporting the foot and ankle joints (Fig. 755.1). Prefabricated orthoses are available, but many children require custom-made orthoses for optimal fit. Orthoses are modified or replaced during periods of growth or changes in function and can be obtained either directly through the orthotist or through the child's physical therapist. In most of the United States, braces must be prescribed by a physician or licensed independent practitioner to obtain insurance coverage, and it is best practice to have a prescription.

The use of an upper limb orthosis can be more conspicuous than its lower limb counterparts, and physicians should analyze the user's psychosocial well-being and tolerance for such device. In addition to patient goals and outcomes, the therapeutic intent of the upper limb orthosis must be considered. The efficacy of the orthosis may be measured by the reduction of the effects of the three Ps: paralysis, pain, and position.

Fig. 755.1 Hinged ankle-foot orthosis. *(Courtesy Ultraflex Systems, Inc., Pottstown, PA.)*

The type of lower-extremity orthosis prescribed is based on the child's diagnosis, functional status, prognosis, and the goals of treatment, with the prescription frequently modified over time as the child changes. Before writing a prescription, the provider performs an examination, which may include an evaluation of the child's gait, strength, tone, and range of motion. There are many types of braces that have specific functions to improve gait. Table 755.1 lists examples of these orthoses and their potential uses.

The most prescribed braces are solid and articulated AFOs. Solid AFOs are used for children with hypertonicity because they help to biomechanically reduce tone and provide stability with standing and walking. Children who are nonambulatory also benefit from wearing solid AFOs to maintain range of motion of the ankle.

Articulated (hinged) AFOs allow the child to have ankle dorsiflexion by permitting forward movement of the tibia and supporting the foot for heel strike. This design makes ambulating on uneven surfaces and using stairs easier because of the movement allowed at the ankle, while still supporting the foot position and maintaining medial-lateral stability of the ankle. Articulated AFOs should not be used in children with cerebral palsy, spina bifida, or other disorders if they have a crouched gait pattern because the hinge in the ankle joint may allow further crouching. In crouched gait, the hips and knees are held in flexion and ankles in dorsiflexion throughout the gait cycle, leading to an inefficient gait pattern.

PROSTHESES

A prosthesis is a device that replaces a missing body part, such as an arm or a leg. Lower-extremity prostheses are used to improve mobility, but upper-limb prostheses are not always needed to improve function because children can be quite independent with a single upper limb. Children with congenital upper limb amputations or deficiencies need to have prosthetic devices fit at the time they begin to sit for them to use the prosthesis functionally, and because, developmentally, young children are not ready to learn to use complicated devices, teaching them to use a mechanical prothesis requires intensive occupational therapy. Myoelectric protheses are too heavy and too hard to use at this age. Children with acquired upper limb amputations may be more likely to adjust to the use of a prosthetic arm.

Lower-limb prostheses are used in children with acquired amputations as a result of trauma or cancer and also in congenital transverse amputations or for those who have undergone surgical correction, as often occurs with longitudinal fibular deficiency or proximal femoral focal deficiency.

There are multiple components to lower-limb prostheses, which include the socket and foot, but may also include a hip and knee joint, depending on the level of amputation. A prosthetist works with the child and family to fabricate the prosthesis. A physician or licensed independent practitioner with experience in prostheses provides the prescription for this device.

The type of prosthesis depends on the age of the child, the level of the amputation, and the status of the residual limb. In very young children, use of a lower-extremity prosthesis follows developmental milestones, with the first prosthesis prescribed at the time the child should be pulling to stand. Addition of joints to the prosthesis also occurs when developmentally appropriate, such as use of a knee joint around the age of 3 years when the child is learning to use stairs.

Advances in technology are helping children who use prostheses achieve a fluid gait pattern that makes their prosthetic use virtually undetectable to the untrained eye. New components and designs allow amputees to lead active lifestyles that may include running, swimming, biking, and mountain climbing.

ASSISTIVE MOBILITY DEVICES

The function of assistive mobility devices is to provide a wider base of support to improve stability during ambulation, reduce the possibility

Table 755.1 Orthotic Options

ORTHOSIS	FUNCTION	COMMENTS
Neoprene thumb abductor	Places thumb in abduction to promote functional use of hand	Will not overcome severe cortical thumb position
Thumb spica	Immobilizes and protects the thumb and provides a stable post against which the index finger can pinch	Need to allow for full metacarpophalangeal (MCP) flexion of the fingers
Resting hand	Preserves balance between extrinsic and intrinsic musculature and provides joint stability; prevents contracture	Pressure at the MCP joint or proximal phalanx should be avoided because it can injure the MCP joint. This splint is to be used for positioning, not function
Wrist cock-up	Supports, immobilizes, or stabilizes wrist in extension, which allows for mechanical advantage in grasp	Must maintain full MCP flexion and thumb motion
Elbow extension	Increases extensor end range of motion (ROM)	Not for severe flexor tone with contracture or fluctuating tone; in that case, use a drop out cast or splint
Gunslinger	Supports shoulder girdle and prevents subluxation	Make sure the edges of splint are not cutting into hip area; check in standing and supine
Myomo	Sensor-activated, power-driven upper limb orthosis can train the arm and hand while providing assistance with bimanual activities	Heavy Minimal growth with a child
Foot orthosis (FO)	Provides support of foot only to keep ankle in subtalar neutral	Not typically customized but can be with a UCBL*
Supramalleolar orthosis (SMO)	Provides medial-lateral support of foot to prevent excessive pronation, supination, or instability	Appropriate for children with low tone such as in Down syndrome. Also useful for young children with equinovarus posture or mediolateral instability
Ankle-foot orthosis (AFO)	Provides support at the ankle and reduces foot drop or plantarflexion tone by keeping the ankle in a neutral position	Commonly used for ambulatory and nonambulatory children Assists with dorsiflexion and inhibits plantarflexion. Requires rocker bottom shoe for rollover in gait
FES activated AFO	Uses functional electrical stimulation to assist dorsiflexion at the appropriate time in the gait cycle	Cannot inhibit plantarflexion Less restrictive than a solid or hinged AFO Can be used with an SMO to provide mediolateral stability at the ankle
Ground reaction ankle-foot orthosis (GRAFO)	Provides knee extension moment to reduce crouching or collapsing into dorsiflexion during standing or walking	Appropriate for children with spina bifida or who have weakness in the plantar flexors who crouch when walking
Knee-ankle-foot orthosis (KAFO)	Provides support at the knee when there is quadriceps weakness to promote an upright posture with standing or walking	Less commonly used because of large size of brace but may be appropriate for child with spina bifida or spinal cord injury
Walking assistance exoskeleton	Bionic robot for use in paraplegic patients	Heavy. Very expensive. Does not grow with a patient. Cannot be used in patients with spared sensation in the legs

*UCBL – University of California Berkley Laboratories, where this maximum control foot orthosis was developed.

of falls, and improve efficiency of gait. The least supportive device is a traditional single-point cane commonly used after an orthopedic injury. For most children with gait abnormalities secondary to neurologic disorders, this is not a functional option because a cane does not provide enough stability. More supportive gait aids, such as forearm (Lofstrand) crutches, are appropriate in children with neurologic disorders; however, use of these devices requires good coordination and strength. Children with cerebral palsy and spina bifida may benefit from these devices.

Walkers provide more support than crutches and canes; they do not require as much strength and coordination to operate. Children with cerebral palsy, for example, may use a reverse walker, which they pull behind them. This reverse configuration provides a wide base of support and stability, helps maintain an erect posture, and allows the child to engage with the environment without the barrier of the walker in front of them. Having the walker behind them also reduces the risk for more serious injury from a forward fall.

For children who require a significant amount of support because of poor head and trunk control, **gait trainers** are often used. These devices allow the child to work on leg movements while the trunk and pelvis are stabilized (Fig. 755.2). Although gait trainers provide a child with moderate to severe motor impairments upright supportive mobility, "gait trainer" is a misnomer in that it is not intended to train a child to walk independently.

WHEELCHAIR

Wheelchairs should be considered as a means of mobility when ambulation is not possible or is difficult outside of the home setting. Children with spinal cord injuries, spina bifida, neuromuscular diseases, or cerebral palsy may benefit from the use of a wheelchair. The goal is to provide a wheelchair that will allow the child to move independently about the environment, including home, school, and the community. Children as young as age 2 years can self-propel a manual wheelchair and operate a power wheelchair. The type of wheelchair prescribed will depend on the child's underlying diagnosis, cognition, vision, motor skills (such as head and trunk control), strength and endurance of upper limbs, musculoskeletal deformities, if present, and medical comorbidities. One must also consider future growth or

Fig. 755.2 Gait trainer. *(Photo copyright 2013 by Rifton Equipment, http://www.rifton.com.)*

anticipated changes in function over time, as well as the family's ability to transport the chair. An important consideration when ordering a pediatric wheelchair is the adjustability to accommodate growth. A typical wheelchair may last 3-5 years with periodic adjustments to growth by a seating specialist. There are many components that can be added to provide more support in the wheelchair, including head rests, lateral trunk support, hip guides, antitippers that prevent the wheelchair from tipping backward, and specialized tires. The seating system is considered a separate item from the wheelchair itself and is, in fact, a seating orthosis. It should be properly fit for the child's current size and seating needs. The function of a seating system is to promote the upright positioning of the head and trunk as well as control of the position of the legs, especially the hips, in sitting. Children with good trunk control will require a simple seat back, while a child with poor trunk control, such as someone with a high cervical spinal cord injury, will require a system that includes a head rest and lateral thoracic supports. The seat itself must be customized to provide a stable base on which the trunk can align. Restraint at the pelvis, such as a seatbelt or bar, helps maintain proper positioning in the chair. Specialized cushions are needed for those with decreased sensation to prevent pressure-related skin sores.

ROBOTIC DEVICES

Rehabilitation robotics is a subspecialty field that is helping to increase independence for individuals with disabilities. Robots are currently defined as machines programmable by a computer and capable of carrying out a complex series of activities automatically. Although there is a wide range of the types of robots used in rehabilitation, a subset of robots provide assistance in the form of adaptive equipment. Most of these robots are wearable; notable exceptions are fully automated voice-controlled feeding systems and speech generating devices. Lower limb devices are designed to help a child progress toward a typical gait pattern and range in complexity from exoskeletons to programable AFOs that provide electrical stimulation to muscles that control foot position and strength across the ankle joint. Upper limb devices are designed to increase the use of a minimally functional arm and hand. Programmable prostheses, such as myoelectric arms and hands, respond to input from the user's neuromuscular system while bionic limbs respond to sensors implanted in the brain. The use of robotic assistive devices is less common than mechanical devices, in part because of availability and in part because of higher cost. The advantage of most robotic assistive devices compared with their mechanical counterparts is the ability of the device to train the user to need it less while providing the assistance required in the moment.

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Chapter 756

Health and Wellness for Children with Disabilities

Meghan A. Klawonn, David M. Kanter, and Margaret A. Turk

DISABILITY

Children with Special Healthcare Needs

The expansion of the *disability* definition to include children with special healthcare needs (CSHCN), chronic conditions, and activity limitations from any cause (e.g., limitations in usual daily activities such as age-appropriate self-care, mobility, communication, and cognition) has made the health issues of the more *traditional* childhood disability types (e.g., cerebral palsy, intellectual disability, spina bifida, congenital musculoskeletal disorders) more difficult to identify. U.S. data note continued increasing prevalence of developmental disabilities and identify developmental, emotional, and behavioral conditions as the leading conditions. Physical health conditions comprise a smaller proportion of disabilities, although mobility and motor control issues may be noted among the aforementioned developmental, behavioral, and emotional conditions. These disabilities contribute to continued economic and health problems into adulthood. Childhood and adolescent health promotion interventions can decrease functional impairment across the life span. Monitoring children with disabilities throughout their development is essential for identifying times when support to children, adolescents, and/or their families is needed to promote positive health outcomes.

Health Promotion Definitions and Background for Disability

The World Health Organization (WHO) defines *health promotion* as "the process of enabling people to increase control over, and to improve, their health." For people with disabilities, this concept is important because they are both underserved and have comparatively large health disparities. The WHO further defines health promotion approaches as including more than health education and consisting of community action, supportive and accessible environments, policy changes, health service modifications, and development of personal skills. Health and wellness programs also include traditional preventive management strategies, such as anticipatory guidance. There is ample evidence that engaging in specific areas of health promotion results in improvement, although the evidence for its influence on adult health is less robust.

Children with disabilities encounter many barriers to healthy behaviors (Table 756.1). Both broad and focused health promotion programs consider severity of condition, barriers and resources, and self-efficacy to achieve health-promoting behaviors. Children with disabilities may also require modeling or assistance to apply healthy behaviors to their particular disability or economic, social, and environmental circumstances.

Individuals with disabilities and their families often view health differently than those without disabilities. Disability may influence health and

Table 756.1 Barriers and Facilitators for Children to Engage in Healthy Behaviors

SELF	FAMILY	INSTITUTION
BARRIERS	BARRIERS	BARRIERS
1. Lack of knowledge and skills 2. Fear of injury or failure 3. Personal choices 4. Fatigue 5. Lack of initiative 6. Limited functional capability	1. Negative attitudes by parents, peers, healthcare providers 2. Limited parental healthy behaviors 3. Stress in the close family network 4. Economic restrictions	1. Inaccessible facilities or resources 2. Needing adult or aide assistance 3. Policies and procedures of facilities or programs 4. Noninclusive providers 5. Transport challenges
FACILITATORS	FACILITATORS	FACILITATORS
1. Education or knowledge about heathy behaviors 2. Engaging child in discussions and decisions 3. Desire to be active 4. Making activities a part of the routine—repetition and consistency promote ongoing activities	1. Promotion of activities by rehabilitation and other healthcare professionals 2. Family support and participation 3. Involvement of friends and peers in activities 4. Models or directions for participation with adaptions 5. Creative and knowledgeable professionals	1. Accessible facilities and opportunities with knowledgeable staff 2. Policies and resources promoting participation 3. Welcoming and inclusive providers: Adaptable approaches

vice versa, but their perception of their own health and wellness does not equate with their level of disability. Experiences as a child with a disability often foreshadow adult behaviors, especially negative attitudes toward therapy, exercise, and activity. Beliefs of parents, families, and healthcare providers also influence the views of health by children with disabilities. Health promotion programs for these children must (1) understand and support the role and well-being of parents, (2) recognize that parents of children with more functional limitations may require more resources and support, (3) involve children with disabilities in the design of programs and decisions about participation, and (4) address barriers to participation, perceived and real (see Table 756.1).

An effective health and wellness program should involve multiple approaches and opportunities for success by considering novel and inclusive approaches, including partnerships with families, school staff, and rehabilitation providers. Effectiveness requires addressing any mismatch between the child's positive sense of health and well-being and that expected by the healthcare providers; recognizing limitations of an education-only model; engaging the child in discussions about the importance of healthy behaviors, ways to engage in healthy behaviors related to the child's disability and circumstances, and decisions about participation; promoting self-efficacy and self-management of health and wellness in preparation for adult healthcare when possible; and parent and family involvement coupled with sensitivity for the high level of support a family may already be providing for a child with a disability.

Anticipatory Guidance, Counseling, and Preventive Care

Preventive healthcare through health education, anticipatory guidance, and participation in screening and immunization schedules is the mainstay of pediatric public health programs (see Chapter 12). *Bright Futures,* developed by the American Academy of Pediatrics and their collaborators and supported by the Maternal and Child Health Bureau, Health Resources, and Services Administration, provides a knowledge base for pediatric healthcare providers and the public about anticipatory guidance, health promotion, and prevention for children and adolescents with a section in the 4th edition titled "Promoting Health for Children and Youth with Special Health Care Needs." For the general population, 25% of parents receive no information, and <50% receive all recommended guidance. Although parents of CSHCNs report similar or better receipt of general preventive information, it is not clear whether those with higher severity of functional limitations receive this guidance or counseling, and whether it is provided in the context of disability and other circumstances.

CSHCNs require typical prevention, as well as more specific counseling or screening related to their disability. Some of this more specific counseling can be managed by specialty care providers, although CSHCNs often have difficulty obtaining appropriate specialty outpatient services. Additional barriers to care, especially with increasing age of the child, are the lack of accessible medical equipment and facilities. Planning for transitions to adult care should begin early, with consideration of environmental access, preparedness for self-management when possible, and knowledge and skills of local healthcare providers. Although discussions of health risks with adolescents about smoking, drinking, and protected sexual activity should be undertaken, the discussions may require a different focus for adolescents with disabilities. Higher violence and abuse rates toward children with disabilities are reported, for which providers must be vigilant. Internet and social media use increases the risk of bullying and other negative experiences. It appears adolescent females with disabilities are more vulnerable than males to this victimization.

The recommendation is to recognize the need for modifications to typical guidance and to be alert for any signs of emotional disturbances. CSHCNs experience family issues with separation/divorce, mental health and substance abuse problems, incarceration, domestic or neighborhood violence, discrimination, parental death, and maltreatment more than those without special needs. Counseling should be broadened to include questions and discussions about conditions associated with the specific disabilities (e.g., epilepsy or cognitive impairments often seen with cerebral palsy, or neurogenic bladder and bowel in spinal cord dysfunction) or secondary conditions, such as pain, osteoporosis/fractures, or the fatigue seen in many CSHCNs. Early recognition of emotional and psychiatric disorders, at early ages and especially during times of transition, can help to address nationally acknowledged unmet mental healthcare needs. There are also signs of comorbidities commonly seen in adulthood, such as cardiovascular and renal conditions, in children with disability.

Physical Activity and Exercise

National health guidelines recommend at least 60 minutes of physical activity daily for children, but any activity increase from sedentary levels to even moderate activity (30-40 minutes of moderate intensity or 20 minutes of more strenuous activity) provides some health benefit. Health professionals should give specific advice about how children with disabilities can increase their level of activity. Exercise and activity increase aerobic capacity, functional ability, and quality of life for children with many kinds of disabilities and chronic diseases. National 24-hour movement guidelines have been established in Canada and Australia, with age-specific recommendations regarding lengths of time to sleep, perform physical activity, and sedentary time. It has been shown that individuals with disabilities meet the 24-hour movement guidelines at lower rates compared to the general population, which in turn may affect mental health. And yet, many healthcare providers and families accept sedentary lifestyles for children and adolescents with disabilities, whatever their functional abilities. Video gaming systems that involve movement can help to overcome this lack of activity because they can provide another way to increase movement. For children with disabilities, school physical education and recess programs can support activities at or greater than the recommendation, and school requirements can reinforce activity expectations; however, there should be monitoring for possible negative affect, poor sense of belonging, and presence of victimization during open recess opportunities. School-based interventions for adolescents with intellectual and developmental disabilities have been shown to increase healthy behaviors, such as engagement in physical activity and increased consumption of fruit and vegetables. Healthy behaviors are in turn associated with improvement in mental health. The need for exercise beyond physical therapy should be clarified to help children understand the benefits and purpose of both. The activities in which youth with disabilities wish to participate can be supported, and shared decision-making should be invoked. Children with disabilities who participate in physical activities report social benefits, such as developing friendships, building a support system, gaining knowledge of self, and acquiring a sense of accomplishment. These factors also contribute to higher adherence to activities. Children with disabilities may also be more likely to participate in physical activities when those activities are supervised and organized, as opposed to free play in an open room. For children with disabilities to engage in physical activity in supported environments, school and public playgrounds must be made sufficiently accessible to support community physical activity. A number of agencies have endorsed the Commit to Inclusion campaign to promote building healthy, inclusive communities for people of all ages with disability (e.g., the President's Council on Fitness, Sports, and Nutrition, along with the National Center on Health, Physical Activity, and Disability; the American Association on Health and Disability; and the Center on Disability at the Public Health Institute).

Physical activity for children and adolescents improves fitness and quality of life for youth with developmental disabilities (Table 756.2). These exercise and fitness programs require 2-3 months of participation, at least twice a week, to achieve any changes, and many of the changes achieved are longer lasting than expected. These programs are not traditional therapy, and participation in therapy is not a substitute. These focused fitness and

Table 756.2 Examples of Effective Exercise Programs for Children with Disabilities

CENTER-BASED FITNESS PROGRAM AND HOME PROGRAM	GROUP AQUATIC AEROBICS	GROUP TRAINING CLASS	ONLINE EXERCISE PRESCRIPTION TOOL
• Children with a variety of disabilities • Group exercise: 2×/wk for 14 wk, warm-up, aerobics, strengthening, cool-down • Home program: 2×/wk for 12 wk using video exercises • *Outcomes:* improved walking efficiency, strength, general function[a]	• Children with a variety of disabilities, 50% able to walk 2×/wk • Recreation to achieve target heart rate; aquatic strengthening program • *Outcomes:* improved walk/run[b]	• Children with cerebral palsy able to walk 2×/wk for 14 wk • Warm-up, circuit training stations (treadmill, balance stairs, closed-chain exercises) • *Outcomes:* improved muscle strength, mobility, function[c]	• Children with a variety of disabilities • 8 wk home exercise program delivered using Physitrack, an online exercise prescription tool • *Outcomes:* equivalent adherence to traditional paper-based method, more easily accessible[d,e]
• Strength • Training	• Walking-jogging program	• Treadmill training program	• Skill-related fitness (SRF)
• Children with cerebral palsy including a majority able to walk with assistive devices 3×/wk for 6 wk • Progressive training program, conducted in the home • *Outcomes:* improved perceptions of strength, walking, stair management, improved psychologic benefits[f]	• Children with down syndrome • 3×/wk for 10 wk, 30 min sessions, achieving 65–70% peak heart rate • *Outcomes:* improved peak exercise time and grade, improved walking capacity[g]	• Children with intellectual disabilities daily for 2 months • Progressive treadmill use with goal of 20-30 min • *Outcomes:* improved heart rate with and without activities[h]	• Adolescents with intellectual disabilities • SRF is a physical fitness component related to sports performance, used to enhance participation with peers in leisure activities • *Outcomes:* positive exercise training effects on agility, power RT, and speed[i]

[a]From Fragala-Pinkham MA, Haley SM, Rabin J, Kharasch VS. A fitness program for children with disabilities. *Phys Ther.* 2005;85(11):1182–1200.
[b]From Fragala-Pinkham M, Haley SM, O'Neil ME. Group aquatic aerobic exercise for children with disabilities. *Dev Med Child Neurol* 2008;50(11):822–827.
[c]From Blundell SW, Shepherd RB, Dean CM, Adams RD, Cahill BM. Functional strength training in cerebral palsy: A pilot study of a group circuit training class for children age 4-8 years. *Clin Rehabil* 2003;17(1):48–57.
[d]From Johnson RW, Williams SA, Gucciardi DF, Bear N, Gibson N. Can an online exercise prescription tool improve adherence to home exercise programmes in children with cerebral palsy and other neurodevelopmental disabilities? A randomised controlled trial. *BMJ Open.* 2020;10(12):e040108.
[e]From Johnson RW, Williams SA, Gucciardi DF, Bear N, Gibson N. Evaluating the effectiveness of home exercise programmes using an online exercise prescription tool in children with cerebral palsy: protocol for a randomised controlled trial. *BMJ Open.* 2018;8(1):e018316.
[f]From McBurney H, Taylor NF, Dodd KJ, Graham HK. A qualitative analysis of the benefits of strength training for young people with cerebral palsy. *Dev Med Child Neurol.* 2003;45(10):658–663.
[g]From Millar AL, Fernhall B, Burkett LN. Effects of aerobic training in adolescents with Down syndrome. *Med Sci Sports Exerc.* 1993;25(2):270–274.
[h]From Lotan M, Isakov E, Kessel S, Merrick J. Physical fitness and functional ability of children with intellectual disability: effects of a short-term daily treadmill intervention. *Sci World J* 2004;4:449–457.
[i]From Jeng SC, Chang C-W, Liu W-Y, Hou Y-J, Lin Y-H. Exercise training on skill-related physical fitness in adolescents with intellectual disability: A systematic review and meta-analysis. *Disabil Health J.* 2017;10(2):198–206.

exercise programs generally require the support and direction of rehabilitation professionals, although programs can be community based in nonmedical surroundings.

Recreation and organized sports are other areas where children and adolescents with disabilities can engage successfully, at times with modifications. Participation improves cardiopulmonary parameters, motor function, social competence, and general sense of well-being. Many children with disabilities require 1-on-1 instruction for development of skills, with a goal of participation in activities with their peers. Perceived barriers to participation in sports differ based on the source: children were concerned about dependency; parents required more information about possible sport participation. Programs through Special Olympics International are an opportunity for children and adolescents to engage in supportive and monitored environments for sport and recreation.

Rehabilitation professionals can assist with problem-solving activity participation, such as by using computerized technologies for "exergaming" (e.g., Wii, Xbox, PlayStation), developing individual or group challenges with mobile devices (e.g., activity trackers), adapting equipment (e.g., modified upper-limb prosthesis to allow baseball glove use or modified bicycle equipment), and knowing of adapted recreation programs in the area (e.g., horseback riding, winter/water sports). Technologies that allow for exercise as part of gaming provide new opportunities for moderate to vigorous exercise in people with disabilities, especially in those with limited use of the lower limbs. Youth with greater functional limitations may not be able to achieve moderate to vigorous exercise, but even light intensity exercise may be enough to give them some health benefits. "Exergaming" programs are viewed as more fun than traditional exercises, which may increase likelihood of participation.

Sleep and Pain

Poor sleep quality or the presence of pain will have an impact on physical activity and general performance in children and youth with disabilities. Regular inquiry about sleep and pain is important because of the higher prevalence of problems in these areas in children with disabilities. Common sleep disturbances include difficulty initiating sleep, frequent sleep disruptions, and reduced sleep duration. Causes are often complex and multifactorial, with some associations with disability type (e.g., obstructive sleep apnea with Down or Prader-Willi syndromes, disrupted sleep patterns with autism, negative bedtime behaviors with attention-deficit/hyperactivity disorder, pain as trigger with cerebral palsy) and comorbidities (e.g., epilepsy, gastroesophageal reflux). Frontline approaches are sleep hygiene and behavioral interventions, and further evaluation may be warranted for targeted interventions (see Chapter 31).

Pain has been described as a cause for behavioral changes, poor sleep, activity interference, and change in school performance in children with a variety of disabilities. Children with cerebral palsy have been most closely studied, with high prevalence of both acute and chronic pain. Routine screening is important for early identification and evaluation for cause, and interventions should be tailored to address the biopsychosocial model of pain management.

Nutrition and Obesity

See also Chapter 65.

Managing the combination of nutrition and physical activity is the key ingredient of weight control. Estimates suggest that children with physical activity limitations were twice as likely as the general population to be overweight, and youth with cognitive impairments are at increased risk. It is unclear if obesity is a cause for the activity limitations or is a result of the limited activity, which may be an important distinction in developing interventions. The concern with obesity contrasts with early life weight gain needs of many children with disabilities, and it may be confusing for parents and families when the focus changes to weight decrease. Confounding factors related to monitoring percent body fat in children with disability include (1) the propensity for some disabilities, often those that are genetically mediated, to be associated with obesity; (2) standards of measurement may not be appropriate for certain diagnoses or disability types (e.g., inaccurate weight [limb deficiencies/amputation, scale inaccessibility], inaccurate height [unable to stand, contractures], no standards related to short stature or muscle wasting); (3) obesity may be a side effect of medication, and this effect must be balanced against the drug benefits (e.g., antipsychotics, steroids); and (4) the social network of family, friends, schools, and healthcare providers may unwittingly negatively influence health habits, including use of food as reward for behavior management. Both children and their parents should be a part of the conversations related to obesity or any weight-related topic. Information must be presented in a direct and understandable way and modified for the child's and parents' needs. Discussion of promoting health through nutrition and physical activity, while problem solving challenges to participation, may be a better approach than explaining body composition and metabolic pathways.

Emotional Health and Leisure Activities

Emotional health is often overlooked in children with disabilities. Youth and adolescents with disabilities appear to be at higher risk for feeling low, stressed, or anxious (especially those with higher levels of limitations), and those with mental health needs may have lower adaptive functioning or a family history of mental illness. While children and young adults diagnosed with autism have received much attention related to emotional support needs, there are increasing reports of this need with most childhood-onset disability conditions, including at ages before teenage years. Sexuality, gender identity, and other sex-related issues can also be reasons for emotional turmoil. Adolescents with physical disabilities participate in fewer social activities, have fewer close or intimate friends, and have fewer plans for ongoing education. There is a risk for continued isolation into adulthood. Passive social media use may exacerbate this problem. Novel programs to improve self-concept and build resilience based on psychoeducational therapy principles, typically developed through interdisciplinary teams, and involving peer groups, parents, and family members, have been shown to successfully promote positive outcomes. Medications may be considered, but effectiveness is not guaranteed, and unwanted side effects may produce more health challenges. Counseling requires insurance support or discretionary funding. There is some early work on using apps to try and help track mental health issues.

Leisure and recreational activities provide social supports, additional stress-coping mechanisms, and ability to develop social skills and a stronger personal identity. Although the negative aspects of social media are often discussed, there are also positive aspects. Adolescents with disabilities may more easily communicate and socialize with peers online, improving their mental well-being. Females with disabilities tend to engage in social or skill-based activities, and males in physical activities, with decreasing participation with increasing age. In general, encouraging socialization through leisure activities, recreation, or sports and physical activity can be a part of counseling in a routine health visit.

Dental Care

Dental care is a frequently unmet healthcare need for children with disabilities, especially for those in low-income families or with more severe impairments. The principal deficits are in receipt of specific dental care (not preventive services). Condition severity may also predict the degree to which parents are interested in oral health–related education and actually engage in oral health efforts. Parents and caregivers play a critical role in oral health support. Challenging behaviors often limit dental care, and the use of behavior management techniques and education programs have been effective in allowing dental care. Dental treatment under anesthesia may be necessary to provide effective oral healthcare.

Role of Healthcare Providers

Primary care and other healthcare providers should be mindful of discussing and promoting health and healthy behaviors with children and adolescents with disabilities and their families (Table 756.3). Initial discussions and preventive screening, including exploration for early signs of cardiovascular or renal diseases and assessing the need for emotional support, are a responsibility of primary care providers individually or in conjunction with specialty care providers. Children with a wide range of impairments should be included in multi-method inclusive research. Innovative strategies for engaging

Table 756.3 Targeting Healthy Behaviors for Children with Disabilities

GENERAL PREVENTION	PHYSICAL ACTIVITY	NUTRITION AND OBESITY
• Recognize risks for less healthy behaviors and facilitators of behavior changes and participation. • Cover typical topics for all children counsel regarding disability or situation context. • Specifically monitor for abuse and violence. • Provide typical age-appropriate adolescent information about smoking, drinking, substance abuse, sexual contacts; refer if unable to provide. • Monitor for disability-specific health conditions; many require referral.	• Promote exercise and activity with an expectation for activity. • Ensure that family and child/adolescent are knowledgeable about benefits and possible adaption. • Review need for possible dietary changes. • Consider referral to community programs and/or rehabilitation professionals	• Recognize obesity can cause limitations and can be the result of poor dietary habits and limited activity. • Follow percent body fat in a consistent way, recognizing the need for accurate measures or limitations of measures (e.g., weight, body mass index [BMI], skinfold thickness, other traditional measures) in many disability conditions. • Ensure that family and child/adolescent are knowledgeable about healthy nutrition. • Consider referral to nutritionist or other professional to engage patient and family in education and behavior change counseling • Review need for increased activity level with dietary intervention.
EMOTIONAL	**HEALTH, RECREATION, AND LEISURE**	**DENTAL**
• Question for sense of anxiety/feeling low, stress management and ability to adapt, and social supports. • Consider medications and counseling based on expected effect, monitor effects/side effects; consider referral, making sure that insurance/payment coverage is available. • Consider recreation and leisure activities to promote social support and ability to develop social skills. • Recommend use of social media in positive ways to enhance connections.	• Question about social activities outside the home: highlight the importance of developing social skills, sense of self, and support networks • Consider referral to community programs or rehabilitation professionals. • Consider recommending online support groups, social groups.	• Discuss more than preventive dental care. • Suggest behavior strategies if there are problems engaging in dental appointments and refer for this service as needed.

children with disabilities have been identified and offer much hope for the future. Parents are more likely to positively engage with a referral to healthcare professionals with expertise in providing a more tailored approach to health promotion after initial advice and support. Strategizing with parents about accessible environments or opportunities can promote inclusive community opportunities for participation. Providers should be willing to discuss intimate relationships and sex-related issues at appropriate times as they do with youth without disabilities—and refer when unable to meet those needs. Family-centered and coordinated care, commonly found in medical homes, can support healthy behaviors and emergency planning for unforeseen events.

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Environmental Health

PART XXXII

Chapter 757

Overview of Environmental Health and Children

Ruth A. Etzel

GLOBAL CLIMATE CHANGE

Pediatricians' primary goal is prevention. One dominant prevention challenge of the 21st century is the climate crisis. The Intergovernmental Panel on Climate Change concluded that the Earth is undergoing adverse global climate change and that anthropogenic (human-made) contributions are significant. These climate changes are creating conditions that have already affected public health, with disproportionate impacts on certain life stages, including children. Children are especially vulnerable to the impacts of climate change because their bodies are growing and developing, they have unique behaviors and interactions with their environment, and they must rely on parents or caregivers to provide for their basic needs. Climate change affects children's health as a result of their exposure to elevated temperatures; more frequent, severe, or longer-lasting extreme weather events; transmission rates of food-borne, waterborne, and vector-borne diseases; increases in air pollution from molds, pollens, and the burning of fossil fuels; and mental health stressors (Fig. 757.1). Natural disasters such as floods and hurricanes, damp housing, and mycotoxin-related illnesses are worsening as temperatures and sea levels rise. The impacts are being felt most among young children and those who are living in poverty. The need to reduce carbon dioxide in the environment has compelled many countries to sign the Paris Agreement. This agreement promises to keep the global temperature rise well below 2°C above preindustrial levels, and to try to limit the temperature increase to 1.5°C. Even though the Paris Agreement began in 2016, its promises have not been kept and the temperature is already 1.2°C higher than in the preindustrial era. Individual actions are another necessary step in carbon dioxide reduction. Parents and caregivers can work to reduce their family's burning of fossil fuels. They also can protect children's health by checking the air quality index and pollen counts and considering a limit to children's outdoor play time if levels are high. Parents can watch for signs of dehydration or overheating in their children and can prevent tick and mosquito bites by using insect repellent and protective clothing. Pediatricians and those who care for children can be highly effective advocates for an urgent governmental response to the climate crisis by speaking out at the community, national, and international level.

LOCALIZED ENVIRONMENTAL HAZARDS

Localized exposures to a wide variety of chemical, biologic, and physical agents can also harm children. Numerous epidemics of disease from chemical, biologic, and physical agents (both natural and human-made) over the past 80 years have documented a variety of adverse outcomes among children (Table 757.1). Some epidemics, such as those caused by the nighttime release of methyl isocyanate from a factory in Bhopal, India, the nuclear meltdown in Chernobyl, and the melamine contamination of infant formula in China, received widespread attention and heightened the awareness of parents and pediatricians about hazards in the environment. For many people, the word *epidemic* conjures up images of hospital isolation wards, poor sanitation, and rapidly spreading infectious diseases. Epidemics of environmental origin often have served to elucidate new hazards for children. Many of the routinely used chemicals understood to be toxic to children were initially identified when a cluster of children was exposed and developed symptoms during a relatively short period of time. Unfortunately, the children served as the "canaries in the coal mine" to indicate that specific chemicals (including thallium, mercury, arsenic, and lead) contained in products for children such as diaper rinses, teething powders, and depilatory agents, posed a threat to their health. The comparison of children to canaries is apt: following underground mine explosions, canaries were used by miners throughout recent history to help detect elevated levels of carbon monoxide gas. Canaries were useful "carbon monoxide detectors" because of their rapid breathing rate and high metabolism, making them more sensitive to the effects of gases, including carbon monoxide. Likewise, young children have a rapid breathing rate and a high metabolic rate and may be more sensitive than adults to chemicals in the environment.

Table 757.1 summarizes major incidents of environmental poisoning that affected children. The characteristics of environmental exposure and the age and developmental stage of the child affect the likelihood of developing health problems. After the release of methyl isocyanate (used in the production of some pesticides) at Bhopal in 1984, an estimated 200,000 children living near the Bhopal chemical plant were affected by the gas release (see Table 757.1). Methyl isocyanate gas is 1.4 times heavier than air; thus higher concentrations of the gas were found near the ground or floor. Because of their short stature, children's breathing zones are closer to the ground or floor than adults' breathing zones; therefore children likely inhaled higher concentrations of the toxic gas. Children exposed to the same levels of methyl isocyanate as adults may have received larger doses because they have relatively greater lung surface area to body weight ratios and higher minute volume to weight ratios. Based on each of the poisoning events listed in Table 757.1, additional precautions were taken to avoid children's unnecessary exposure to the specific product or chemical implicated.

Although major poisonings such as those listed in Table 757.1 have caused substantial morbidity and mortality among children, environmental health hazards may also result in more subtle effects that may not manifest until later in life. In addition to the exposures received during large outbreaks, children receive smaller doses of chemicals on an almost daily basis through the water they drink, the food they eat, and the air they breathe. Because of their unique vulnerability, they may exhibit symptoms from these exposures earlier than do adults.

TOXINS VERSUS TOXICANTS

A toxin is a poisonous substance produced naturally by a living organism (e.g., aflatoxin). A toxicant is a poisonous substance made by humans or introduced into the environment by human activity (e.g., dioxins). Synthetic chemicals are referred to as toxicants.

MYCOTOXINS

Children's exposures to mycotoxins, the toxins produced by certain fungi on grains, nuts, and other crops, will likely increase as the

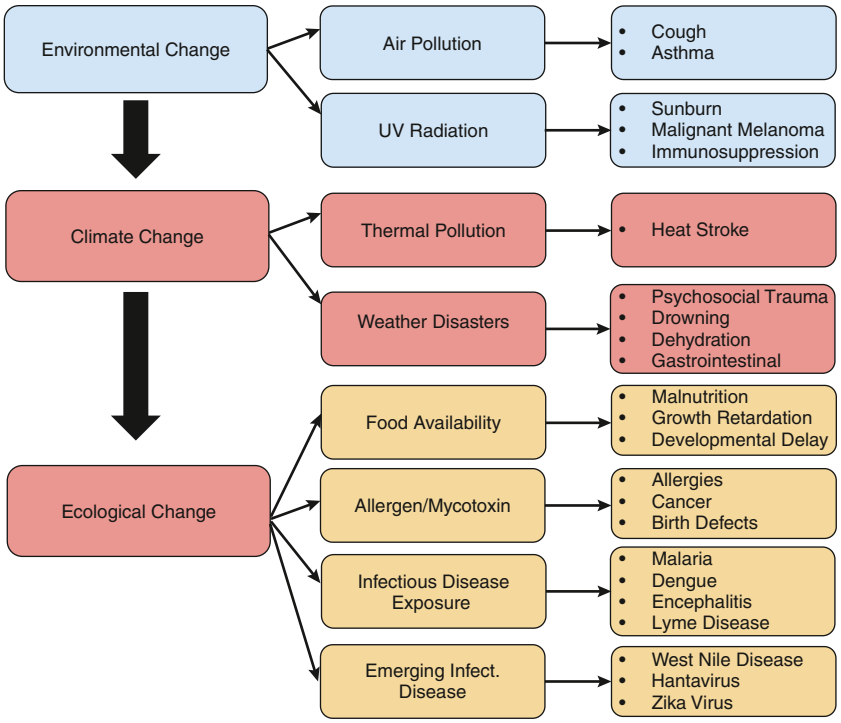

Fig. 757.1 The relationship between environmental change, climate change, ecologic change, and child health. *(Adapted from Bunyavanich S, Landrigan CP, McMichael AJ, et al. The impact of climate change on child health. Ambul Pediatr. 2003;3:44–52. Fig. 2.)*

Table 757.1 Epidemics of Environmental Disease Affecting Children

CONTAMINANT	VEHICLE	DATE	COUNTRY	APPROX. # SICKENED	ILLNESS	APPROX. # WHO DIED
Thallium	Depilatory agents	1930	Grenada	16	Thallotoxicosis	13
Methylmercury	Fish and shellfish	1956	Japan	2,265	Cerebral palsy	1,784
Arsenic	Contaminated milk powder	1955	Japan	11,778	Fever, diarrhea darkened skin, swollen abdomen	113
Hexachlorobenzene	In human milk after pregnant women ate HCB-treated seed grain	1957	Turkey	~200	Pembe yara (pink sore) rash, weakness convulsions	<2 yr ~200
Methyl isocyanate	Leak from chemical plant	1984	India	<15 yr: 200,000	Coughing, eye irritation choking death	All ages 2,500-5,000
Dioxin	Chemical plant explosion	1976	Italy	193 (88%)	Chloracne	0
Radiation	Chernobyl	1986	Ukraine	<18 yr: 4,000	Thyroid cancer	~8
Radiation	Scrapped medical machine stolen from hospital	1987	Goiânia, Brazil	249	Acute radiation syndrome	4 (1 child)
Fungi	Water-damaged homes	1990s	Ohio, US	30	Pulmonary hemorrhage	5
Aflatoxin	Grain	2004	Kenya	317	Aflatoxicosis	125
Melamine	Infant formula	2008	China	290,000	Kidney stones	6
Lead	Small-scale gold mining	2010	Nigeria	>2,000	Seizures, death	200

climate changes because their production is influenced by temperature, humidity, and rainfall. Exposure to mycotoxins results in different health outcomes dependent on the route of exposure. Exposure from eating or drinking may lead to gastrointestinal illness, tremors, and cancer in adulthood; exposure via breathing may result in acute respiratory illness during infancy. There also is emerging evidence linking mycotoxin exposures among children, especially those in developing countries, to stunted growth.

Pediatric Conditions Linked to Mycotoxin Exposures

Exposures to mycotoxins have been linked to at least two conditions that affect children: neural tube defects and acute pulmonary hemorrhage.

Neural Tube Defects

Studies of an epidemic of birth defects in 1990 in south Texas suggested an association between maternal ingestion during pregnancy of high levels of fumonisin, universally present in corn and in corn-based products, and birth defects such as anencephaly and spina bifida. Fumonisins are known to interfere with cellular folate uptake.

Infant Pulmonary Hemorrhage

Several studies of a 1994 epidemic of acute pulmonary hemorrhage in Cleveland, Ohio, documented a novel association between life-threatening pulmonary hemorrhage and the presence of the toxigenic mold *Stachybotrys* in the water-damaged homes in which the infants were living. *Stachybotrys* produces mycotoxins that are lipid soluble and readily absorbed by the airways, as well as a hemolysin and several proteinases that can degrade vascular collagen. In subsequent years, *Stachybotrys* and other toxigenic fungi including *Trichoderma* have been associated with acute pulmonary hemorrhage among infants in other areas of the United States, Canada, and New Zealand. The rapidly growing lungs of infants are especially vulnerable to the effects of the trichothecene mycotoxins produced by *Stachybotrys* and *Trichoderma*.

FOOD-BORNE DISEASES CAUSED BY ENVIRONMENTAL EXPOSURES

Contamination of food with viruses and bacteria is a major cause of childhood food-borne diseases (see Chapter 387), and children are also at risk from a variety of noninfectious food-borne hazards in the environment, which include natural hazards such as mycotoxins and synthetic persistent organic pollutants such as dioxins (see Chapter 759; Table 757.2).

Table 757.2 Food-Borne Illnesses (Noninfectious)

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Antimony	5 min to 8 hr usually <1 hr	Vomiting, metallic taste	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Arsenic	Few hours	Vomiting, colic, diarrhea	Several days	Contaminated food	Urine; may cause eosinophilia	Gastric lavage BAL (dimercaprol)
Cadmium	5 min to 8 hr usually <1 hr	Nausea, vomiting, myalgia, increase in salivation, stomach pain	Usually self-limited	Seafood, oysters, clams, lobster, grains, peanuts	Identification of metal in food	Supportive care
Ciguatera fish poisoning (ciguatera toxin)	2-6 hr	**GI:** abdominal pain, nausea, vomiting, diarrhea	Days to weeks to months	A variety of large reef fish, grouper, red snapper, amberjack, and barracuda (most common)	Radioassay for toxin in fish or a consistent history	Supportive care, IV mannitol; children more vulnerable
	3 hr	**Neurologic:** paresthesias, reversal of hot and cold, pain, weakness				
	2-5 days	**Cardiovascular:** bradycardia, hypotension, increase in T-wave abnormalities				
Copper	5 min to 8 hr usually <1 hr	Nausea, vomiting, blue or green vomitus	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Mercury	1 wk or longer	Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma Pregnant women and developing fetuses are especially vulnerable	May be protracted	Fish exposed to organic mercury, grains treated with mercury fungicides	Analysis of blood, hair	Supportive care
Mushroom toxins, short-acting (museinol, muscarine, psilocybin, coprius artemetaris, ibotenic acid)	<2 hr	Vomiting, diarrhea, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction	Self-limited	Wild mushrooms (cooking may not destroy these toxins)	Typical syndrome and mushroom identified or demonstration of the toxin	Supportive care

Continued

Table 757.2 Food-Borne Illnesses (Noninfectious)—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Mushroom toxin, long-acting (amanitin)	4-8 hr diarrhea; 24-48 hr liver failure	Diarrhea, abdominal cramps, leading to hepatic and renal failure	Often fatal	Mushrooms	Typical syndrome and mushroom identified and/or demonstration of the toxin	Supportive care, life-threatening, may need life support
Nitrite poisoning	1-2 hr	Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate brown–colored blood	Usually self-limited	Cured meals, any contaminated foods, spinach exposed to excessive nitrification	Analysis of food, blood	Supportive care, methylene blue
Pesticides (organophosphates or carbamates)	Few minutes to few hours	Nausea, vomiting, abdominal cramps, diarrhea, headache, nervousness, blurred vision, twitching, convulsions, salivation, and meiosis	Usually self-limited	Any contaminated food	Analysis of food, blood	Atropine: 2-PAM (pralidoxime) is used when atropine is not able to control symptoms and is rarely necessary in carbamate poisoning
Puffer fish (tetrodotoxin)	<30 min	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Death usually in 4-6 hr	Puffer fish	Detection of tetrodotoxin in fish	Life-threatening, may need respiratory support
Scombroid (histamine)	1 min to 3 hr	Flushing, rash, burning sensation of skin, mouth, and throat, dizziness, urticaria, paresthesias	3-6 hr	Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, and mahi mahi	Demonstration of histamine in food or clinical diagnosis	Supportive care, antihistamines
Shellfish toxins (diarrheic, neurotoxic, amnesic)	Diarrheic shellfish poisoning (DSP)—30 min to 2 hr	Nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever	Hours to 2-3 days	A variety of shellfish, primarily mussels, oysters, scallops, and shellfish from the Florida coast and the Gulf of Mexico	Detection of the toxin in shellfish; high-pressure liquid chromatography	Supportive care, generally self-limiting
	Neurotoxic shellfish poisoning (NSP)—few minutes to hours	Tingling and numbness of lips, tongue, and throat, muscular aches, dizziness, reversal of the sensations of hot and cold, diarrhea, and vomiting				
	Amnesic shellfish poisoning (ASP)—24-48 hr	Vomiting, diarrhea, abdominal pain and neurologic problems such as confusion, memory loss, disorientation, seizure, coma				
Shellfish toxins (paralytic shellfish poisoning)	30 min to 3 hr	Diarrhea, nausea, vomiting leading to paresthesias of mouth, lips, weakness, dysphasia, dysphonia, respiratory paralysis	Days	Scallops, mussels, clams, cockles	Detection of toxin in food or water where fish are located; high-pressure liquid chromatography	Life-threatening, may need respiratory support

Table 757.2 Food-Borne Illnesses (Noninfectious)—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Sodium fluoride	Few minutes to 2 hr	Salty or soapy taste, numbness of mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock, collapse	Usually self-limited	Dry foods (e.g., dry milk, flour, baking powder, cake mixes) contaminated with sodium fluoride–containing insecticides and rodenticides	Testing of vomitus or gastric washings, analysis of food	Supportive care
Thallium	Few hours	Nausea, vomiting, diarrhea, painful paresthesias, motor polyneuropathy, hair loss	Several days	Contaminated foods	Urine, hair	Supportive care
Tin	5 min to 8 hr, usually <1 hr	Nausea, vomiting, diarrhea	Usually self-limited	Metallic container	Analysis of food	Supportive care
Vomitoxin	Few minutes to 3 hr	Nausea, headache, abdominal pain, vomiting	Usually self-limited	Grains such as wheat, corn, barley	Analysis of food	Supportive care
Zinc	Few hours	Stomach cramps, nausea, vomiting, diarrhea, myalgias	Usually self-limited	Metallic container	Analysis of food, blood, and feces, saliva, or urine	Supportive care

BAL, Bronchoalveolar lavage; GI, gastrointestinal; IV, intravenous.
Adapted from Centers for Disease Control and Prevention. Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. *MMWR.* 2004;53(No. RR-4):1–33.

Aflatoxins

Aflatoxins are poisonous substances that are formed as a result of mold growth on peanuts, corn, figs, oil-seeds, tobacco, and other products. The International Agency for Research on Cancer (IARC) has classified aflatoxin B1 as a group I carcinogen (known to be carcinogenic to humans). Ingestion of elevated levels of aflatoxin also can result in acute aflatoxicosis, characterized by vomiting, abdominal pain, hepatitis, and sometimes death.

Ochratoxin A

The mycotoxin ochratoxin A, produced by many different species of *Aspergillus* molds, is toxic to the kidneys. Ochratoxin A contaminates many foods, including barley, rye, and other cereals, cereal-derived foods, dry fruits, beans, cocoa, coffee, beer, wine, poultry, eggs, pork, and milk. Ochratoxin A is teratogenic, immunotoxic, genotoxic, and mutagenic. The IARC has indicated that ochratoxin is a possible human carcinogen (category 2B).

Fumonisins

Fumonisins are mycotoxins that may contaminate cornmeal and cereals. The fumonisins are known to interfere with sphingolipid metabolism. Consuming foods contaminated with fumonisins during pregnancy has been linked to an increased risk of having a child with a neural tube defect and an increased risk of esophageal cancer in adulthood.

Deoxynivalenol

This mycotoxin, often called *vomitoxin* because its predominant effect is vomiting, can be present in foods made from wheat and corn. Even after the grain is baked or cooked, vomitoxin retains its toxicity. Multiple epidemics of vomiting illness that occurred in China during 1961 to 1985 were associated with ingesting grain contaminated with vomitoxin. In India in 1987, almost 100 people started vomiting after they ate wheat products that contained vomitoxin and other mycotoxins. For infants, the estimated tolerable daily intake is 1.5 µg/kg body weight. A suspected epidemic of vomitoxin-related illness that affected about 1,700 school children in the United States in 1997-98 was linked to burritos that had measurable levels of vomitoxin of 0.3 parts per million (ppm; the advisory level set by the U.S. Food and Drug Administration for adults is 1 ppm).

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Chapter 758

Biologic Effects of Ionizing Radiation on Children

Samuel L. Brady and Donald P. Frush

DIAGNOSTIC IMAGING, RADIATION THERAPY

Ionizing radiation is produced when energy is absorbed within an atom such that a bound electron is liberated, and the atom becomes ionized. Exposure to ionizing radiation is characterized by three

categories: (1) **absorbed dose**, (2) **equivalent dose**, and (3) **effective dose**. In terms of radiation interaction with humans, absorbed dose is defined as the energy imparted (i.e., absorbed) within a mass of tissue from a radiation source. Absorbed dose is calculated based on the attenuation properties of the irradiated tissue (e.g., attenuation is greater in bony tissue due to its higher electron density and mass than water equivalent, soft tissue organs). The units of absorbed dose, as defined by the International Commission of Radiation Units, are the **Gray** (Gy), the preferred unit, and the older radiation absorbed dose **(rad)**. There are different types of radiation including x-ray, γ-ray, α particles (helium nucleus stripped of all electrons), β particles (unbound electrons), neutrons, and protons. Not all radiation has the same effect on biologic tissue for a given absorbed dose; for example, β particles are quite superficial, protons deposit most of their energy deeper within the body, and α particles and neutrons cause significantly more damage than x-rays or γ-rays. Diagnostic imaging uses x-rays and γ-rays. The therapeutic use of radiation for cancer treatment primarily uses x-rays, β particles, and protons depending on their application and location of disease within the body. **Equivalent dose** is a term used to define the relative effectiveness to cause biologic damage. The International Commission on Radiological Protection (ICRP) gives x-rays, γ-rays, and β particles a relative weighting of 1, protons a weighting of 2, neutrons a weighting of 2.5-20 (neutron weighting factor depends on the energy of the neutron), and α particles a weighting of 20. Thus, for the same level of radiation exposure to an organ, the equivalent dose, i.e., the relative level of biologic damage, would be higher for absorbed doses from protons compared with x-rays. **Effective dose** is a term that represents "the sum of the weighted [applying organ and tissue weighting factors] equivalent doses for the radiosensitive tissues and organs of the body" (National Council on Radiation Protection and Measurements). A list of relative organ and tissue weighting factors defined by the ICRP is provided in Table 758.1. Equivalent dose and effective dose are measured in units of **sievert** (Sv), with levels in diagnostic imaging typically in millisieverts (mSv), and the **rem** (older unit) (Table 758.2). Effective dose is not applied as a metric of dose to an individual but is a population average. Effective dose is not adjusted based on real or potential radiation susceptibilities for tissues for either gender or age.

Nuclear medicine and PET imaging examinations are described by the amount of radioactivity given, commonly injected intravenously. Administered radioactivity is referred to as the administered radiopharmaceutical dose, commonly defined in millicuries (mCi) or megabecquerels (MBq). Radiopharmaceutical dose may be converted to effective dose by applying correction factors provided in ICRP reports 53, 80, 106, and 128.

Table 758.1 Tissue Radiosensitive Weighting Factors; ICRP Report 103

TISSUE	TISSUE WEIGHTING FACTOR (W_T)	$\sum w_T$
Red bone marrow, colon, lung, stomach, breast, remainder tissues*	0.12	0.72
Gonads	0.08	0.08
Bladder, esophagus, liver, thyroid	0.04	0.16
Bone surface, brain, salivary glands, skin	0.01	0.04
Total		1.00

*Remainder tissues: Adrenal glands, extrathoracic region, gallbladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix

For the average adult, ionizing radiation exposure occurs from both natural (60%) and medical (40%) sources, and for the average pediatric-age individual, ionizing radiation exposure occurs primarily from natural sources (91%) as compared to medical sources (9%) (National Council on Radiation Protection and Measurements). Radon gas accounts for the majority of natural radiation exposure. For the adult population, the percentage contribution from medical imaging to the total ionizing radiation exposure had been increasing in the late 20th and early 21st century, but is now declining since 2006. As of 2016, for the average adult, CT imaging comprised 63% of the total of ionizing radiation procedures (Fig. 758.1A), but medical imaging accounted for only 42% of the average adult population exposure to ionizing radiation; this has decreased slightly in the past decade due to technologic advances in imaging equipment and how we use the equipment in practice. For the pediatric patient population, CT remains the primary source of medical radiation exposure, accounting for 84% of the total medical exposure (annual per capita exposure) from ionizing radiation (see Fig. 758.1B). Despite efforts to educate the medical community and the public on radiation safety and the guiding principle of keeping radiation dosing "as low as reasonably achievable (ALARA)," understanding of sources, amounts, and potential risks of ionizing radiation can still be limited. Some imaging procedures do not produce ionizing radiation (Table 758.3), and not all ionizing radiation-producing modalities expose a child to the same amount of radiation (Table 758.4). To facilitate choosing the appropriate imaging modality for a patient's clinical indications, American College of Radiology appropriateness criteria have been published (https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria) to assist referring physicians in making the most appropriate imaging or treatment decision for a specific clinical condition.

BIOLOGIC EFFECTS OF RADIATION

Biologic effects of radiation are divided into **tissue reactions** (previously known as **deterministic effects**) and **stochastic effects**. Tissue reactions do not occur below a threshold absorbed dose, and severity is directly related to the magnitude once the threshold is exceeded. No evidence of tissue reactions has been demonstrated from radiation dose levels typical of diagnostic imaging examinations (i.e., <100 mGy), but complicated interventional procedures have on rare occasions led to these effects. Typical tissue reactions can present as temporary hair loss (epilation) and skin reddening (erythema), which occur in regions of peak dose of >2 Gy (Table 758.5). Cataracts have been reported to occur with acute exposure of >0.5 Gy.

The second type of biologic effect is the **stochastic effects** that are of concern because they are assumed to potentially occur at any dose; that is, there is no threshold. Stochastic effects are most commonly discussed as cancer risk but also include heritable effects. The probability of a stochastic effect increases with rising level of absorbed dose, but not the severity. Cancer, if radiation induced, is not more severe with higher doses. It is generally accepted by the scientific and medical community that stochastic effects may be caused by any level of radiation striking vulnerable tissue (most importantly DNA, but cytoplasm also may be at risk) and causing irreversible damage. The most widely accepted model representing stochastic effects is the **linear no (dose) threshold (LNT) model**. This model maintains that any level of radiation dose has a potential risk, although this risk is currently uncertain at effective dose levels below 50-100 mSv. Greater than this range, there is a recognized, although very small, statistically significant risk of a stochastic effect. In the LNT model, no level of radiation exposure is assumed to be safe.

Table 758.2 Radiation Measurements

UNITS	RADIOACTIVITY	ABSORBED DOSE	EFFECTIVE DOSE	EXPOSURE
Common units	Curie (Ci)	rad	rem	Roentgen (R)
SI units*	Becquerel (Bq)	Gray (Gy)	Sievert (Sv)	Coulombs/kg

CONVERSION EQUIVALENTS
1 millicurie (mCi) = 37 megabecquerels (MBq)
100 rad = 1 Gy (1 rad = 1 cGy)
100 rem = 1 Sv (1 rem = 10 mSv)
Background radiation dose is approximately 10 μGy/day (1 millirad/day)

*SI units: International System of Units.

Radiation can cause permanent cell injury leading to carcinogenesis, genetic variants, or cell death. The biologic effects of radiation result primarily from damage to DNA. **Direct effect** reactions occur mainly through interactions of high **linear energy transfer (LET)** particles, such as α particles or neutrons, directly with the DNA structure. A similar mechanism also can occur with x-ray or γ-ray photons by directly liberating an electron from atoms (called a recoil electron) near the DNA structure. The kinetic energy of the recoil electron or high LET particles may directly cleave chemical bonds in the DNA structure.

An **indirect effect** is caused by the formation of free radicals. This is the more common mechanism with x-rays and γ-rays used in medical imaging. Approximately 80% of the cell is water, so most of the energy deposited in a cell results in the production of aqueous free radicals. This occurs when the absorbed x-ray or γ-ray photon energy is converted to recoil electrons that create ion radicals (H_2O^+ and H_2O^-). The ion radicals promptly decay (10^{-18} to 10^{-3} seconds) into free radical species (OH^-, H^+, H_3O^+). Approximately two thirds of DNA damage is believed to be caused by this indirect effect through creation of hydroxyl (OH^-) free radicals, which then primarily reacts with DNA by attaching to the hydrogen bound to the deoxyribose carbon resulting in a base release from the DNA structure and strand break of the DNA helix. The biochemical changes that follow either direct or indirect effects take hours or days to manifest, whereas the physiologic changes leading to the likely complex cascade of a variety of factors for cancer induction may take years to decades to manifest.

The results from DNA injury are variable. The cell containing the damaged DNA almost always repairs itself and continues as a viable cell for miotic division. In some instances, the cell might die; one form of cell death is called **apoptosis**, which is a common pathway to eliminate heavily damaged and potentially mutable cells. Damage to a single base pair from radiation exposure is the most prevalent and least significant effect. Ninety percent of single-strand DNA breaks are repaired within an hour by naturally occurring DNA repair processes; therefore they usually have little biologic significance because each strand is repaired with use of the opposite strand as a template. Though less likely, a pathogenic variant can result from single-strand break repair if inaccurate repairs occur; however, large regions of the DNA genome on somatic cells are not active or do not have genes that are expressed. Inaccurate repair in these regions of the genome lead to minimal biologic effect and are sufficient to produce viable cells.

Breakage of both strands of DNA (i.e., double-strand break) is the least common event, but more problematic. The ultimate outcome for cell viability depends on the proximity of the break in each strand. If widely separated (greater than 10 base pairs), which is essentially two remote single-strand breaks, repairs occur rather seamlessly. If the breaks in the two strands are opposite or near each other (separated by less than 10 base pairs), repair is more difficult as there is no reciprocal base pair to serve as a "memory" template. Radiation-induced double-stranded breaks generally lead to cell death or **chromosomal misrepair,** potentially leading to pathogenic gene variants that may result in carcinogenesis.

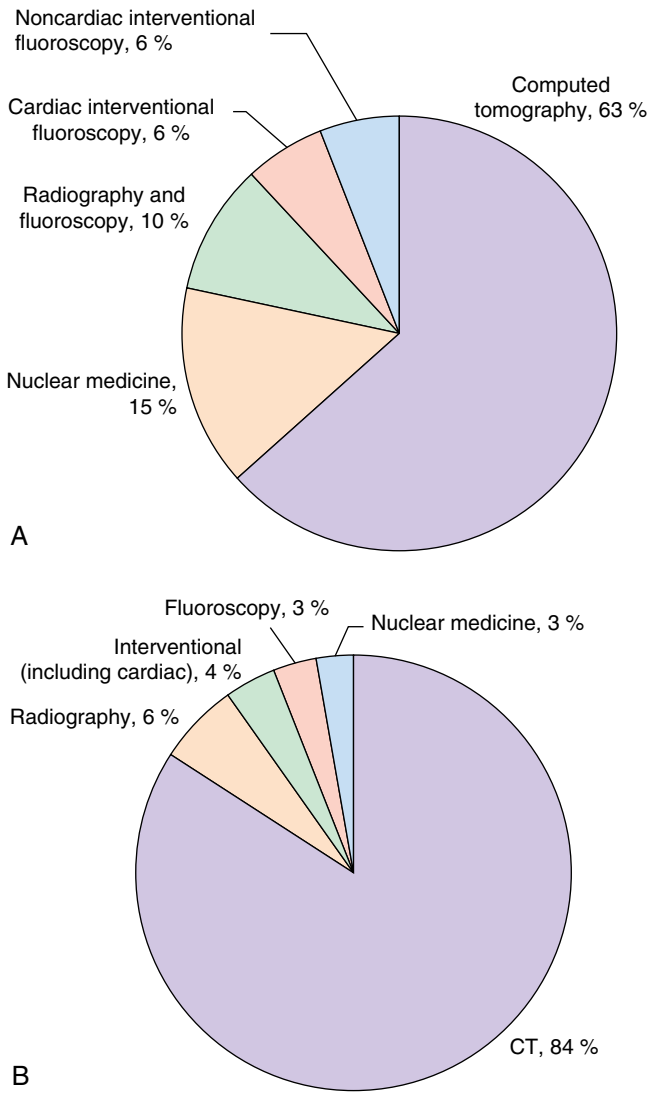

Fig. 758.1 Percentage radiation exposure by diagnostic imaging modality for (A) adult and (B) pediatric populations. *(Adapted with permission of the National Council on Radiation Protection and Measurements, Report 184: Medical Radiation Exposure of Patients in the United States, 2019. Figs. 14.3 and 12.2.)*

When misrepaired DNA damage occurs, aberrations may then be produced in chromosomes, resulting in an *unstable aberration* (usually lethal to dividing cells) or a *stable aberration.* Stable aberrations can result in failure of chromosomes to reunite (leading to deletions) or in abnormal rearrangement of chromosomes, such

as reciprocal translocation or aneuploidy. Although it is logical to think that these abnormalities in chromosomes lead to variants that can activate oncogenes or protooncogenes, or cause variants in tumor-suppressor genes (see Chapter 541), few radiation-induced cancers show specific translocations such as would be associated with activation of specific oncogenes or known tumor-suppressor genes. An exception is the radiation induction of papillary thyroid carcinoma in children, which probably results from activation of the RET oncogene (see Chapter 607).

A longitudinal study of the lifetime risks of excess cancer mortality to irradiation has been evaluated in atomic bomb survivors. More than 120,000 survivors since 1950 have been followed since exposure; additionally, 3,600 in utero survivors and their 77,000 progeny have been followed since 1945. Individual radiation doses were estimated by considering the person's location in relation to distance from the epicenter and individual shielding situations (such as line of sight with respect to buildings and terrain). Radiation types were mixed, and most of the exposure was direct gamma irradiation; neutron exposure was out to approximately 2,000 m. Age at exposure, lifestyle, and other factors were considered in the analytic models when calculating cancer occurrence (Fig. 758.2).

The pediatric population is approximately two to three times more sensitive to radiation-induced carcinogenesis compared with middle-age adults; however, the risk even in this population is indirectly related to age where the neonate is more sensitive than the older child to an identical radiation exposure. Because of the higher risks associated with breast and thyroid cancer, females are also more sensitive than males. It must be understood that cancer rates in this study are mortality figures; the incidence of cancer is approximately twice that of the mortality incidence for all ages. The Centers for Disease Control and Prevention (CDC) reports no scientific evidence demonstrating noncancerous effects (e.g., malformations, growth, intellectual disability, etc.) from in utero exposure <50 mGy, an exposure level that is greater than essentially any single diagnostic examination using ionizing radiation. Additionally, noncancerous effects may only increase slightly with exposure levels between 50 and 500 mGy. In utero radiation exposure is associated with an excess risk of developing (all types) childhood cancer: 1% (<100 mGy), 1–6% (100-500 mGy), and >6% (>500 mGy) as compared to 0.7% naturally. Children are at increased risk of stochastic risks for identical levels of exposure seen in adults because (1) children are growing rapidly, with many

Table 758.3 Imaging Modalities

MODALITY	SOURCE
Radiography (digital plain film x-ray)	Radiation (x-ray)
Fluoroscopy and fluoroscopically guided procedures	Radiation (x-ray)
Ultrasonography	Sound beams
Computed tomography	Radiation (x-ray)
Magnetic resonance imaging	Magnetic field with radiofrequency
Nuclear medicine (including positron emission tomography)	Radiation (administered isotope)

Table 758.4 Average Radiation Dose by Imaging Test for Pediatric Population*

EXAMINATION (0-18 YEARS)	EFFECTIVE DOSE (mSv)
Interventional fluoroscopy: AP and lateral abdomen	0.2-1.1 mSv/min
Interventional fluoroscopy: head	0.02-0.08 mSv/min
Interventional fluoroscopy: cardiac	0.1-1 mSv/min
Digital radiography: 2-view chest	0.04-0.06
Digital radiography: 2-view abdomen	0.1-0.6
Computed tomography: brain	0.8-2
Computed tomography: chest	0.5-4
Computed tomography: abdomen/pelvis†	1-9
Nuclear medicine (^{99m}Tc methylene diphosphonate: bone)	2-5
Positron emission tomography (^{18}F-FDG; whole body)	2-11

*Background radiation reference = 0.01 mSv/day or 3 mSv/yr.
†Radiation dose upper limit includes young adult age population.

Table 758.5 Tissue Reaction Dose Levels

INJURY	APPROXIMATE THRESHOLD
SKIN	
Transient erythema	2 Gy (200 rad)
Dry desquamation	8 Gy (800 rad)
Moist desquamation	15 Gy (1,500 rad)
Temporary epilation	2 Gy (200 rad)
Permanent epilation	7 Gy (700 rad)
EYES	
Cataracts (acute)	2 Gy (200 rad)*

*Has been reported as occurring between 0.5 and 1 Gy.

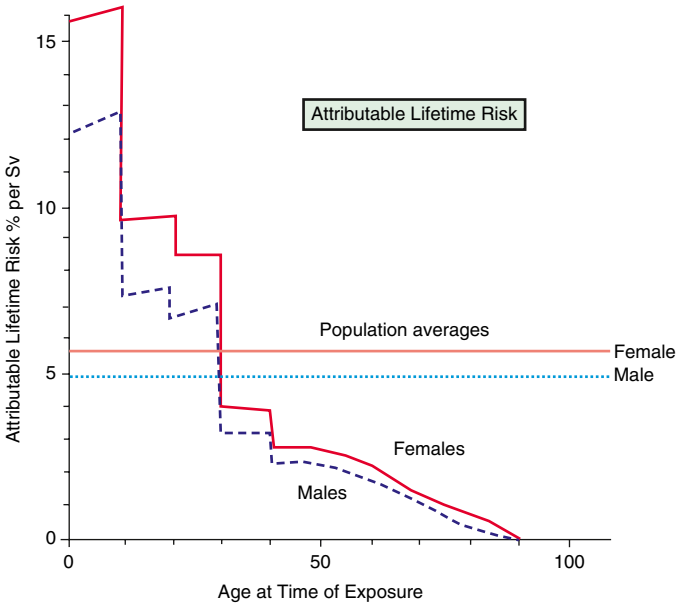

Fig. 758.2 Lifetime risk of excess cancer per sievert (Sv) as a function of age at the time of exposure. Data from the atomic bomb survivors. The average risk across all ages in a population is approximately 5% per Sv, but the risk varies considerably with age: children are much more sensitive than adults. At early ages, girls are more sensitive than boys. *(From Hall EJ. Introduction to session I: Helical CT and cancer risk. Pediatr Radiol. 2002;32:225–227.)*

Table 758.6 Inherited Human Syndromes Associated with Sensitivities to X-Rays

Ataxia-telangiectasia	Fanconi anemia
Basal cell nevoid syndrome	Gardner syndrome
Cockayne syndrome	Nijmegen breakage syndrome
Down syndrome	Usher syndrome

Modified from Davis JT, Frush DP. Biologic effects of diagnostic radiation on children. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*, 13th ed. Philadelphia: Elsevier; 2019: p. 5; and Hall EJ. *Radiobiology for the Radiologist*, 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2006: p. 41.

cells undergoing mitotic activity dependent on undamaged DNA and chromosomes, and (2) radiation-induced tumors (except leukemia) take a relatively long time to develop and children have a longer lifetime. Policies relating to the use of therapeutic abortion have been established by the ICRP and American College of Obstetricians and Gynecologists, which state that fetal doses <100 mGy should not be considered a reason for terminating pregnancy, and that every woman should be counseled that exposure from a single diagnostic procedure does not result in tissue effects to the fetus.

Most childhood tumors occur sporadically, but 10–15% of cases have a strong familial association. Familial tumors have specific chromosomal deletions in common. In some of these tumors (e.g., retinoblastoma), the two-hit hypothesis is apparent (see Chapter 541). Individuals with certain congenital diseases are at higher risk for the development of tumors after irradiation. Table 758.6 lists diseases that are associated with sensitivity to radiation.

RADIATION EXPOSURE IN DIAGNOSTIC IMAGING OF CHILDREN

Imaging modalities utilizing ionizing radiation for diagnostic purposes (e.g., CT, nuclear medicine, PET, radiography, and fluoroscopy or fluoroscopically guided procedures) are commonly utilized; however, increased awareness of the long-term risk for cancer induction and mortality has led to declining pediatric CT use over the past decade. The European EPI-CT study found a significant dose-response relationship between CT-related radiation exposure and brain cancer as well as hematologic malignancies in a large international study cohort, supporting the concept that stochastic effects are a dose-dependent probability, with the probability of an effect increasing with radiation dose. Therefore it is important that we use the lowest dose necessary to get sufficient diagnostic images. Various federal agencies, healthcare accrediting bodies, and national professional organizations support this goal and provide recommendations or requirements for all imaging examinations to have some retrievable radiation dose estimate, and for institutions and clinics that provide ionizing radiation imaging services to track and review patient examination dose levels annually, comparing these dose levels with expected dose ranges and external benchmarks.

Dose reporting and aggregating software provides the ability to collect and analyze individual examination doses and gives healthcare providers a powerful tool to correct outlier examinations (i.e., over exposures), over utilization, and address other systemic errors present in imaging clinics (such as radiation dose creep with time).

DECREASING UNNECESSARY DIAGNOSTIC RADIATION IN CHILDREN WHILE STILL OBTAINING DIAGNOSTIC IMAGES

Ultimately, the lowest radiation dose examination is the imaging examination performed without ionizing radiation. For an increasing number of indications, utilization of nonionizing radiation modalities such as ultrasound or MRI may be the first consideration for diagnosis. Selecting the correct examination is the responsibility of the requesting healthcare provider and may involve consultation with the radiologist, preferably with pediatric expertise. Clinical decision support algorithms are also available to assist with examination appropriateness (e.g., American College of Radiology's Appropriateness Criteria). The risk of using ionizing radiation for imaging should be weighed against other risks during imaging. CT (depending on the indication and region examined) may detect as many abnormalities as MRI, but CT involves ionizing radiation. However, sedation is often required to successfully obtain MRI imaging in young children; in these cases, consideration of the relative risks of cognitive impairment from moderate sedation and anesthetic versus potential radiation risks use should come into play.

Reducing Radiation from the CT Examination

The most common source of medical radiation for all ages is CT. CT offers the ability to acquire high-quality volumetric imaging datasets in seconds. For many years, adult parameters for CT settings were used for children, which led to dosages for children much higher than the dosage for adults. This occurs because lower energy x-rays that would have been absorbed in the near field in an adult pass into the entire child, with relatively greater organ irradiation for the same exposure. When comparing dosages given to newborns and adults during CT scanning of the head, with the same parameters in both groups, the dosage given to newborns can be four times that of the dosage given to adults; with abdominal imaging, the dosage is increased by 60%. It is the role of the radiologist and technologist, with the help of a medical physicist, to develop and monitor protocols that tailor the examination to the individual indication and for the variabilities in sizes found in the pediatric population.

Modern CT scanners have many tools to help administer the appropriate amount of radiation dose to a pediatric patient and acquire the necessary diagnostic image quality from the imaging examination. Radiologists should work in conjunction with medical physicists and vendor supplied application specialists to tailor specific examination protocols to the pediatric patient population by establishing appropriate scan parameters such as the kilovoltage (kV). Scan range should be limited to only the necessary area for diagnosis (e.g., a chest only scan should begin at the lung apices and extend to no more than a little below the lowest lung base). Multiphasic scanning should be only obtained when justified; for example, in pediatric abdominopelvic CT multiple phases should be necessary in no more than approximately 5% of examinations.

Technologic advances for modern CT scanners are using reconstruction algorithms, such as statistical iterative reconstruction (IR), model-based IR, and deep learning reconstruction (DLR), as well as photon counting technology. These algorithms have been shown to allow the reduction of radiation dose for IR algorithms by 15-30% and DLR algorithms by 44-83% in some patient populations while maintaining equivalent diagnostic confidence to the pre-dose reduced image datasets. Other practical steps to reduce pediatric population radiation dose include replacing older CT scanners with technologically advanced scanners; monitoring institution dose values, which can be compared with available benchmarks, such as **diagnostic reference levels (DRLs)**; and performing only examinations that are justified. Advances in technology and attention to proper performance of examinations have contributed to overall reductions in pediatric patient population doses by >50% during the past two decades.

RADIATION THERAPY: ACUTE AND LATE EFFECTS

Radiation therapy uses high doses to kill malignant cells. The sensitivity of normal cells is quite close to that of malignant cells, and to achieve significant cure rates, radiation oncologists must accept a given percentage of serious complications (5–10%). Radiation causes tissue loss plus injury to the underlying vasculature. The vascular change may be progressive, leading to arteriocapillary fibrosis and irreparable injury, in turn leading to further tissue loss.

The acute effects of therapy (occurring less than 3 months after therapy begins) are usually related to the area of the body being irradiated (except fatigue, which can begin during this time period). These acute effects include radiation-induced pneumonitis, dermatitis, mucositis and esophagitis, cerebral edema, and swelling of the organ irradiated. There may be changes in bowel movement patterns. Of these, one of the most severe acute reactions is pneumonitis. It can manifest within

Table 758.7 Late Effects of Radiation Therapy in Children Treated for Cancer

SYSTEM	LATE EFFECT	DOSE (GY)
Musculoskeletal	Muscular hypoplasia	>20
	Scoliosis, kyphosis, lordosis	>20
	Osteocartilaginous exostosis/ osteochondroma	>12
Neuroendocrine (cranial or cranial spinal)	Impaired growth hormone	>15
	Adrenocorticotropic hormone deficiency	>30
	Thyrotropin-releasing deficiency	>40
	Precocious puberty (females mostly)	>18
	Gonadotropin deficiency	>30
Gonad failure	Ovarian failure	>10
	Testicular failure	>3
Central nervous system dysfunction	Structured changes	>18
	Cognitive changes/Processing speed	Variable
Other	Pulmonary fibrosis	>15
	Nephropathy	>20
	Liver disease	>30 (>60% liver volume)
	Cerebral arteriopathy	>50
	Eye impairment (cataracts, legally blind, double vision, dry eyes)	>5
	Hearing loss	>30
	Dental abnormalities	>20
	Cardiac impairment	>30

24 hours of irradiation when there is an exudation of proteinaceous material into the alveoli and interalveolar edema. Most often, however, radiation pneumonitis begins 2-6 months after the beginning of radiation with a clinical presentation of fever, cough, congestion, and pruritic pain. The late effects of therapy (beginning more than 3 months after therapy) are numerous (Table 758.7). The most common are abnormalities of musculoskeletal development, endocrine/reproductive function, pulmonary function, neurocognition, hearing loss, cardiac function, eye impairment, and dental abnormalities.

As of 2020, there are more than 500,000 childhood cancer survivors in the United States. The risk of developing a second cancer among cancer survivors is over fivefold higher than the general population. Second cancers account for 2.3% of all cancers in children; this reflects an overall standard incidence rate (SIR) of 5.5%. Primary malignancies with the highest cumulative incidence of a second neoplasm in the order of frequency are retinoblastoma (10.4%), CNS cancers (7.4%), cancers of bone (7.2%), soft tissue sarcomas (6.5%), hepatic cancer (5.9%), and neuroblastoma (5.9%) [data from the U.S. Surveillance, Epidemiology, and End Results program (SEER)]. Table 758.8 relates second cancers to primary cancer and latency period. Almost 70% of the second neoplasms are in the field of the original irradiation. Radiation therapy increases the risk of second cancers in a dose-dependent manner for nongenetic neoplasms.

The exact complications depend on the location of the treatment field. In children, because of the location of many childhood tumors, the normal brain is commonly in the treatment field. Standard irradiation of the brain in children results in cortical atrophy in more than half of patients who receive 20-60 Gy; 26% are left with white matter changes (leukoencephalopathy) and 8% with calcifications. The younger the child is at the time of irradiation, the greater the atrophy. Some patients also demonstrate mineralizing microangiopathy. Radiation-induced changes of the brain are potentiated by methotrexate administered before, during, or after radiation therapy.

Cerebral necrosis is a serious complication of radiation-induced vascular disease. It is usually diagnosed 1-5 years after irradiation but can occur up to a decade later. Brain necrosis may manifest as headache, increased intracranial pressure, seizures, sensory deficits, and psychotic changes.

Spinal cord irradiation may result in **radiation myelitis,** which may be either transient or permanent. Acute transient myelitis often appears 2-4 months after irradiation. Patients with myelitis usually present with **Lhermitte sign,** a sensation of little electrical shocks radiating down the spine into the arms and legs, occurring with neck flexion or other movements that stretch the spinal cord. Reversal of transient myelopathy usually occurs between 8 and 40 weeks and does not necessarily progress to delayed necrosis.

Delayed myelopathy occurs after a mean latent period of 20 months but can occur earlier if the total dose or the dose per fraction is high. It usually manifests as discontinuous deterioration and is irreversible. In the cervical and thoracic regions, sensory dissociation develops, followed by spastic and then flaccid paresis. In the lumbar cord, flaccid paresis is dominant. The mortality for high thoracic and cervical lesions reaches 70% with death commonly being due to pneumonia and urinary tract infections.

CNS irradiation may affect growth by compromising function of the pituitary-hypothalamic axis and leading to diminishing growth hormone production and release. Non–growth hormone tropins may also be affected by CNS irradiation, leading to gonadotropin deficiency or precocious puberty. Central hypothyroidism can also develop. CNS irradiation also compromises bone mineral deposition both locally (in the radiation field) and systemically.

Irradiation has other effects specific to children. Scoliosis and hypoplasia of bones may occur if fractionated treatment schemes exceed 4,000 rad. Fractionated doses higher than 25 Gy can result in slipped capital femoral epiphyses. An increase in the incidence of benign osteochondromas has been reported after childhood irradiation. Chest wall irradiation in females (besides causing breast cancer) may impair breast development and/or cause fibrosis and atrophy of breast tissue.

WHOLE BODY IRRADIATION

Uncontrolled Large- or Small-Scale Exposure to Radiation

Large-scale exposure to radiation can occur in an event of nuclear accidents, war, or terrorist attacks (Fig. 758.3). Radiation as well as explosive and thermal injury need to be considered.

Clinical Manifestations

A large single exposure of penetrating radiation can result in **acute radiation syndrome** (Table 758.9). The signs and symptoms of this syndrome result from damage to major organ systems that have different levels of radiation sensitivity, modulated by the rate at which the radiation exposure occurred. Delivery of 1 Gy in 1 minute would be symptomatic, but delivery of 1 cGy/day for 100 days would not be symptomatic.

The **hematopoietic syndrome** results from acute whole body doses >0.7-10 Gy; where healthy patients will almost always recover from doses <2 Gy. The dose that kills 50% of a population in 60 days is approximately 3.5-4.5 Gy, where effective blood transfusions and antibiotics may extend the dose range to 5-8 Gy. Doses >8 Gy almost always lead to hematopoietic-induced death. Symptoms of exposure consist of a *prodromal phase* during which the patient will experience nausea/vomiting, diarrhea, and fatigue within the first 12 hours, with symptoms usually lasting up to 48 hours. A *latent period* of 2-3 weeks, during which patients may feel quite well, follows. Although patients are asymptomatic, bone marrow impairment has occurred. The most obvious laboratory finding is lymphocyte depression (Table 758.10). Maximal bone marrow depression occurs approximately 30 days after exposure, when hemorrhage and infection can be major problems. If the bone marrow was not completely eradicated, a *recovery phase* then ensues. This radiation effect is similar to what occurs when whole body irradiation (given as 12 Gy in two treatments) is used

Table 758.8 Second Cancers and Their Relationship with Primary Cancers

SECOND CANCERS	PRIMARY CANCERS	LATENCY (MEDIAN IN YEARS)	RISK FACTORS
Brain tumors	ALL; brain tumors; HD	9-10	Radiation; younger age
Myelodysplastic syndromes/ acute myelogenous leukemia	ALL; HD; bone tumors	3-5	Topoisomerase II inhibitors; alkylating agents
Breast cancer	HD; bone tumors; soft tissue sarcomas; ALL; brain tumors; Wilms tumors; NHL	15-20	Radiation; female gender
Thyroid cancer	ALL: HD; neuroblastoma; soft tissue sarcomas; bone tumors; NHL	13-15	Radiation; younger age; female gender
Bone tumors	Retinoblastoma (heritable); other bone tumors; Ewing sarcoma; soft tissue sarcomas; ALL	9-10	Radiation; alkylating agents; removal of the spleen
Soft tissue sarcomas	Retinoblastoma (heritable); soft tissue sarcomas; HD; Wilms tumors; bone tumors; ALL	10-11	Radiation; younger age; anthracyclines

ALL, Acute lymphocytic leukemia; HD, Hodgkin disease; NHL, non-Hodgkin lymphoma.
From Bhatia S, Sklar S. Second cancers in survivors of childhood cancer. *Nat Rev Cancer.* 2002;2:124–132.

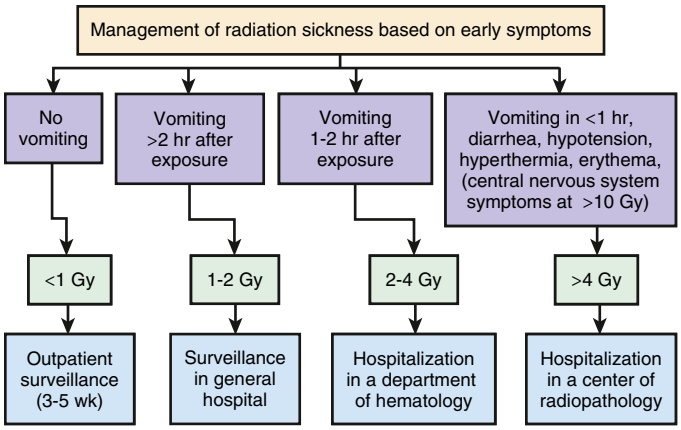

Fig. 758.3 Management algorithm for radiation sickness at different levels of medical care, depending on the appearance of early symptoms and the estimated radiation dose to the whole body. *(From Turai I, Veress K, Günalp B, et al. Medical response to radiation incidents and radionuclear threats. BMJ. 2004;328:568–572.)*

to obliterate the bone marrow in children with leukemia before bone marrow transplantation.

The **gastrointestinal (GI) syndrome** occurs from acute whole body doses >6-10 Gy. Prompt onset of nausea, vomiting, and diarrhea follows. There is a latent period of approximately 1 week if intense medical treatment is administered. Following the latent period, recurrence of GI symptoms, sepsis, and electrolyte imbalance occurs, which results in death at about 2 weeks postexposure from GI tract and bone marrow destruction.

At dose levels exceeding 20-50 Gy, the **cardiovascular/CNS syndrome** predominates. Nausea, vomiting, prostration, hypotension, ataxia, and convulsions are almost immediate. The latent period occurs between 4 and 6 hours postexposure followed by severe manifestation of the initial illness stage leading to eventual coma and death within 2-3 days.

Treatment

For the hematopoietic and GI syndromes, treatment is supportive involving transfusions and Neupogen (filgrastim), Neulasta (pegfilgrastim) and other hematopoietic growth factors, fluids, and, if infected antibiotics and antiviral agents. Stem cell (bone marrow) transplantation may be needed in severe cases.

Localized Irradiation

Clinical Manifestations

Because localized exposure involves a small amount of tissue, systemic manifestations may be less severe, and patients may survive even if locally absorbed doses are very high. The hand is the most common site for accidental localized irradiation injuries, usually as a result of picking up or playing with lost radiation sources. The second most common accidental site is the thigh and buttocks, predominantly from placing unsuspected highly radioactive sources in the pockets.

Table 758.11 lists the skin changes that occur after a single acute, localized irradiation. As opposed to other forms of thermal burns, signs of irradiation appear a period of days *after* the exposure. Vascular insufficiency may appear months to years later and cause ulcerations or necrosis in formerly healed areas. The penetrability of the radiation is an important factor in the outcome of local radiation injury. Beta particles from heavy radiation fallout can cause superficial skin burns because they have low penetrability.

Some tissues that may receive localized radiation exposure are relatively radiosensitive. **Cataract formation** (see Chapter 668) may occur with single γ-ray exposures in the range of <1 Gy. Such cataracts usually take from 2 months to several years to develop. **Oligospermia** may take up to 2 months to develop. Transient infertility in men may result from doses as low as 0.15 Gy, and permanent sterility may occur in males at dose levels between 3 and 6 Gy.

Treatment

Skin therapy is directed at prevention of infections. Treatment of localized injuries usually involves class II to III topical steroids and plastic surgery and grafting, if the radiation exposure was not deeply penetrating (see Chapter 89). The nature of the surgery depends on the dose at various depths in tissue and the location of the lesion. The full expression of radiation injury often is not apparent for 1-2 years due to slow arteriolar narrowing that can cause delayed necrosis. After relatively penetrating radiation, amputation may be necessary because of obliterative changes in small vessels.

INTERNAL CONTAMINATION

Epidemiology

Accidents involving internal contamination are rare and are usually the result of misadministration in hospital settings or voluntary ingestion of unsuspected contaminated radioactive materials. Other possible causes of internal contamination of children include ingestion of breast milk from mothers who have had diagnostic nuclear medicine scans and radiation exposure when a parent or sibling receives a therapeutic dose of iodine-131.

Table 758.9 Acute Radiation Syndrome

SYNDROME	DOSE*	PRODROMAL STAGE	LATENT STAGE	MANIFEST ILLNESS STAGE	RECOVERY
Hematopoietic (bone marrow)	>0.7 Gy (>70 rads) *(mild symptoms may occur as low as 0.3 Gy or 30 rads)*	• Symptoms are anorexia, nausea and vomiting • Onset occurs 1 hr to 2 days after exposure • Stage lasts for minutes to days	• Stem cells in bone marrow are dying, although patient may appear and feel well • Stage lasts 1-6 wk	• Symptoms are anorexia, fever, and malaise • Drop in all blood cell counts occurs for several weeks • Primary cause of death is infection and hemorrhage • Survival decreases with increasing dose • Most deaths occur within a few months after exposure	• In most cases, bone marrow cells will begin to repopulate the marrow • There should be full recovery for a large percentage of individuals from a few weeks up to 2 yr after exposure • Death may occur in some individuals at 1.2 Gy (120 rads) • The $LD_{50}/60$† is about 2.5-5 Gy (250-500 rads)
Gastrointestinal (GI)	>10 Gy (>1,000 rads) *(some symptoms may occur as low as 6 Gy or 600 rads)*	• Symptoms are anorexia, severe nausea, vomiting, cramps, and diarrhea • Onset occurs within a few hours after exposure • Stage lasts about 2 days	• Stem cells in bone marrow and cells lining GI tract are dying, although patient may appear and feel well • Stage lasts <1 wk	• Symptoms are malaise, anorexia, severe diarrhea, fever, dehydration, and electrolyte imbalance • Death is due to infection, dehydration, and electrolyte imbalance • Death occurs within 2 wk of exposure	• The LD_{100}‡ is about 10 Gy (1,000 rads)
Cardiovascular (CV)/ central nervous system (CNS)	>50 Gy (5,000 rads) *(some symptoms may occur as low as 20 Gy or 2,000 rads)*	• Symptoms are extreme nervousness and confusion; severe nausea, vomiting, and watery diarrhea; loss of consciousness; and burning sensations of the skin • Onset occurs within minutes of exposure • Stage lasts for minutes to hours	• Patient may return to partial functionality • Stage may last for hours but often is less	• Symptoms are return of watery diarrhea, convulsions, and coma • Onset occurs 5-6 hr after exposure • Death occurs within 3 days of exposure	• No recovery is expected

*The absorbed doses quoted here are "gamma equivalent" values. Neutrons or protons generally produce the same effects as γ-, β-, or x-rays but at lower doses. If the patient has been exposed to neutrons or protons, consult radiation experts on how to interpret the dose.
†The $LD_{50}/60$ is the dose necessary to kill 50% of the exposed population in 60 days.
‡The LD_{100} is the dose necessary to kill 100% of the exposed population.
From Centers for Disease Control and Prevention. Acute radiation syndrome: a fact sheet for clinicians. Table 1. https://www.cdc.gov/nceh/radiation/emergencies/arsphysicianfactsheet.htm.

Table 758.10 Expected Outcome Based on Absolute Lymphocyte Count After Acute Penetrating Whole Body Irradiation

MINIMAL LYMPHOCYTE COUNT WITHIN FIRST 48 HR AFTER EXPOSURE	PROGNOSIS
1,000-3,000 (normal range)	No significant injury
1,000-1,500	Significant but probably nonlethal injury, good prognosis
500-1,000	Severe injury, fair prognosis
100-500	Very severe injury, poor prognosis
<100	Lethal without compatible bone marrow donor

Clinical Manifestations

The hazards from internal contamination depend on the nature of both the radionuclide (particularly in terms of its solubility in water, half-life, biologic half-life, and radioactive emission) and the chemical compound.

Treatment

The most effective treatment requires knowledge of both the radionuclide and the chemical form. Treatment must be instituted quickly to be effective (Table 758.12). **Removal treatment** involves cleaning a contaminated wound and performing gastric lavage or administration of cathartics in the case of ingestion. Administration of alginate-containing antacids (e.g., Gaviscon) also usually helps in removal by decreasing absorption in the GI tract. An example of **blocking therapy** is the administration of potassium iodine or other stable iodine-containing compounds to patients with known internal contamination with radioactive iodine. The stable iodine effectively blocks the thyroid, although its effectiveness decreases rapidly as time elapses after the contamination. The recommended dose of potassium iodine is 16 mg

for neonates (up to 1 month of age); 32 mg for children ages 1 month to 3 years; 65 mg for children ages 3-18 years (if less than 70 kg), and 130 mg for adults and adolescents >70 kg. Each dose protects for only 1 day. **Dilution therapy** is used in cases of tritium (radioactive hydrogen as water) contamination. Forcing fluids promotes excretion. Cases of internal contamination with transuranic elements (americium and plutonium) may require **chelation therapy** with calcium diethylenetriamine pentaacetate.

Prussian blue is a drug approved by the FDA for patients with internal contamination with cesium or thallium. It can speed fecal elimination of radioactive cesium from the body. It acts by intercepting the cesium coming into the gut from the bile. Prussian blue prevents

Table 758.11 Skin Changes After a Single, Acute, Localized Radiation Exposure

APPROXIMATE THRESHOLD (GY)	CHANGE
2-4	Primary erythema within hours of exposure (appears more quickly after larger doses)
3	Second phase erythema (develops during the manifestation phase of local radiation injury); appears 14-21 days after exposure
3	Temporary epilation (14-18 days after exposure)
7	Definitive epilation (25-30 days after exposure)
10	Dry desquamation (20-28 days after exposure)
15	Moist desquamation, possible ulceration (15-25 days after exposure)
25	Desquamation with blistering, ulceration, and necrosis (>21 days after exposure)

Data from the International Atomic Energy Agency. *Safety Reports Series, No. 101: Medical management of radiation injuries*, 2020. https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1891_web.pdf

Table 758.12 Decontamination of Common Elements in Industrial and Medical Accidents

ELEMENT	EMISSIONS	CRITICAL ORGAN	EFFECTIVE $T_{1/2}$*	DECONTAMINATION
Cesium-137	Beta, gamma	Total body	70 days	Prussian blue (Radiogardase) 3 g po 3 times/day (adults and adolescents); 1 g po 3 times/day (2-12 yr old); consider lavage and purgatives
Cobalt-60	Beta, gamma	Total body	10 days	Lavage, purgatives, penicillamine
Iodine-125, iodine-131	Beta, gamma	Thyroid	Iodine-125, 42 days; iodine-131, 8 days	Potassium iodide: 0-1 mo, 16 mg/day >1 mo to 3 yr, 32 mg/day >3 mo to 3 yr, 32 mg/day >3 to 12 yr and <70 kg, 65 mg/day adults or ≥70 kg, 130 mg/day; consider lavage
Iridium-192	Beta, gamma	Lung	74 days	Lavage for large quantities
Technetium-99 m	Gamma	Total body	5 hours	Potassium perchlorate to reduce thyroid dose
Tritium-3	Beta	Total body	12 days	Forced fluids
Uranium-235, uranium-238	Alpha	Kidney,† bone, liver, lung	Can be permanent if in bone	Bicarbonate to alkalinize the urine

*Effective $t_{1/2}$ combines radioactive and chemical properties and rates of elimination without decontamination efforts.
†The kidney is most vulnerable to large amounts of uranium because of the chemical properties of this heavy metal. Uranium can ultimately be deposited in bone.
po, Per os; *qd*, once per day.
Data from U.S. Food and Drug Administration. Prussian blue, Radiogardase, package insert. Available at: http://www.fda.gov/cder/drug/infopage/prussian_blue/default.htm; U.S. Food and Drug Administration. Guidance: Potassium iodide as a thyroid blocking agent in radiation emergencies. Available at: http://www.fda.gov/cder/guidance/4825fnl.htm; *Management of Persons Accidentally Contaminated with Radionuclides*. NCRP Report No. 65. Bethesda, MD: National Council on Radiation Protection and Measurements; 1980; and Jarrett D, ed. *Medical Management of Radiation Casualties: Handbook*. 2nd ed. AFRRI Special Publication 03-1. Bethesda, MD: Armed Forces Radiobiology Research Institute; 2003. Available at: http://www.afrri.usuhs.mil.
From Linder JA, Linder LS: Radiation accident—dispersed exposure. In Ciottone GR (ed). *Ciottone's Disaster Medicine*, 2nd ed. Philadelphia: Elsevier, 2016. Table 108-1.

Table 758.13 Nuclear Regulatory Commission Guidelines on Breastfeeding During the Period During a Nuclear Medicine Examination

RADIOPHARMACEUTICAL	BREASTFEEDING CESSATION
^{11}C, ^{13}N, ^{15}O, ^{82}Rb	None
^{18}F-labeled	12 hr
^{68}Ga-labeled	12 hr
^{99m}Tc-labeled	24 hr
^{123}-I Sodium iodide	7 days
^{111}In-leukocytes	7 days
^{99m}-Tc labeled	No interruption*
^{201}Tl chloride	14 days
^{67}Ga and ^{89}Zr	28 days
^{177}Lu, diagnostic	35 days
^{131}I-NaI	Stop breastfeeding
^{177}Lu, therapeutic	Stop breastfeeding
^{223}Ra and all alpha emitters	Stop breastfeeding

*The guideline for ^{99m}Tc compounds is a 24-hr interruption for >1110 MBq administered, 12 hr for 444-1110 MBq, and no interruption for <444 MBq administered. The normally administered activity is below activities that require any interruption.

From Dilsizian V, Metter D, Palestro C, Zanaonico P. The Advisory Committee on Medical Uses of Isotomes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials, 2018, p. 12. https://www.nrc.gov/docs/ML1803/ML18033B034.pdf

cesium from being absorbed again from the gut. Prussian blue can be given days after ingestion, unlike potassium iodine, which must be given initially in the first 12-24 hours after exposure.

In the case of breastfeeding after a nuclear medicine procedure, two primary concerns are considered: (1) the internal dose to the infant passed through the excreted milk and (2) the dose from the radiopharmaceutical absorption in the female breast that exposes the infant to external γ-rays while undergoing decay. Most imaging radiopharmaceuticals are below the activity calculated to expose the infant to a dose of 1 mSv via either internal or external mode of exposure. Table 758.13 provides a comprehensive list of radiopharmaceuticals and the recommended period for breastfeeding cessation by the U.S. Nuclear Regulatory Commission. In the case of delaying breastfeeding, pumped milk may be stored for the times indicated in Table 758.13, after which they will be safe to feed the infant.

EXTERNAL CONTAMINATION

The presence of external radioactive contamination on a patient's skin is not an immediate medical emergency. Management involves removing and controlling the spread of radioactive materials. If a patient has suspected surface contamination and no physical injuries, decontamination can be performed relatively easily. If substantial physical trauma or other life-threatening injuries are combined with external contamination, surface decontamination should proceed only after the patient has been stabilized physiologically. In many accident situations, essential medical care may be delayed inappropriately by hospital emergency staff because of fear of radiation or spread of contamination in the hospital. After a radiation accident, triaging of patients is critical and is based on exposure and symptoms (see Fig. 758.3).

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Chapter 759

Chemical Pollutants

Joel A. Forman and Lauren M. Zajac

More than 85,000 new synthetic chemicals have been developed in the past 75 years. These chemicals are used in millions of products, ranging from food packaging to clothing, building materials, motor fuels, cleaning products, cosmetics, medical products, toys, and baby bottles.

Synthetic chemicals are widely disseminated in the environment. The Toxic Release Inventory of the U.S. Environmental Protection Agency (EPA) reports that in 2021, of 29.3 billion pounds of production-related chemical waste managed, nearly 3.3 billion pounds (11%) were discharged into air, water, and land in the United States. These chemicals are detected today in even the most remote corners of the planet, such as the polar icecaps and in the ocean depths.

All people are at daily risk of exposure to synthetic chemicals, and children are especially likely to be exposed to the nearly 3,000 chemicals that are produced in amounts of 1 million pounds or more per year, designated by the EPA as high-production-volume chemicals. Biomonitoring data on blood and urine levels of more than 400 high-production-volume chemicals are obtained annually by the Centers for Disease Control and Prevention in a sample of the U.S. population through the National Health and Nutrition Examination Survey (NHANES). These data document that most Americans, including children, are routinely exposed to scores of synthetic chemicals; exposure often falls disproportionately on poor children and children of color. Examples are wide ranging and include lead, air pollutants, endocrine disrupting chemicals like phthalates, and many others.

Toxic chemicals are exported in ever-increasing quantities to the world's poorer countries as these countries undergo industrial development. Environmental safeguards in those countries are typically not as stringent as in high-income countries, and the potential for serious exposure is therefore high. Examples of tragedies that have resulted from the movement of toxic chemicals to low- and middle-income countries include the Bhopal disaster in India, in which hundreds were killed and thousands injured by methylisocyanate gas released by an explosion in a pesticide production facility, and the ongoing export each year of more than 2 million tons of newly produced asbestos to the world's poorest countries, where this asbestos is responsible for nearly 200,000 deaths annually from asbestosis, lung cancer, and malignant mesothelioma.

SYNTHETIC CHEMICALS AND HUMAN HEALTH

A recurrent pattern is that chemicals are brought to market with great enthusiasm, presumed harmless, and undergo little or no premarket safety testing. Then years or decades later, after they had come into wide use, the chemicals were found to be harmful to children's health.

Often the first cases of disease caused by these chemicals are clinically severe, but as time passes, evidence of widespread subclinical toxicity comes to light.

Classic historical examples of epidemics caused by inadequately tested toxic chemicals include the following:

- *Tetraethyl lead:* This was added to gasoline in the United States from the early 1920s until 1980. It was responsible for widespread lead poisoning, initially evident as an epidemic of acute toxicity manifesting as encephalopathy, seizures, and even death, but later demonstrated to have caused subclinical neurotoxicity and reduction in IQ across two generations of U.S. children (see Chapter 761).
- *Dichlorodiphenyltrichloroethane (DDT):* This pesticide very nearly led to extinction of the osprey and the American bald eagle and more recently has been linked to increased risk for breast cancer among women exposed decades ago in utero.

- *Polychlorinated biphenyls (PCBs)*: These are highly persistent pollutants banned from production in the United States in 1977, which continue today to contaminate major lakes and rivers and have been found also to be responsible for loss of IQ and disruption of behavior in children.
- *Chlorofluorocarbons:* These destroy the ozone.

Other examples of synthetic chemicals that came into wide use with little assessment of their safety and are now recognized as causing harm to children's health include the following:

- *Phthalates:* These chemicals are added to plastics, cosmetics, medical equipment like intravenous tubing, and common household products that are now linked to increased risk for reproductive abnormalities in male infants and heightened risk of behavioral abnormalities such as attention-deficit/hyperactivity disorder (see Chapter 50).
- *Polybrominated diphenyl ethers:* These are used as flame retardants in carpets, furniture, and electronic equipment and are now linked to persistent loss of intelligence and disruption of behavior in children.
- *Bisphenol A:* A plastics chemical linked to neurodevelopmental disorders.

These chemicals are all produced in volumes of millions of tons per year, are widely disseminated in the environment, and are detectable in the bodies of nearly all Americans. Only decades after their introduction are these chemicals' risks to children beginning to be recognized.

CHILDREN'S UNIQUE SUSCEPTIBILITY TO SYNTHETIC CHEMICALS

The health effects of synthetic chemicals are especially serious when exposure occurs during windows of vulnerability in early life such as during pregnancy, infancy, and early childhood. Children are highly vulnerable to chemical pollutants for several reasons:

1. Children have proportionally greater exposure to environmental pollutants than adults. Because they drink more water, eat more food, and breathe more air per kilogram of body weight, children are more heavily exposed to pollutants in water, food, and air. Children's hand-to-mouth behavior and their play close to the ground further magnify their exposures.
2. Children's metabolic pathways, especially in the first few months after birth, are immature. Although in some instances children are better able than adults to cope with environmental toxicants because they cannot metabolize these chemicals to their active forms, more commonly children are not as able as adults to detoxify and excrete chemical pollutants.
3. Infants and children are growing and developing, and their complex, fast-moving, and highly choreographed developmental processes are exquisitely sensitive to disruption by chemical pollutants. Exposures to even minute doses of toxic chemicals during windows of vulnerability in early development have been shown to cause a wide array of diseases in childhood and to increase risk for chronic disease and disability lifelong (Table 759.1).
4. Because children have many future years of life, they have time for the development of multistage chronic diseases that may be triggered by early exposures.

Table 759.1 Effects of Selected Chemical Pollutants on Infants and Children

CHEMICAL POLLUTANT	EFFECT(S)
Air pollution	Asthma, other respiratory diseases, sudden infant death syndrome
Asbestos	Mesothelioma and lung cancer
Benzene, nitrosamine, vinyl chloride, ionizing radiation	Cancer
Environmental tobacco smoke	Increased risk of sudden infant death syndrome and asthma
Ethyl alcohol	Fetal alcohol syndrome after intrauterine exposure
Lead	Neurobehavioral toxicity from low-dose exposure
Methyl mercury	Developmental neurotoxicity
Organophosphate insecticides	Developmental neurotoxicity
Per- and poly-fluoroalkyl substances (PFAS)	Increased cholesterol levels, altered liver function tests, decreased antibody response to childhood vaccines
Polychlorinated biphenyls	Developmental neurotoxicity
Polybrominated diphenyl ethers	Developmental neurotoxicity
Phthalates	Developmental neurotoxicity and reproductive impairment
Trichloroethylene	Elevated risk of leukemia after intrauterine exposure

SAFETY TESTING OF SYNTHETIC CHEMICALS

Legally mandated testing of chemicals for safety and toxicity coupled with strict controls on dangerous chemicals are the linchpins of chemical safety. Strong chemical safety policies are needed to protect children against disease and death caused by chemicals. A fundamental problem in environmental pediatrics today is that chemical safety policies in many countries are weak. Only approximately 65% of high-production-volume chemicals have been tested for their safety or potential hazard to human health, and fewer than 30% have been assessed for their pediatric or developmental toxicity.

Failure to test chemicals for safety and toxicity reflects the chemical industry's unwillingness to take responsibility for the products they produce coupled with long-standing failure of the previous U.S. federal law on chemical safety, the Toxic Substances Control Act (TSCA). Only five chemicals were banned or controlled under the original TSCA law: PCBs, the ozone-destroying chlorofluorocarbons, and three known human carcinogens—dioxin, asbestos, and hexavalent chromium.

To address the problem of exposure to untested chemicals, countries have enacted stronger chemical safety legislation. In 2007, the European Union enacted the Registration, Evaluation, Authorization, and Restriction of Chemical Substances (REACH) legislation. This law places responsibility on industry to generate data on potential risks of commercial chemicals and to register this information with the European Chemical Agency in Helsinki. The European Union is using this information to craft regulations to protect children's health. Since 2009 REACH has restricted more than 1,000 toxic substances.

In June 2016, the United States passed legislation to revamp TSCA. This law—the Frank R. Lautenberg Chemical Safety for the 21st Century Act—requires the EPA to assess the safety of any new chemical before it is allowed to enter the market, to prioritize safety testing of existing chemicals, and to use a risk-based standard to evaluate chemical safety that considers only hazards to health and is blind to the costs of protective action. This law holds much promise for improving the protection of children's health against toxic chemicals, but it also includes a federal preemption clause that could inhibit state-based protective regulations. Transparency, oversight, and advocacy is critical to ensuring that the law is implemented in a timely manner that is true to the intent to prioritize children's health.

The UN Environment Programme (UNEP) is the United Nations agency responsible for chemical safety. UNEP has called for "a global commitment to the sound management of chemicals. The agency supports and tracks the progress of international agreements and treaties limiting the manufacture, environmental release and global transport of persistent pollutants, pesticides, hazardous waste, and mercury." The Strategic Approach to International Chemicals Management, a program supported by UNEP, provides a platform for coordinating international control of toxic chemicals and hazardous waste across a broad

range of stakeholders. UNEP has worked closely with the World Health Organization (WHO) to coordinate the removal of lead from gasoline in countries around the world.

SYNTHETIC CHEMICALS AND DISEASE IN CHILDREN

A large and growing body of evidence documents that toxic chemicals can cause disease, disability, and death in children. High-dose exposures can cause acute, clinically evident disease. Lower-dose exposures can cause subclinical injury (injury that is very real but detectable only through special testing), such as decreases in intelligence, shortening of attention span, reductions in fertility, and slowing of lung growth. When exposure to a neurotoxic pollutant is widespread, the resulting widespread subclinical neurotoxicity can reduce the intelligence, creativity, and economic productivity of entire societies.

Exposures to toxic chemicals in early life are linked not only to increased risks of disease in childhood, but also to increased risks of disease in later life. This recognition, termed the *developmental origins of health and disease concept*, derives from studies conducted by Barker and colleagues who found that undernutrition in utero is associated decades later with increased risks for hypertension, obesity, diabetes, and cardiovascular disease. Epigenetic programming of gene expression during windows of vulnerability in early development appears to be the underlying mechanism. Increased risks for disease in adult life have now been associated also with early-life exposures to toxic chemicals and appear to be mediated through epigenetic changes in gene expression. Among the health problems linked to toxic chemical exposures in early life are decreased cognition in adults who were exposed as children to lead, neurobehavioral disorders in children exposed to a range of developmental neurotoxicants, and cancer.

CHEMICAL POLLUTANTS OF MAJOR CONCERN

Air Pollutants

Air pollution—ambient air pollution and household air pollution—is the world's largest environmental threat to health and, according to the WHO, is responsible for an estimated 6.7 million deaths each year. The air pollutants of greatest concern for children's health are particulate matter (especially fine particulates less than 2.5 microns in aerodynamic diameter), photochemical oxidants (especially ozone), oxides of nitrogen, sulfur oxides, and carbon monoxide; these are the "criteria air pollutants" regulated by the U.S. EPA in the Clean Air Act. In the United States, approximately 60% of children live in areas that do not meet national ambient air quality standards (NAAQS), most commonly particulate matter and ozone. Globally, ambient levels of air pollutants can be magnitudes higher than the United States.

Fuel combustion is the principal source of air pollution. In high- and middle-income countries, combustion of fossil fuels—coal, oil, and gas—accounts for most air pollution. In low-income and lower middle-income countries, the major source is burning of biomass, such as wood, dung, straw, and charcoal. Coal is the single most highly polluting fossil fuel and the most important source of the greenhouse gas emissions that drive global climate change, but fixed and mobile oil and gas combustion are also major contributors. As the climate changes, wildfires are becoming more common and are further contributing to air pollution and climate change.

Elevated levels of ambient air pollutants are associated with respiratory problems in children, including decreased expiratory volume, wheezing, exacerbations of asthma, and slowed lung growth. Slowed lung growth leads to decreased lung volume and increases risk for respiratory disease in childhood, adolescence, and adult life. Long-term improvements in ambient air quality, especially reductions in levels of particulates and oxides of nitrogen, are associated with statistically and clinically significant improvements in lung growth in children, effects that appear likely to persist into adulthood and to reduce lifetime risk of pulmonary and cardiovascular disease.

Aside from the criteria air pollutants, other pollutants emitted from mobile, stationary, and area sources are considered *hazardous air pollutants* (HAPs), which are known or suspected to cause cancer, reproductive effects, or birth defects. Some common examples are metals such as mercury (neurotoxin), asbestos (mesothelioma, lung cancer), and volatile organic compounds such as polychloroethylene (reproductive effects, cancer). Diesel exhaust is a particularly concerning source of air pollution as it contains fine and ultrafine particulates (capable of reaching alveoli and getting absorbed into bloodstream) and multiple HAPs (e.g., formaldehyde), and has been classified by the International Agency for Research on Cancer as a known human carcinogen.

The effects of household air pollution on children's health are magnified by the fact that many children spend 80–90% of their time indoors, and pollutant levels can be 2-5 times higher indoors especially in poorly ventilated spaces. In 2020, the WHO estimated that 237,000 children <5 years old died from illnesses attributable to household air pollution. Secondhand tobacco smoke (SHS) is an especially hazardous constituent of indoor air pollution and a powerful trigger for asthma (see Chapter 759.1). Household products, particularly some disinfectants, cleaners, paints, and floor finishes, have also been connected to respiratory tract irritation and increased asthma morbidity. Allergens in indoor air can contribute to respiratory problems and include cockroach, mite, mold, and cat and dog allergens.

HEALTH HAZARDS OF UNCONVENTIONAL NATURAL GAS DEVELOPMENT (FRACKING)

Unconventional natural gas development (UNGD) using high-volume horizontal hydraulic fracturing (fracking) has made possible the cost-effective extraction of natural gas from previously inaccessible underground shale deposits and has catalyzed a 16-fold increase in fracking wells in the United States between 2000 and 2020. Natural gas has surpassed coal to become the major source of electricity generation in North America.

In fracking, large volumes of water containing a mix of chemicals (whose composition is a closely guarded secret) are injected at very high pressure through deep wells into shale deposits to break apart the rock and allow release of gas. The gas is brought up to the wellhead through return pipes, collected, and sent to market. In some areas, gas and oil occur together, and the gas may be burned off (flared) at the wellhead while the more valuable oil is piped to market.

The hazards of fracking to children's health include:

- *Toxic air pollution by volatile organic compounds released from fracking wells such as benzene, ethyl-benzene, hydrogen sulfide (H_2S), n-hexane, and methane:* Benzene and ethyl-benzene are known human carcinogens, H_2S and n-hexane are neurotoxicants, and methane is a climate pollutant that contributes to greenhouse gas emissions.
- *Traffic-related air pollution resulting from the large volumes of diesel truck traffic required to bring piping, chemicals, and water to drilling operations:* Diesel exhaust contains coarse and fine particulates, polycyclic aromatic hydrocarbons (PAHs), and formaldehyde, and has been classified by the International Agency for Research on Cancer as a known human carcinogen.
- *Water pollution by toxic chemicals:* Leaks of toxic materials into waterways occur commonly during fracking operations; in addition, much of the water injected into the wells returns to the surface containing proprietary injected chemicals, along with high concentrations of salt dissolved from underground deposits and naturally occurring radioactive materials. These chemicals have been shown to contaminate both ground and surface waters. Water pollution is a particularly severe problem in arid regions with limited water supplies.
- *Radon released from underground deposits:* Radon has been shown to contaminate air near wellheads, and high concentrations of radon have been identified in shipped gas. Additional, nonchemical hazards of fracking include incessant noise, high risk of vehicular injury to children from fast-moving heavy trucks on poorly maintained rural roads, societal disruption in rural communities, and extensive degradation of the environment.

Lead

See Chapter 761.

Mercury

See Chapter 760.

Asbestos

Between 1947 and 1973, asbestos was sprayed as insulation on classroom walls and ceilings in approximately 10,000 schools in the United States. It was also widely utilized in homes as pipe insulation and in floor tiles. Subsequent deterioration or unsafe removal of this asbestos can release asbestos fibers into the air. Asbestos is not a health hazard so long as it is intact, but once it becomes airborne, it can be inhaled by children to produce adverse health effects. Asbestos is a human carcinogen, and the two principal cancers caused by asbestos are lung cancer and mesothelioma. U.S. federal law requires that all schools be inspected periodically for asbestos and that the results be made public. Removal by an EPA-certified contractor is required only when asbestos is visibly deteriorating or is within the reach of children. In most cases, placement of barriers (drywall walls or drop ceilings) provides appropriate protection.

Pesticides

Pesticides are a diverse group of chemicals used to control insects, weeds, fungi, and rodents, and are used in large quantities in agriculture, homes, schools, parks, gardens, and recreational areas. Children are at risk of exposure when pesticides are used inside or outside in places where children live, learn, and play, and in rural areas they can be exposed to pesticide drift from fields that have been sprayed. Children employed in agriculture or living in migrant farm camps are at risk of direct exposure to pesticides. Diet is another major route of exposure because children are exposed to residual levels of multiple pesticides on fruit and vegetables, especially fruits and vegetables imported from countries where pesticide use is heavier than in the United States. Children can be acutely overexposed to pesticides and clinically evident poisoning results. High-dose exposure to neurotoxic insecticides such as the organophosphate and carbamate pesticides can cause acute neurotoxicity. Both classes of pesticides act through inhibition of acetylcholinesterase and are responsible for the largest number of acute poisoning cases. Symptoms include meiosis, excess salivation, abdominal cramping, vomiting, diarrhea, and muscle fasciculation. In severe cases, the child may experience loss of consciousness, cardiac arrhythmias, and death by respiratory arrest. The war gas sarin is an organophosphate. See Chapter 94 for treatment of poisoning from drugs, chemicals, and plants.

Pesticides can also cause a range of chronic toxic effects that include polyneuropathy and central nervous system (CNS) dysfunction (organophosphates), hormonal disruption and reproductive impairment (DDT, kepone, dibromochloropropane), cancer (aldrin, dieldrin, chlorophenoxy herbicides [2,4,5-T]), and pulmonary fibrosis (paraquat).

Prenatal exposure to the organophosphate pesticide **chlorpyrifos** at levels that produce no evident toxicity in pregnant women has been associated with neurodevelopmental disability in children with reduced cognitive function (lowered IQ), disordered executive function, and functional and anatomic changes in the brain discernible by functional magnetic resonance imaging (fMRI).

Two classes of pesticides of concern are synthetic herbicides and the neonicotinoid insecticides. Herbicides account for about 48% of total pesticide use, and their application is increasing. A major use of herbicides is in production of *genetically modified (GM) food crops*, mainly corn and soybeans that are engineered to be tolerant to **glyphosate (Roundup)**, the most used herbicide worldwide. Herbicides can be sprayed on herbicide-resistant crops throughout the growing season, and glyphosate-resistant, "Roundup-Ready," GM crops account for more than 90% of all corn and soybeans planted in the United States.

Studies of agricultural workers exposed occupationally to glyphosate and other herbicides have found evidence for increased incidence of non-Hodgkin lymphoma. On the basis of these studies and convergent results from toxicologic studies, the International Agency for Research on Cancer has determined that glyphosate is a "probable human carcinogen." Measurable levels of glyphosate metabolites are commonly detected in the urine of Americans.

The **neonicotinoids** are a class of neurotoxic pesticides developed in the 1980s to replace the organophosphates and carbamates. Use of neonicotinoids rose dramatically in the early 2000s, and the neonicotinoid insecticide, imidacloprid, is one of the most widely used insecticides in the world. A growing body of evidence indicates that neonicotinoids are toxic to bees and other pollinators at concentrations found currently in agricultural areas, and neonicotinoids are suspected of contributing to bee colony collapse disorder. In 2020, the EPA proposed a number of restrictions and precautions for neonicotinoid use. More than a dozen states have also introduced legislation limiting neonicotinoids, and several European countries have banned or severely restricted their use. Almost no information is available on the possible developmental or pediatric toxicity of the neonicotinoids. This is another example of a new pesticide in widespread use without prior testing for health impacts on children.

Children's exposures to pesticides can be reduced by minimizing applications to lawns, gardens, schools, and playgrounds; adapting techniques of integrated pest management; and reducing pesticide applications to food crops. Pediatricians and parents can look to resources including the National Pesticide Information Center (NPIC) and the EPA for guidance on integrated pest management and safer use of pesticides in and around the home. Consumption of organic produce has been shown to dramatically reduce pesticide exposure in school-age children. Families can choose organic produce when available and cost-competitive but should not avoid a diet rich in fruits and vegetables if organic options are not feasible.

Persistent Organic Pollutants: Per- and Poly-fluoroalkyl Substances and Chlorinated Hydrocarbons

Per- and Poly-fluoroalkyl Substances. Per- and poly-fluoroalkyl substances (PFAS) are a group of synthetic chemicals that have been used in industrial processes and consumer products because they are resistant to water and heat, and do not break down in the environment. In addition, they can move through soil into drinking water sources and can build up in fish and wildlife (bioaccumulate). They may make clothing stain resistant and also reduce friction. PFAS are also known as "forever chemicals" due to their persistence in the environment, as their strong carbon-fluorine chain is resistant to degradation. NHANES has documented universal exposure to some PFAS due to their ubiquity in consumer products (e.g., nonstick pans, take-out food containers, water-resistant textiles) and the food chain. PFAS have also been detected in drinking water sources (both municipal systems and private wells) across the United States. In March 2023, the EPA proposed a draft of enforceable maximum contaminant levels (MCLs) for six different PFAS chemicals in public drinking water systems; the final regulations are expected by the end of 2023. Several states have enacted their own MCLs for various PFAS compounds; these state MCLs will have to become at least as stringent as the federal MCLs (once finalized).

Ingestion of contaminated food, water, or household dust is the major route of exposure to these chemicals. PFAS can cross the placenta and enter breastmilk. The half-life in the body can be days to decades, depending on the specific PFAS compound. Epidemiologic studies suggest a link between PFAS exposure and increased cholesterol levels, altered liver function tests, decreased antibody response to childhood vaccines, increased risk of preeclampsia/high blood pressure during pregnancy, and cancer (kidney and testicular). Health outcome studies in highly exposed communities are ongoing.

Chlorinated Hydrocarbons. The chlorinated hydrocarbons are a large and diverse class of chemicals that include insecticides (DDT), plastics (polyvinyl chloride), electrical insulators (PCBs), and solvents (trichloroethylene). Highly toxic chlorinated dioxins and furans are formed during synthesis of chlorinated herbicides or as by-products of plastic combustion. These materials are widely dispersed and highly persistent in the environment. Dioxins and furans are known human carcinogens. Brominated flame retardants are used in carpets, furniture, and computers and are environmentally persistent.

The embryo, fetus, and young child are at particularly high risk of injury from halogenated hydrocarbons. All of these compounds are lipid soluble. They readily cross the placenta, and they accumulate in breast milk. Intrauterine exposure to PCBs and brominated flame retardants has been linked to persistent neurobehavioral dysfunction

in children manifested by cognitive impairment (reduced IQ), shortening of attention span, and behavioral disorders.

Consumption of fish from contaminated waters is a major source of children's exposure to PCBs. Children can be exposed in utero or through breast milk. To protect children and pregnant women against PCBs in fish, government agencies have issued advisories concerning fish consumption for certain lakes and rivers. Combustion of medical wastes containing polyvinyl chloride and the use of chlorine to bleach paper products are major preventable sources of environmental dioxin emissions and should be discouraged. Older fluorescent light ballasts that were installed decades ago in schools in the United States are another source of PCB exposure. PCB-containing ballasts should be removed from schools as soon as possible to prevent environmental contamination. Removal must be performed by trained workers.

Endocrine Disruptors

Endocrine disruptors are synthetic chemicals that mimic, block, or alter the actions of normal hormones such as estrogen, testosterone, growth hormone, insulin, and thyroid hormone. Synthetic endocrine disruptors are manufactured in volumes of millions of pounds per year. They include phthalates, bisphenol A, perchlorate, certain pesticides, brominated flame retardants, certain metals, and dioxins. These chemicals are widespread today in consumer products such as soaps, shampoos, perfumes, and plastics. They are widely disseminated in the environment and encountered in air, food, and drinking water.

Exposures to endocrine disruptors in early human development are especially hazardous. Even extremely low-dose exposures during critical early periods can lead to lasting impairments in organ function and to increased risk of disease. Reproductive effects are one consequence of early life exposures to endocrine disruptors. Endocrine disruption is implicated in the epidemiologic observations of a trend toward earlier thelarche and menarche in females, with rising rates of testicular cancer and hypospadias, and with diminishing sperm counts. Among the most clearly documented reproductive effects of early life exposures to endocrine disruptors are adenocarcinoma of the vagina in women and cryptorchidism in men whose mothers took diethylstilbestrol (DES). Another well-documented effect is shortening of the anogenital distance, a measure of in utero feminization, in infant males whose mothers had elevated exposures to phthalates during pregnancy.

Early life exposures to endocrine disruptors can have adverse effects on brain development. Prenatal exposure to low molecular weight phthalates is associated with shortening of attention span in children 4-9 years old, as well as with increased risk for autistic behaviors. Prenatal exposure to bisphenol A has also been linked to behavioral anomalies.

Endocrine disruptors have been reported to have adverse impacts on lipid metabolism and to increase the risk for obesity. Higher urinary levels of bisphenol A are associated with obesity-related outcomes, such as cardiovascular disease, in a cross-sectional analysis of NHANES 2003-2004 data in adults.

Early life exposures to endocrine disruptors, most notably DDT, are linked with increased risk for cancer. A long-term epidemiologic study of women in California found that those who were exposed in utero to high levels of DDT have increased risk for breast cancer in adult life 40-50 years later.

Environmental Carcinogens

Leukemia and brain cancer, the two most common forms of pediatric malignancy in the United States, both increased in incidence from 1972 to 2018, despite declining mortality. The cumulative increase in incidence for childhood leukemia was more than 20%, and for brain and CNS cancer more than 40%. In the same time period, testicular cancer in young men, ages 15-30 years, more than doubled in incidence and is occurring at younger ages. These increases are too rapid to be of genetic origin and are not likely due to better diagnostic capabilities. They are most probably the result of still undefined exposures in the environment. Cancer is now the second-leading cause of death in American children, surpassed only by injuries.

Children may be exposed to carcinogenic pollutants in utero or after birth. Children appear more sensitive than adults to certain chemical carcinogens and also to ionizing radiation (see Chapter 758). The potential for chemical carcinogenesis in utero was initially recognized with the discovery that clear cell adenocarcinoma of the vagina could develop in young women who were exposed in utero to DES.

Carcinogenesis may be associated with exposures in the home and community. Children of asbestos workers and children who have grown up near asbestos plants have been found to have an elevated incidence of mesothelioma. Children who attended elementary school in communities containing synthetic rubber plants have been shown to be at increased risk of leukemia as a result of their exposure to 1,3-butadiene, a known human carcinogen and a major component of synthetic rubber. Children who grow up on farms have elevated rates of leukemia; pesticides are suspected of playing an etiologic role. Intrauterine exposure to trichloroethylene via contaminated drinking water has been associated with an increased incidence of leukemia among females living near an industrial facility and industrial waste site.

Routes of Exposure

Transplacental. Heavy metals such as lead and mercury, fat-soluble compounds such as PCBs and DDT, and endocrine disruptors such as phthalates, readily cross the placenta. They may have serious and irreversible toxic effects on the developing nervous, endocrine, and reproductive organs, even at very low levels. The American College of Obstetricians and Gynecologists have recognized the hazards of environmental exposures during pregnancy and provide detailed guidance for counseling to reduce these exposures in their 2021 statement Reducing Prenatal Exposure to Toxic Environmental Agents (Table 259.2).

Water. Approximately 200 chemicals have been detected at various levels in water supplies including contaminants like lead, solvents, pesticides, and emerging chemicals like PFAS. Lead is an especially common contaminant. Water supplies are generally lead-free at the source but can become contaminated by lead that dissolves from lead pipes and from lead-containing plumbing fixtures. Lead is especially likely to dissolve from pipes and plumbing when the water is acidic, as happened in Flint,

Table 759.2 Toxic Chemicals or Pollutants and Reported Association with Adverse Reproductive Health Outcomes*

CHEMICAL OR POLLUTANT WITH REPORTED ADVERSE ASSOCIATION	POTENTIAL HEALTH EFFECT
Antineoplastic drugs, bisphenol A (BPA), cigarette smoke, ethylene oxide, formaldehyde, polybrominated diphenyl ether (PBDE) flame retardants, solvents	Infertility and miscarriage
Air pollutants from fracking, ambient air pollutants, antineoplastic drugs, cigarette smoke, ethylene oxide, formaldehyde, perfluorochemicals (PFAS),* pesticides, phthalates, PBDEs, toluene	Preterm birth and low birthweight
Ambient air pollutants, BPA, lead, mercury, pesticides, phthalates, PBDE flame retardants, polychlorinated biphenyls (PCBs)	Neurodevelopmental impairment

*Associations noted are from reports of animal and limited human studies. Although there are reported associations between exposures and adverse obstetric outcomes, an association does not necessarily mean that the exposure is a cause of the outcome. More research is needed to understand if there is causality and, if so, at what level of exposure or use of a specific product.

Modified from American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Reducing prenatal exposure to toxic environmental agents: ACOG Committee Opinion, Number 832. *Obstet Gynecol.* 2021;138(1):e40–e54. Table 1.

Michigan, in 2014. The highest levels of lead occur in water that has been standing in lead pipes overnight. It is wise therefore to run water for 2-3 minutes each morning before making up infant formula. Solvents and components of gasoline such as methyl tertiary-butyl ether and benzene are commonly encountered in groundwater. Chemical contaminants from gas drilling can contaminate water in areas where fracking is taking place. Herbicides, such as glyphosate and atrazine, are commonly found contaminants in drinking water in agricultural areas.

In the United States, the EPA regulates approximately 90 drinking water contaminants including organic chemicals, inorganic chemicals, radionuclides, and infectious agents in public water systems. The municipal water systems are responsible for ensuring that the regulated contaminants are below MCLs and will notify customers of any exceedance and steps to address the issue. Those families using private wells, however, are responsible for testing their water on a regular basis. Families with well water can be directed to the EPA private well website or their local health department for guidance on the recommended tests.

Air. Vehicular emissions are the major source of urban air pollution, notably ground-level ozone and particulate matter. Diesel exhaust is a human carcinogen. Coal-fired power plants are another major source of outdoor air pollution. In rural areas, wood smoke can contribute to air pollution. Pediatricians and parents can follow local air quality alerts that include recommendations to reduce risk especially for sensitive groups (airnow.gov). Children living in the vicinity of smelters and chemical production plants can be exposed to toxic industrial emissions such as lead, benzene, and 1,3-butadiene. Specific information about toxic air pollution release in a community can be obtained via the Toxics Release Inventory (www.epa.gov/toxics-release-inventory-tri-program).

Food. Many chemicals are intentionally added to food to improve appearance, taste, texture, or preservation, but many such chemicals have been poorly tested for potential toxicity. Residues of many pesticides are found in both raw and processed foods. Levels of pesticides are lower in organic produce than in conventionally grown fruits and vegetables. Children who consume organic produce have substantially lower urinary pesticide levels than children who eat conventional produce. Elevated levels of methylmercury can be found in large predator fish such as swordfish, shark, king mackerel, and tuna sushi; families should be encouraged to follow fish advisories. Baby foods can contain trace amounts of metals, and rice and rice-based products (especially those made of brown rice) can have inorganic arsenic.

Breast Milk. Breast milk provides many benefits to infants including protection from illness, reduction in allergic diseases like asthma, and reduced risk of obesity, among many others. Breast milk can also be a route of exposure to environmental chemicals including fat-soluble persistent organic pollutants, pesticides, and metals. In almost all situations, the benefits of breastfeeding outweigh the risks of these exposures, and numerous professional organizations support breast milk as the first choice for infant feeding. In addition, chemical regulation can further reduce unnecessary exposure through this route.

Work Clothes. Illnesses in children sometimes may be traced to contaminated dust from parents' work clothes; toxicity from lead, beryllium, dioxin, organophosphate pesticides, and asbestos has occurred. Such exposure (termed *fouling the nest*) can be prevented by providing facilities at work for changing and showering. If facilities are not available, caregivers can be advised to change clothes and shoes before returning home and wash work clothes separately from household laundry. Some work activities and hobbies that occur at home can also expose children to toxins including metals like lead and solvents.

School. Children may be exposed in schools, kindergartens, and nurseries to lead paint, molds, asbestos, tobacco smoke, pesticides, and hazardous arts and crafts materials. Substantial opportunities for prevention exist in the school environment, and pediatricians are often consulted for advice. The EPA has school related environmental health materials (www.epa.gov/schools) that can be shared with stakeholders.

Child Labor. Four to five million children and adolescents in the United States work for pay, and child labor is widespread around the world. Working children are at high risk of physical trauma and injury. They also may be exposed to a wide range of toxic chemicals, including pesticides in agriculture and lawn work, asbestos in construction and building demolition, and benzene in pumping gasoline.

THE PHYSICIAN'S ROLE

Pediatricians have time and again played key roles in the initial recognition of diseases caused by toxic chemicals. Every pediatrician needs to be an "alert clinician" open to the possibility of discovering new diseases in children caused by hazardous exposures in the environment. In considering the origins of noninfectious disease, pediatricians should ask about the home environment, parental occupation, unusual exposures, and neighborhood factories. An environmental cause is particularly likely when several unusual cases of disease or constellations of findings occur together. Any adolescent with a traumatic injury may have been injured at work.

The history is the single most important instrument for obtaining information on environmental exposures (Table 759.3). Information about current and past exposures (including questions about work and travel to or residence in developing countries) should be sought routinely for every new patient. The age of the patient can help focus questions and provide anticipatory guidance on key exposures of concern, such as screening for common sources of lead exposure in young children. Patients with asthma should be evaluated for exposure to common allergens (mold, cockroaches, dust mites) and irritants (tobacco smoke, strong odors). Children with neurodevelopmental disorders should be assessed for pica and other behaviors that increase their risk of toxic exposures. Consider targeted environmental health history questions in patients with illness of unclear causation. Changes in patterns of exposure or new exposures may be especially important. If suspicious information is elicited, more detailed follow-up should be pursued. Referral to a state or local health department or to a Pediatric Environmental Health Specialty Unit may be indicated (https://www.pehsu.net/). Accurate diagnosis of an environmental cause of disease can lead to better care of sick children and prevention of disease in other children.

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759.1 Tobacco

Judith A. Groner

Cigarette smoking is the single most preventable cause of morbidity and mortality, contributing to over 480,000 annual deaths in the United States. The most common reason that people smoke is nicotine addiction, and people who start smoking at an earlier age are more likely to develop a severe addiction than those who start when they are older. In 2022, 4.5% of middle school students and 16.5% of high school students reported current tobacco use (see Chapter 157.2). While youth use a variety of tobacco products, e-cigarettes are the most common. E-cigarettes work by heating liquid to produce an aerosol that is then inhaled into the lungs; this process is called **vaping**. While the long-term health effects of vaping are still being evaluated, the 2019 E-cigarette or Vaping Use-Associated Lung Injury (EVALI) epidemic drew attention to the dangers associated with e-cigarette use (see Chapter 450).

COMPOSITION OF SECONDHAND SMOKE AND TOXICITIES

Along with active tobacco use, secondhand tobacco smoke (SHS) exposure is a very serious health hazard for both children and adults. SHS is a mixture of approximately 7,000 chemicals and is made up of the mainstream smoke exhaled by the smoker and side-stream smoke expelled from the end of a lit tobacco product. At least 70 carcinogens have been identified in SHS, along with 250 chemicals that are toxic to the CNS, immune system, heart, and liver.

SHS also contains particulate matter, which is an independent health hazard. Particulate matter is microscopic solid and liquid matter suspended in air, which can be inhaled and enter the circulation. The most studied of these include polycyclic aromatic hydrocarbons (PAHs) and the tobacco-specific nitrosamines, which are both carcinogenic. Most particulate matter in side-stream smoke is unfiltered by the smoker

Table 759.3 Clinical Tools for Incorporating Environmental Health into Patient Care

Tips for implementing a focused environmental health history:

1. *Age:* Patient age can help direct screening questions and anticipatory guidance on key exposures of concern, such as lead screening questions for young children. Refer to American Academy of Pediatrics (AAP) Bright Futures or the Pediatric Environmental Health Toolkit for age-specific information.
2. *Location*: Local environmental conditions can help direct environmental guidance. For example, in rural communities with high prevalence of private wells for drinking water, families can be counseled on the importance of routine well water testing.
3. *Symptoms*: Consider environmental exposures in the differential diagnosis. For example, carbon monoxide exposure should be on the differential for families presenting with headaches and flulike symptoms (afebrile, no cough).
4. *Asthma*: assess for common environmental asthma triggers in the home such as mold, cockroaches, mice, environmental tobacco smoke, furry pets, cleaning chemicals, strong odors/fragrances
5. *Neurodevelopmental disorders*: assess for pica behavior and other risk factors that may increase the likelihood of exposures (e.g., lead); assess for use of alternative medications

Components of environmental health history (can be adapted based on patient scenario):

General home health and safety:
- Age and condition of home (lead paint in pre-1978 home)
- Carbon monoxide and fire alarms
- Heat and cooking sources (stove ventilation, safe space heater use)
- Tobacco smoke
- Radon (test basement and first/second floors)
- Cleaning products-safe storage and use (e.g., bleach)

Common indoor allergens:
- Water leaks/mold
- Pests (cockroaches, mice) and pesticide use

Water and food:
- Drinking water source (well water requires routine testing)
- Fish advisories (methylmercury) for pregnant persons and children
- Fresh produce (rinse well before eating)
- Rice-based products (vary grains to reduce arsenic exposure)

Jobs and hobbies:
- Caregiver jobs (contaminant transfer from clothing, shoes)
- Adolescent jobs (safety)
- Hobbies in the home (paints, chemicals)
- Sun protection outdoors
- Noise from headphones, toys

Resources and tools for clinical practice:

Environmental history forms:
- National Environmental Education Foundation (NEEF) has a general environmental history and an asthma-focused environmental history (English and Spanish): www.neefusa.org/resource/pediatric-environmental-history
- World Health Organization (WHO) Paediatric Environmental Health History (Green Page) provides a series of concise questions to assess potential exposures: https://www.who.int/publications/m/item/children-s-environmental-record--green-page

Evidence-based clinical resources:
- The Green Book: American Academy of Pediatrics. *Pediatric Environmental Health*. 4th ed. Etzel RA, Balk SJ, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2019.
- Pediatric Environmental Health Specialty Unit (PEHSU). One PEHSU is located in each of the 10 federal regions in the United States. The PEHSUs provide online classroom materials, resources, and access to network of experts in pediatric and reproductive environmental health: www.pehsu.net
- The Pediatric Environmental Health Toolkit is an online clinical tool that providers can use to access information on common exposures, including identification of sources of exposure and provision of targeted anticipatory guidance: https://peht.ucsf.edu.
- Bright Futures provides guidance for well child care for children and adolescents (includes key environmental anticipatory guidance): https://brightfutures.aap.org/.
- American College of Obstetricians and Gynecologists (ACOG). Reducing Prenatal Exposure to Toxic Environmental Agents: https://pubmed.ncbi.nlm.nih.gov/34259492/

Resources for patients:
- Prescriptions for Prevention are tools that link patients to evidence-based simple steps to reduce or prevent common environmental exposures (English and Spanish): https://nyscheck.org/rx
- National Institute of Environmental Health Sciences (NIEHS). Environmental health topics: https://www.niehs.nih.gov/health/topics/index.cfm

and is in the submicron (<1 μm diameter) range, meaning that it is classified as fine particulate matter. These are smaller than the particles in mainstream smoke and can penetrate deeper into the lungs, resulting in higher toxicity through oxidative stress and inflammation. Short- and long-term exposure to fine particulate matter contributes to the aggravation of asthma and other respiratory diseases, lung and other cancers, cardiovascular disease, and death.

SHS concentration in the indoor environment depends on the number of cigarettes smoked in a period, the volume of the room, the ventilation rate, and other processes that eliminate pollutants from the air. There are multiple mechanisms by which SHS causes injury to the respiratory tract, and injury to the cardiovascular system is due to endothelial cell dysfunction due to smoke exposure and its prothrombotic effects.

THIRDHAND SMOKE

Thirdhand smoke (THS) was defined in 2011 as consisting of the residual tobacco smoke pollutants that remain on surfaces and in dust after tobacco has been smoked. These toxins are reemitted into the gas phase or react with oxidants and other compounds in the environment to yield secondary pollutants. These residual pollutants can be detected in the indoor environment well after being generated. About half the particulate matter from SHS is still airborne after 5-6 hours. Many chemicals, such as nicotine and some PAHs, exist in both the gaseous and the particulate phase of SHS. Classified as "semi-volatile," their ability to change form according to environmental conditions means that they remain detectable in the indoor environment for longer periods after active smoking has ceased. These components in dust and on surfaces can be ingested, inhaled, or even absorbed through the skin. The health implications of THS are not well understood, but there is growing evidence both in vitro and in vivo of health harms of THS exposure, particularly respiratory symptoms. Young children are at higher risk of health issues due to THS absorption because of their hand to mouth behaviors, crawling near surfaces, time spent in the home, and increased respiratory rate.

TOBACCO USE AND EXPOSURE IS A HEALTH RISK DISPARITY

Tobacco use, and hence childhood exposure, is found disproportionately among socially disadvantaged low-income populations, who can least afford tobacco and SHS-related illness and evidenced-based treatment for nicotine addiction. There has been a profound decrease in smoking rates among the middle and upper classes within the United States since the 1960s (83% decrease), but the rate of decrease is much less (39%) among lower income groups. The smoking rate for the overall U.S. population is approximately 12.5%, but it is as high as 32% among adults with a high school equivalency degree. Because of these disparities in smoking rates among adults, children born into low-income homes are more likely to be exposed to SHS. More than 38% of U.S. children age 3-11 years were exposed to tobacco smoke from 2017 to 2018, based on a biologic marker of exposure, serum cotinine levels. Children from low-income homes have the highest rates of biologically measured SHS exposure; for every decrease in family income ratio, serum cotinine levels increase by 1.18 ng/L among children. Having a parent who smokes has also been shown to be an independent risk factor for food insecurity in children.

MATERNAL SMOKING DURING PREGNANCY AND TOBACCO SMOKE EXPOSURE DURING PREGNANCY

The effects of maternal smoking on the fetus are profound and can be divided into pregnancy-related and long-term effects. Fetal exposure is one of the most important modifiable risk behaviors for childhood and long-term health.

Pregnancy-Related Effects

Maternal smoking increases the risk of placenta-associated complications of pregnancy, with an increased rate of placental abruption and placenta previa among maternal smokers. Both active maternal smoking and secondhand maternal tobacco smoke exposure have been shown to reduce birthweight and to increase the risk of preterm birth. In utero tobacco exposure from either maternal active tobacco product use or maternal SHS exposure increases the rate of stillbirth. Smoking both during and after pregnancy is a risk factor for **sudden infant death syndrome (SIDS)**; one study found that any smoking during pregnancy was associated in a doubling of SIDS risk and that there was a linear correlation between the average number of cigarettes smoked daily and an increased risk for SIDS. These associations are modifiable by public policy. Several countries in Europe have shown decreased perinatal complications after comprehensive smoke-free laws; within the United States, pregnancy complications and SIDS are inversely related to tobacco taxation levels.

Long-Term Effects

Maternal smoking in early pregnancy is considered causal for orofacial clefts (Surgeon General Report 2014).

Both active smoking during pregnancy and SHS exposure of the mother increases the *child's* later risk of being overweight or obese. This finding may appear surprising due to the long-known relationship between smoking during pregnancy and low birthweight. This relationship has been shown in multiple epidemiologic studies and is robust to adjustment for potential confounders, such as parental body mass index (BMI), breastfeeding, family diet, and lifestyle.

Maternal smoking during pregnancy has been associated with both an increased risk of learning problems and neurobehavioral issues during childhood. The adverse effects of prenatal smoking on child neurodevelopment include poor language development and reduction in cognitive functioning. Prenatal exposure to smoking may also reduce the child's motor performance, mental development (measured by the Bayley Scales of Infant Development), IQ scores, and language development through age 3 years. This exposure may also increase the risks of several child behavioral problems, including externalization of aggressive and hyperactive behavior, prolonged periods of verbal or physical aggression and socially undesirable behavior (conduct disorder) throughout childhood, and delinquency in later childhood. In one study, a dose-response relationship with increasing severity of poor school performance was related to the number of cigarettes the mother smoked during pregnancy.

Maternal Smoking During Pregnancy and Lung Development

Smoking during pregnancy is associated with poor lung growth and function in the offspring and with a greater risk for wheezing between age 2-4 years. According to the Surgeon General Report (2014), there is sufficient evidence to consider this relationship to be causal.

POSTNATAL SECONDHAND SMOKE EXPOSURE—EFFECTS ON THE CHILD

Respiratory

Children exposed to SHS have a higher rate of asthma prevalence and greater asthma severity. The Surgeon General Report (2006) concluded that there is a causal relationship between parental smoking and cough, phlegm, wheezing, and breathlessness, along with asthma, among school-age children. Children with SHS exposure have a weakened response to inhaled corticosteroids. Children with asthma who are SHS-exposed are more likely to have an acute care visit, an overnight hospital stay, and a higher number of hospital admissions than children with asthma and no SHS exposure. The rate of hospital readmissions for asthma has been associated with the level of the child's saliva cotinine, a biomarker of smoke exposure, and this is true even at very low levels of exposure.

Tobacco smoke exposure is a cause of lower respiratory tract infection in children. Findings of the Surgeon General in 2006 were updated by a systemic review of parental and household smoking and risk of lower respiratory tract infections in infancy in 2011. The strongest relationship was for bronchiolitis, where the risk of any household smoke exposure was increased in the first two years of life.

SHS exposure during childhood increases the rate of middle ear disease, including acute, recurrent otitis media and chronic middle ear effusion. The Surgeon General Report (2006) rated this evidence as sufficient to infer a causal relationship between parental smoking and middle ear disease in children.

Cardiovascular Effects

Tobacco smoke exposure during adulthood has been linked to an increased risk of cardiovascular disease. Evidence links childhood exposure to findings of preclinical atherosclerosis. These include increased carotid intima-media thickness and decreased flow-mediated dilation, both indirect tests for preclinical changes leading to atherosclerosis during adulthood. Other findings have included increased inflammation as measured by C-reactive protein, abnormal lipid profiles, higher blood pressure, and increased rates of metabolic syndrome among SHS-exposed children and youth.

Infection

Childhood exposure to SHS is related to increased rates of invasive meningococcal disease in children less than 5 years old. SHS in the home doubled the risk of invasive meningococcal disease with some evidence of a dose-response relationship. The strongest effect was seen in children under 5 years, with SHS exposure more than doubling the rate of meningococcal disease. This relationship was seen both with prenatal smoking and postnatal exposure.

SHS exposure has also been shown to increase the severity of influenza among children hospitalized for the disease. Children with SHS exposure were 4.7 times more likely to be admitted to intensive care and had a 70% longer length of stay than nonexposed children, after controlling for multiple potential confounding factors.

Healthcare Utilization

Children and teens age 3-19 years who are SHS-exposed had higher healthcare utilization compared with nonexposed peers based on an analysis of NHANES data from 2009–2012. Children with high SHS exposure based on serum cotinine were almost three times more likely to have an overnight hospital stay and two times as likely to have a higher number of total hospital admissions as children with no exposure.

Special Vulnerable Pediatric Populations

There is evidence that SHS exposure exacerbates disease processes among children with significant chronic health conditions. Children with sickle cell disease who are exposed to SHS have increased morbidity, specifically increased rates of emergency department visits, and hospitalizations for vasoocclusive crisis and acute chest syndrome (see Chapter 511.1). In addition, tobacco smoke exposure is also associated with pulmonary function abnormalities among children with sickle cell disease, independent of their baseline disease.

Children with cystic fibrosis (CF) are another vulnerable population in which SHS exposure presents an additive threat to overall health. Core health issues for this group of children include problems with growth, lung function, and pulmonary infections (see Chapter 454). SHS-exposed children with CF had decreased growth between 4 and 12 months compared with non–SHS exposed infants. Furthermore, tobacco smoke exposure was associated with increased bronchodilator responsiveness and air trapping, and with increased methicillin-resistant *Staphylococcus aureus* and anaerobic growth on respiratory culture. Tobacco smoke exposure can be considered a modifiable risk factor for children with sickle cell disease and CF.

TREATMENT FOR TOBACCO USE AND SECONDHAND TOBACCO SMOKE EXPOSURE

There is no risk-free level of youth tobacco use or SHS exposure. Thus the best method to treat tobacco use and SHS exposure is to eliminate this exposure by helping adolescents and their caregivers quit smoking. Methods to reduce exposure such as "smoking outside" or wearing a "smoking jacket" have not been shown to eliminate biochemically confirmed SHS exposure. A meta-analysis of six controlled trials aimed specifically at SHS exposure reduction for children (not parental smoking cessation) showed some reduction in tobacco smoke pollution post intervention. However, all homes had significant tobacco-related air pollution at the end of the study period.

The pediatric office has long been considered an excellent venue for pediatricians to screen for youth tobacco use as well as children's SHS exposure and to intervene with youth and their caregivers. The American Academy of Pediatrics (AAP) recommends that providers:

1. Inquire about tobacco use and tobacco smoke exposure as part of health supervision visits and visits for diseases that may be caused or exacerbated by tobacco smoke exposure.
2. Include tobacco use prevention as part of anticipatory guidance.
3. Address parent/caregiver tobacco dependence as part of pediatric healthcare.
4. Offer tobacco dependence treatment and/or referral to adolescents who want to stop smoking.

The United States Preventative Services Task Force also recommends that primary care clinicians provide school-age children and adolescents who have not started to use tobacco with interventions (including education or brief counseling) to prevent initiation of tobacco use. The "Ask-Counsel-Treat" (ACT) model developed by the AAP provides tips on addressing youth tobacco use in the office (available at https://www.aap.org/en/patient-care/tobacco-control-and-prevention/youth-tobacco-cessation/tobacco-use-considerations-for-clinicians/); it is recommended that screening begin at age 11. The Clinical Effort Against Secondhand Smoke Exposure (CEASE) is a program that trains pediatricians and their office staff to systematically provide cessation counseling and interventions to caregivers who smoke. The CEASE model is (1) **ask** if anyone in the home or who cares for the child smokes; (2) **assist** the patient or caregiver with quitting by providing brief counseling, pharmacotherapy, or appropriate referrals; and (3) **refer** the smoker to evidence based cessation treatments, including telephone-based Quitlines or Text to Quit services. The CEASE model (found at https://www.massgeneral.org/children/cease-tobacco) involves training pediatricians to provide smoking cessation pharmacotherapy to caregivers who wish to quit smoking; it includes tools to both identify caregivers who smoke and facilitate pediatric healthcare providers' delivery of counseling, medications, and referral for tobacco treatment.

Despite the AAP recommendations for pediatricians to incorporate these methods into practice, a meta-analysis in 2016 of controlled trials in routine healthcare settings of child SHS exposure reduction did not show an intervention effect. However, three controlled trials of maternal postpartum smoking relapse prevention did demonstrate beneficial outcomes of the intervention.

Decreasing smoking initiation among youth will prevent the children of the future from SHS exposure. Ninety percent of smokers initiate use before 19 years of age, and 80% of youth who are smokers persist in smoking in adulthood. Of those, half will die earlier than their nonsmoking peers. After many years of individual states working to enact stricter tobacco laws, new federal legislation known as Tobacco 21 was signed in 2019 that raised the minimum age for sale of tobacco products from 18 to 21 years nationwide. By increasing the age of tobacco purchase to 21 years, there is hope that a whole generation of smoking can be prevented.

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759.2 Marijuana Smoke Exposure

Karen M. Wilson

Unlike tobacco smoke exposure, which has long been recognized as a cause of morbidity and mortality among nonsmokers, marijuana smoke exposure is far less well studied. In 2021, 13.2 million persons age 12 years or older used marijuana on a daily or almost daily basis in the past 12 months, an increase from the 5.7 million daily or almost daily users in 2013 (see Chapter 157.3). The use of marijuana has been increasing in both acceptability and legality in the past 20 years. Current use of marijuana is more common among males and younger adults (18-34 years vs 35 years or older), and those with less than a high school degree. As of 2023, 38 states allow the legal use of marijuana for medical reasons, and 24 states plus Washington DC and Guam have legalized its recreational use. Analysis of poison control center calls for exposure to marijuana for children under 6 years of age showed an increase of 148% from 2006 to 2013; from 4.2/1 million children to 10.4/1 million. Tobacco-smoking parents with young children residing in the home are four times more likely to use marijuana as compared with nontobacco smoking parents. About 38% of young children in the United States are exposed to tobacco smoke, compared to an estimate of 15% of children exposed to marijuana smoke. Studies examining the presence of biomarkers of marijuana smoke exposure have found an exposure prevalence of 16% in young children hospitalized for bronchiolitis in Colorado, and 21% in children 0-3 years being seen at a clinic in New York City.

COMPONENTS OF MARIJUANA SMOKE

While marijuana can also be aerosolized or ingested as hash oil or leaf, combusted marijuana is still the most common form. A recent analysis of data from the U.S. National Health and Nutrition Examination Survey (NHANES) finds that daily marijuana users have higher levels of combustion biomarkers (e.g., volatile organic compounds and polycyclic aromatic hydrocarbons (PAHs) than nonusers. In addition to the particulates and other chemicals of combustion, marijuana comprises two primary active chemicals: Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Exposure to combustion products likely extends to adjacent nonusers, as has been shown for tobacco smoke. Most states with legal marijuana use do not have any restrictions on combustible marijuana use in the presence of children.

IMPACT OF MARIJUANA SMOKE EXPOSURE

While there is clear research on the dangers of secondhand tobacco smoke (SHS), there have been very few studies examining the impact of marijuana smoke exposure. Secondhand marijuana smoke contains particulate matter that is known to be harmful when inhaled, in addition to other toxic and carcinogenic chemicals such as volatile organic compounds, PAHs, and aromatic amines. Studies in adults have demonstrated that it is possible to get a "contact high" from intense exposure. Even brief exposures have been found to impair vascular endothelial function in animal models. Children can be exposed to secondhand and thirdhand marijuana smoke when parents or other household contacts smoke indoors, similar to children living with tobacco smokers. Also similar to tobacco, children could be exposed to marijuana smoke through incursions from neighboring apartments; in a New York City sample, 31% of parents reported marijuana incursions, whereas 34% reported tobacco incursions. Neonates can be exposed to marijuana prenatally or through breast milk. Prenatal exposure has been linked to growth restriction and neonatal intensive care admissions, as well as behavioral issues such as impulsivity. Prenatal exposure has also been linked to impaired executive functioning in young adulthood. One study examined the role of indoor cannabis smoke and health; although they found increased particulates in homes with cannabis use, there was no statistically significant difference in health outcomes.

TREATMENT

In the absence of convincing data showing that marijuana is not harmful, parents should be counseled to avoid exposing their children to marijuana smoke, to lock marijuana in a safe place out of reach of any children, to avoid edibles in appealing or non–child proof packaging, and to be cautious about their own level of impairment if they do choose to use legal marijuana.

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Chapter 760

Heavy Metal Intoxication

Prashant V. Mahajan

Lead, mercury, arsenic, and cadmium, four of the World Health Organization's (WHO) "Ten chemicals of greatest public health concern," are the heavy metals posing the greatest threats to humans. The most prevalent of these exposures is lead (see Chapter 761).

Heavy metal intoxication results in multiorgan toxicity through widespread disruption of vital cellular functions. A meticulous history of environmental exposure may be necessary to correctly identify heavy metals as the source of the protean manifestations associated with such exposure. Arsenic exposure can occur from contaminated food or water; globally, more than 140 million people are estimated to be chronically exposed to drinking water containing high arsenic levels. Mercury exposure occurs primarily through food; fish is a major source of methyl mercury exposure.

ARSENIC

Arsenic is a metalloid that exists in four forms: elemental arsenic, arsine gas, inorganic arsenic salts (pentavalent arsenate form or trivalent arsenite form), and organic arsenic compounds. Toxic manifestations are higher in the more soluble and higher-valence compounds. **Arsine gas** is the most toxic form of arsenic. Mass poisonings from exposure to arsenic have occurred throughout history, including one in 1998 in Wakayama, Japan, in which 70 people were poisoned. Children may be poisoned after exposure to inorganic arsenic found in pesticides, herbicides, dyes, homeopathic medicines, and certain contaminated folk remedies from China, India, and Southeast Asia (see Chapter 94). Soil deposits contaminate artesian well water. Groundwater contamination with arsenic is a common problem in developing countries and has been reported to be a common well contaminant in many areas of the United States as well (Fig. 760.1). The Southwest has the highest arsenic concentrations in the country with more than 16% of sampled wells exceeding the maximum contaminant level. Food products (e.g., rice, organic brown rice syrup, fruit juices) cooked in contaminated water may absorb arsenic, thus concentrating it in the food (Fig. 760.2). The WHO and United States Environmental Protection Agency (EPA) have set 10 μg/L as the upper limit of safety. In many parts of Asia and South America, this limit is frequently exceeded. Arsenic concentrations in a quarter of the wells in Bangladesh exceed 50 μg/L, and 35-77 million of the 125 million inhabitants of Bangladesh regularly consume arsenic-contaminated water. Occupational exposure may occur in industries involved in the manufacturing, mining, smelting, or refining of glass, pottery, electronic and semiconductor components, and lasers. Although arsenic is no longer produced in the United States, it is produced in many countries and is imported into the United States for industrial use. Organic arsenic compounds may be found in seafood, pesticides, and some veterinary pharmaceuticals. In contrast to mercury, the organic forms of arsenic found in seafood are nontoxic.

Pharmacokinetics

Elemental arsenic is insoluble in water and bodily fluids, and thus is insignificantly absorbed and nontoxic. Inhaled arsine gas is rapidly absorbed through the lungs. The inorganic arsenic salts are well absorbed through the gastrointestinal tract, lungs, and skin. The organic arsenic compounds are well absorbed through the gastrointestinal tract. After acute exposure, arsenic initially is bound to the protein portion of hemoglobin in the red blood cells (RBCs) and rapidly distributed to all tissues. Inorganic arsenic is methylated and is eliminated predominantly by the kidneys, with approximately 95% excreted in the urine and 5% excreted in the bile. Most of the arsenic is eliminated in the first few days, with the remainder slowly excreted over a period of several weeks. Arsenic concentrates in hair, nails, and skin. Arsenic can also accumulate in the fetus, as it can cross the placenta. Measurement of the distance of **Mees lines** (transverse white striae on the nail) from the nailbed can provide an estimate of time of exposure (nails grow at the rate of 0.4 mm/day) (Fig. 760.3).

Pathophysiology

After exposure to arsine gas, absorbed arsine enters RBCs and is oxidized to arsenic dihydride and elemental arsenic. Complexing of these derivatives with red cell sulfhydryl groups results in cell membrane instability and massive hemolysis. The inorganic arsenic salts poison enzymatic processes vital to cellular metabolism. Trivalent arsenic binds to sulfhydryl groups, resulting in decreased production of

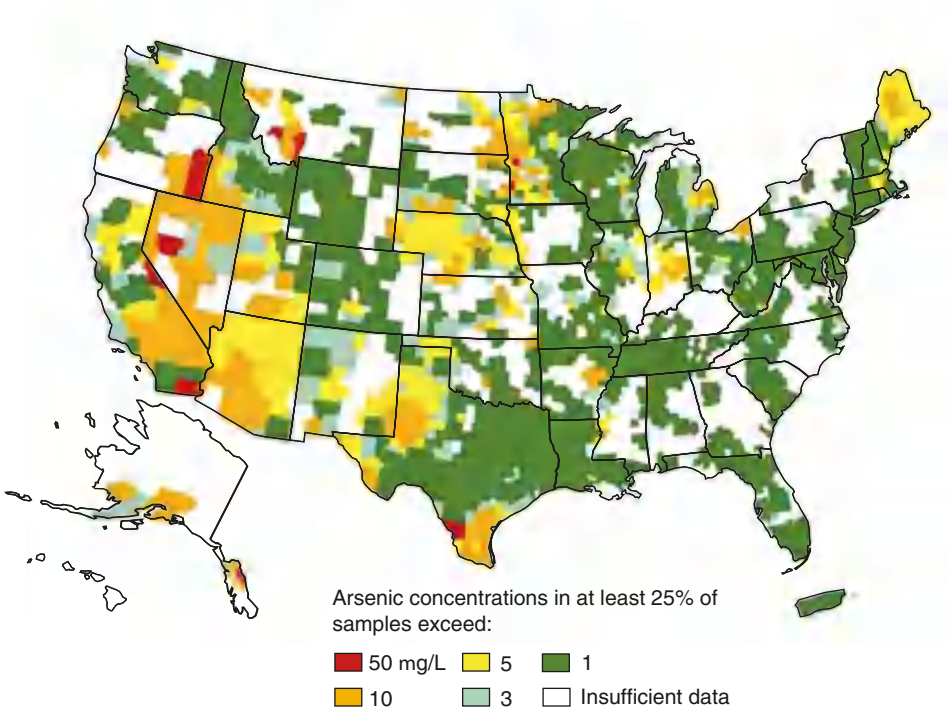

Fig. 760.1 U.S. Geological Survey map of arsenic in groundwater. Groundwater may also contain elevated concentrations of arsenic from agricultural runoff, contamination from runoff from wood preservatives containing arsenic, improperly disposed arsenical chemicals, or mining. For the latest on the US Geological survey: https://www.usgs.gov/mission-areas/water-resources/science/arsenic-and-drinking-water#overview. *(Modified from Agency for Toxic Substances and Disease Registry: Arsenic toxicity. What Are the Routes of Exposure for Arsenic? Fig 1.* https://www.atsdr.cdc.gov/csem/arsenic/what_routes.html.*)*

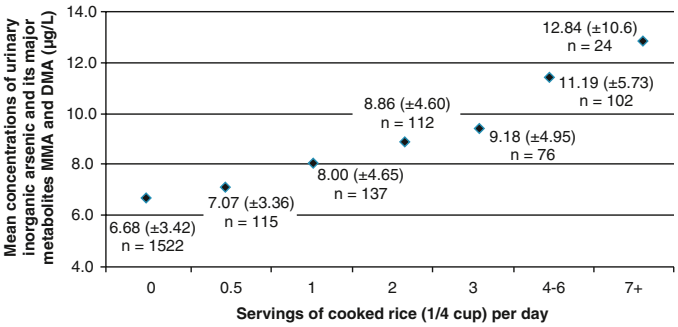

Fig. 760.2 Mean concentrations of urinary inorganic arsenic and its major metabolites monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) by categories of rice intake in children ages 6-17, National Health and Nutrition Examination Survey (NHANES) 2003-2008, excluding subjects with recent seafood consumption. *(From Lai PY, Cottingham KL, Steinmaus C, et al. Arsenic and rice: Translating research to address health care providers' needs. J Pediatr. 2015;167[4]:797–803. Fig. 1.)*

Fig. 760.3 Mees lines. Transverse white bands are clearly visible on the nails. *(From Chauhan S, D'Cruz S, Singh R, et al. Mees' lines. Lancet. 2008;372[9647]:1410.)*

adenosine triphosphate through the inhibition of enzyme systems such as the pyruvate dehydrogenase and α-ketoglutarate complexes. Pentavalent arsenic may be biotransformed to trivalent arsenic or substituted for phosphate in the glycolytic pathway, resulting in uncoupling of oxidative phosphorylation.

Clinical Manifestations

Arsine gas is colorless, odorless, nonirritating, and highly toxic. Inhalation causes no immediate symptoms. After a latent period of 2-24 hours, exposed individuals experience massive hemolysis, malaise, headache, weakness, dyspnea, nausea, vomiting, abdominal pain, hepatomegaly, pallor, jaundice, hemoglobinuria, and renal failure (Table 760.1). Acute ingestion of arsenic produces gastrointestinal toxicity within minutes to hours and is manifested as nausea, vomiting, abdominal pain, and diarrhea. Hemorrhagic gastroenteritis with extensive fluid loss and third spacing may result in hypovolemic shock. Cardiovascular toxicity includes QT interval prolongation, polymorphous ventricular tachycardia, congestive cardiomyopathy, pulmonary edema, and cardiogenic shock. Acute neurologic toxicity includes delirium, seizures, cerebral edema, encephalopathy, and coma. Lethal doses of arsenates are 5-50 mg/kg; lethal doses of arsenites are <5 mg/kg.

Table 760.1 Effects of Arsenic on Organ Systems

ORGAN SYSTEM	EFFECTS OF ARSENIC
Gastrointestinal system	Submucosal vesicles, watery or bloody diarrhea, severe hematemesis, pancreatitis, jaundice, toxic hepatitis
Cardiovascular system	Reduced myocardial contractility, prolonged QT intervals, tachyarrhythmias, torsades de pointes, pericarditis Vasodilation, hypotension, shock
Kidneys	Hematuria, proteinuria, oliguria, renal failure
Nervous system	Toxic encephalopathy with seizures, headache, cerebral edema, and coma Chronic exposure: peripheral painful sensorimotor neuropathy, paresthesias
Hematologic and lymphatic system	Anemia, leukopenia, and thrombocytopenia; acute hemolysis with arsine gas, basophilic stippling
Liver	Fatty degeneration with central necrosis
Skin	Desquamation, alopecia, hyperkeratosis, nail changes (Mees lines), brown pigmentation Chronic exposure: hyperkeratosis, hyperpigmentation
Teratogenic	Neural tube defects in the fetus
Oncologic	Urologic cancer, other malignancies

Late sequelae include hematuria, proteinuria, and acute kidney injury. A delayed sensorimotor peripheral neuropathy may appear days to weeks after acute exposure, secondary to axonal degeneration. Neuropathy manifests as painful dysesthesias followed by diminished vibratory, pain, touch, and temperature sensation; decreased deep tendon reflexes; and in the most severe cases, an ascending paralysis with respiratory failure mimicking Guillain-Barré syndrome (see Chapter 656). Adult survivors of infant arsenic poisoning experience higher mortality from disorders of the nervous system compared with adults without such exposure.

Subacute toxicity is characterized by prolonged fatigue, malaise, weight loss, headache, chronic encephalopathy, peripheral sensorimotor neuropathy, leukopenia, anemia, thrombocytopenia, chronic cough, and gastroenteritis. Mees lines in the nails become apparent 1-2 months after exposure in approximately 5% of patients. Dermatologic findings include alopecia, oral ulceration, peripheral edema, a pruritic macular rash, and desquamation.

Chronic arsenic toxicity causes significant morbidity in children resulting in skin lesions, lung disease, and deficits in intellectual function. **Chronic exposure** to low levels of arsenic is usually from environmental or occupational sources. Over the course of years, dermatologic lesions develop, including hyperpigmentation, hypopigmentation, hyperkeratoses (especially on the palms and soles), squamous and basal cell carcinomas, and **Bowen disease** (cutaneous squamous cell carcinoma in situ). Encephalopathy and peripheral neuropathy may be present. Hepatomegaly, hypersplenism, noncirrhotic portal fibrosis, and portal hypertension occur. **Blackfoot disease** is an obliterative arterial disease of the lower extremities associated with chronic arsenic exposure that has been described in Taiwan. Carcinogenicity of chronic arsenic exposure is reflected in increased rates of cancers of the skin, lung, liver, bladder, and kidney as well as of angiosarcomas. Arsenic is carcinogenic, possibly through epigenetic dysregulation. The effects of prenatal exposure to arsenic are uncertain but may include low birthweight.

Laboratory Findings

The diagnosis of arsenic intoxication is based on characteristic clinical findings, a history of exposure, and elevated urinary arsenic values, the last of which confirm the exposure. A spot urine arsenic level should be determined for symptomatic patients before chelation, although initially the result may be negative. Because urinary excretion of arsenic is intermittent, definitive diagnosis depends on a 24-hour urine collection. Concentrations greater than 50 µg/L in a 24-hour urine specimen are consistent with arsenic intoxication (Table 760.2). Urine specimens must be collected in metal-free containers. Ingestion of seafood containing nontoxic arsenobetaine and arsenocholine can cause elevations of urinary arsenic. Blood arsenic levels rarely are helpful because of their high variability and the rapid clearance of arsenic from the blood in acute poisonings. Elevated arsenic values in the hair or nails must be interpreted cautiously because of the possibility of external contamination. Abdominal radiographs may demonstrate ingested radiopaque arsenic.

Later in the course of illness, a complete blood cell count may show anemia, thrombocytopenia, and leukocytosis, followed by leukopenia, karyorrhexis, and basophilic stippling of RBCs. The serum concentrations of creatinine, bilirubin, and transaminases may be elevated; urinalysis may show proteinuria, pyuria, and hematuria; and examination of the cerebrospinal fluid may show protein elevations.

MERCURY

Mercury exists in three forms: elemental mercury, inorganic mercury salts, and organic mercury (Table 760.3). **Elemental mercury** is present in thermometers, sphygmomanometers, barometers, batteries, gold or silver smelting processes, and some latex paints produced before 1991. Workers in industries producing these products may expose their children to the toxin when mercury is brought home on contaminated clothing. Vacuuming of carpets contaminated with mercury and breaking of mercury fluorescent light bulbs may result in elemental mercury vapor exposure. Severe inhalation poisonings have resulted from attempts to separate gold from gold ore by heating mercury and forming a gold-mercury amalgam. Elemental mercury has been used in folk remedies by Asian and Mexican populations for chronic stomach pain, by Latin Americans and Caribbean natives in occult practices, and as a skin-lightening agent. Dental amalgams containing elemental mercury release trace amounts of mercury. An expert panel for the National Institutes of Health concluded that existing scientific evidence does not indicate that dental amalgams pose a health risk and should not be replaced merely to decrease mercury exposure. A 2009 WHO expert panel concluded that a global near-term ban on amalgam would be problematic for public and dental health. However, this committee recommended that alternatives to amalgam should be sought as part of a phase-out of the use of mercury-containing amalgams.

Inorganic mercury salts are found in pesticides, disinfectants, antiseptics, pigments, dry batteries, and explosives and as preservatives in some medicinal preparations. **Organic mercury** in the diet, especially fish containing methyl mercury, is a major source of mercury exposure among the general population. Industries that may produce mercury-containing effluents include chlorine and caustic soda production, mining and metallurgy, electroplating, chemical and textile manufacturing, paper and pharmaceutical manufacturing, and leather tanning. Mercury compounds in the environment are methylated to methyl mercury by soil and water microorganisms. Methyl mercury in the water rapidly accumulates in fish (swordfish, king mackerel, fresh tuna, tile fish, shark) and other aquatic organisms, which are in turn consumed by humans. To address concerns that maternal consumption of large quantities of fish during pregnancy may expose the fetus to concentrations of mercury with adverse consequences, the longitudinal Seychelles Child Development Study has been ongoing since the late 1980s. The first cohort of the study involved nearly 800 mother–child pairs, with subsequent cohorts enrolled. Despite a high maternal fish intake (mean of 12 fish meals per week), follow-up of children at least through 9 years of age has revealed no consistent adverse developmental effects. Well-known large outbreaks of methyl mercury intoxication include the incidents in Japan in the 1950s (**Minamata disease,** from consumption of contaminated seafood) and in Iraq in 1971 (from consumption of grain treated with a methyl mercury fungicide).

Thimerosal is a mercury-containing preservative used in some vaccines. Thimerosal contains 49.6% mercury by weight and is metabolized to ethyl mercury and thiosalicylate. During an ongoing review of biologic products in response to the U.S. Food and Drug Administration (FDA) Modernization Act of 1997, the FDA determined that infants who received thimerosal-containing vaccines at multiple visits might have been exposed to more mercury than recommended by federal guidelines. As a precautionary measure, the American Academy of Pediatrics, American Academy of Family Physicians, Advisory Committee on Immunization Practices, and U.S. Public Health Service issued a joint recommendation in 1999 that thimerosal be removed from vaccines as quickly as possible. *In the United States, thimerosal has been removed from all vaccines in the recommended childhood immunization schedule.* Infants and children who have received thimerosal-containing vaccines do not need to undergo blood, urine, or hair testing for mercury because the concentrations of mercury would be quite low and would not require treatment. The larger risks of not vaccinating children far outweigh any known risk of exposure to thimerosal-containing vaccines. Studies do *not* demonstrate a link between thimerosal-containing vaccines and autism spectrum disorders (see Chapter 58), and no evidence supports a change in the standard of practice regarding administration of thimerosal-containing vaccines in areas of the world where they are used. A rise in blood mercury levels following a single dose of hepatitis vaccine was seen in preterm infants, but the clinical significance is unknown.

Pharmacokinetics

Inhaled elemental mercury vapor is 80% absorbed by the lungs and is distributed rapidly to the central nervous system because of its high lipid solubility. The elemental mercury is oxidized by catalase to the mercuric ion, which is the reactive form that causes cellular toxicity. Elemental mercury liquid is poorly absorbed from the gastrointestinal tract, with less than 0.1% being absorbed. The half-life of elemental mercury in the tissues is approximately 60 days, with most of the excretion occurring in the urine.

Inorganic mercury salts are approximately 10% absorbed from the gastrointestinal tract and cross the blood-brain barrier to a lesser extent than elemental mercury. Mercuric salts are more soluble than mercurous salts and therefore produce greater toxicity. Elimination occurs primarily in the urine, with a half-life of approximately 40 days.

Table 760.2 Acceptable and Toxic Levels of Arsenic and Mercury

	ARSENIC	MERCURY
Molecular weight	74.9 Da	200.59 Da
Acceptable blood level	<5 µg/L (<0.665 nmol/L)	<10 µg/L (<50 nmol/L)
Acceptable urine level	<50 µg/L (<6.65 nmol/L) 24-hr urine sample	<20 µg/L (<100 nmol/L)
Intervene at blood level		>35 µg/L (>175 nmol/L)
Intervene at urine level	>100 µg/L (>13.3 nmol/L) 24-hr urine sample	>150 µg/L (>750 nmol/L)

Table 760.3 Differential Characteristics of Mercury Exposure

	ELEMENTAL	INORGANIC (SALT)	ORGANIC (ALKYL)
Primary route of exposure	Inhalation	Oral	Oral
Primary tissue distribution	CNS, kidney	Blood (transient, acute), kidney, CNS (delayed)	CNS, kidney, liver, blood, hair
Clearance	Kidney, GI	Kidney, GI	Methyl: GI Aryl: kidney, GI
CLINICAL EFFECTS CNS	Tremor	Tremor, erethism (irritability)	Paresthesias, ataxia, tremor, tunnel vision, dysarthria
Pulmonary	+++	—	—
Gastrointestinal	+	+++ (caustic)	+
Renal	+	+++ (acute tubular necrosis)	+
Acrodynia	+	++	—
Therapy	BAL, succimer	BAL, succimer	Succimer (early)

+, mild; ++, moderate; +++, severe; BAL, British antilewisite (also known as dimercaprol); CNS, central nervous system; GI, gastrointestinal.
From Sue YJ. Mercury (heavy metals). In: Nelson LS, Howland MA, Lewin NA, et al., eds. *Goldfrank's Toxicologic Emergencies,* 11th ed. New York: McGraw-Hill; 2019: Table 95.3.

Methyl mercury is the most avidly absorbed of the organic mercury compounds, with approximately 90% absorbed from the gastrointestinal tract. The lipophilic, short-chain alkyl structure of methyl mercury allows it to distribute rapidly across the blood-brain barrier and placenta. Methyl mercury is approximately 90% excreted in the bile, with the remainder being excreted in the urine. The half-life is 70 days.

Pathophysiology

After absorption, mercury is distributed to all tissues, particularly the central nervous system and kidneys. Mercury reacts with sulfhydryl, phosphoryl, carboxyl, and amide groups, resulting in disruption of enzymes, transport mechanisms, membranes, and structural proteins. Widespread cellular dysfunction or necrosis results in the multiorgan toxicity characteristic of mercury poisoning.

Clinical Manifestations

Five syndromes describe the clinical presentation of mercury poisoning. **Acute inhalation of elemental mercury vapor** results in rapid onset of cough, dyspnea, chest pain, fever, chills, headaches, and visual disturbances. Gastrointestinal findings include metallic taste, salivation, nausea, vomiting, and diarrhea. Depending on the severity of the exposure, the illness may be self-limited or may progress to necrotizing bronchiolitis, interstitial pneumonitis, pulmonary edema, and death from respiratory failure. Younger children are more susceptible to pulmonary toxicity. Survivors may demonstrate restrictive lung disease. Renal dysfunction and neurologic disturbances (ataxia, persistent weakness, emotional lability) may develop subacutely. Chronic exposure to volatilized elemental mercury in dental amalgams has not been found to be of any clinical significance.

Acute ingestion of inorganic mercury salts (typically secondary to ingestion of a button battery) can manifest in a few hours as corrosive gastroenteritis, signified by metallic taste, oropharyngeal burns, nausea, hematemesis, severe abdominal pain, hematochezia, acute tubular necrosis, cardiovascular collapse, and death.

Chronic inorganic mercury intoxication produces the classic triad consisting of tremor, neuropsychiatric disturbances, and gingivostomatitis. The syndrome may result from long-term exposure to elemental mercury, inorganic mercury salts, or certain organic mercury compounds, all of which may be metabolized to mercuric ions. The tremor starts as a fine intention tremor of the fingers that is abolished during sleep but that may later involve the face and progress to choreoathetosis and spasmodic ballismus. Mixed sensorimotor neuropathy and visual disturbances may also be present. The neuropsychiatric disturbances include emotional lability, delirium, headaches, memory loss, insomnia, anorexia, and fatigue. Renal dysfunction ranges from asymptomatic proteinuria to nephrotic syndrome.

Acrodynia, or **pink disease**, is a rare idiosyncratic hypersensitivity reaction to mercury that occurs predominantly in children exposed to mercurous powders. The symptom complex includes generalized pain, paresthesias, and an acral (hands, feet) rash that may spread to involve the face. The rash typically is red-pink, papular, pruritic, and painful; it may progress to desquamation and ulceration. Morbilliform, vesicular, and hemorrhagic variants have been described. Other important features include anorexia, apathy, photophobia, and hypotonia, especially of the pectoral and pelvic girdles. Irritability, tremors, diaphoresis, insomnia, hypertension, and tachycardia may be present. Some cases initially were diagnosed as pheochromocytoma. The outcome is good after removal of the source of mercury exposure.

Methyl mercury intoxication (also known as **Minamata disease** after the widespread mercury poisoning that occurred at Minamata Bay in Japan in people who had ingested contaminated fish) manifests as delayed neurotoxicity that appears after a latent period of weeks to months. It is characterized by ataxia; dysarthria; paresthesias; tremors; movement disorders; impairment of vision, hearing, smell, and taste; memory loss; progressive dementia; and death. Infants exposed in utero are the most severely affected, with low birthweight, microcephaly, profound developmental delay, cerebral palsy, deafness, blindness, and seizures. Although there is significant residual morbidity from methyl mercury neurotoxicity, observations on long-term follow-up of children exposed in Iraq reveal complete or partial resolution in most cases.

Laboratory Findings

The diagnosis of mercury intoxication is based on characteristic clinical findings, a history of exposure, and elevation of whole blood or urine mercury values, the last of which confirms the exposure. Thin-layer and gas chromatographic techniques can be used to distinguish organic from inorganic mercury. Blood should be collected in special tubes for trace elements from laboratories that capably perform those tests. Levels <10 μg/L in whole blood and <20 μg/L in a 24-hour urine specimen are considered normal (see Table 760.2). Although blood mercury levels may reflect acute exposure, they decrease as mercury redistributes into the tissues. Urine mercury levels are most useful for identifying long-term exposures, except in the case of methyl mercury, which undergoes minimal urinary excretion. Urinary mercury levels are used in monitoring efficacy of chelation therapy, whereas blood levels are used primarily in monitoring organic mercury poisonings. Hair analysis for mercury is not reliable because hair reflects

both endogenous and exogenous mercury exposure (hair avidly binds mercury from the environment). Abdominal radiographs may demonstrate ingested radiopaque mercury.

Urinary markers of early nephrotoxicity include microalbuminuria, retinol-binding protein, β_2-microglobulin, and *N*-acetyl-β-D-glucosaminidase. Early neurotoxicity may be detected with neuropsychiatric testing and nerve conduction studies, whereas severe central nervous system toxicity is apparent on CT or MRI.

TREATMENT OF ARSENIC AND MERCURY INTOXICATION

The principles of management for arsenic and mercury intoxication include prompt removal from the source of poisoning, aggressive stabilization and supportive care, decontamination, and chelation therapy when appropriate. Once the diagnosis is suspected, the local poison control facility should be contacted, and care coordinated with physicians who are familiar with the management of heavy metal poisoning.

Supportive care for patients exposed to arsine gas requires close monitoring for signs of hemolysis, including evaluation of the peripheral blood smear and urinalysis. Transfusion of packed RBCs may be necessary, as may administration of intravenous fluids, sodium bicarbonate, and mannitol to prevent renal failure secondary to the deposition of hemoglobin in the kidneys. After inhalation of elemental mercury vapor, patients require careful monitoring of respiratory status, which may include pulse oximetry, arterial blood gas analysis, and chest radiography. Supportive care involves administration of supplemental oxygen and, in severe cases, intubation and mechanical ventilation.

Acute ingestion of inorganic arsenic and mercury salts results in hemorrhagic gastroenteritis, cardiovascular collapse, and multiorgan dysfunction. Fluid resuscitation, pressor agents, and transfusion of blood products may be required for management of cardiovascular instability. Severe respiratory distress, coma with loss of airway reflexes, intractable seizures, and respiratory paralysis are indications for intubation and mechanical ventilation. Renal function must be monitored carefully for signs of renal failure and the need for hemodialysis.

Gastrointestinal decontamination after ingestion of inorganic arsenic and mercury salts has not been well studied. Because of the corrosive effects of these compounds, induced emesis is not recommended, and endoscopy may be considered before gastric lavage. Arsenic and mercury are not well adsorbed to activated charcoal, but its use may be helpful if coingestants are suspected. Whole bowel irrigation is used to remove any radiopaque material remaining in the gastrointestinal tract.

Chelation for acute arsenic and mercury poisoning is most effective when administered as soon as possible after exposure. Chelation should be continued until 24-hour urinary arsenic or mercury levels return to normal (<50 μg/L for arsenic and <20 μg/L for mercury), the patient is symptom-free, or the remaining toxic effects are believed to be irreversible. The efficacy of chelation in long-term exposures is reduced because heavy metal in the tissue compartment is relatively nonexchangeable and some degree of irreversible toxicity has already occurred.

Dimercaprol, also known as *2,3-dimercaptopropanol* or *British antilewisite (BAL)*, is the chelator of choice for a patient who cannot tolerate oral therapy, as often is true for critically ill patients and after ingestion of the corrosive inorganic arsenic and mercury salts. Dimercaprol is available in 3-mL ampules at a concentration of 100 mg/mL for deep intramuscular (IM) injection. It is formulated in a peanut oil and benzyl benzoate suspension; as such, it is not suitable for patients with peanut allergy. For **arsenic poisoning**, the recommended regimen of dimercaprol is 2.5 mg/kg IM q4 hours for six doses, then every 6 hours for four doses, then every 8 hours for three doses, then every 12 hours for two doses, followed by once daily for 10 days. For severe arsenic poisoning, the dose of dimercaprol is increased to 3.5-5 mg/kg; the same dosing interval is followed. The dose of dimercaprol for **inorganic mercury poisoning** is 5 mg/kg every 4 hours IM for 24-48 hours, and then 2.5 mg/kg IM q12 hours for 10 days. The dimercaprol–heavy metal complex is excreted in the urine and bile. A period of 5 days between courses of chelation is recommended. Adverse effects of dimercaprol include pain at the injection site, hypertension, tachycardia, diaphoresis, nausea, vomiting, abdominal pain, a burning sensation in the oropharynx, and a feeling of constriction in the chest. Dimercaprol may cause hemolysis in glucose-6-phosphate dehydrogenase–deficient individuals. It is important to note that dimercaprol is contraindicated for chelation of methyl mercury because dimercaprol redistributes methyl mercury to the brain from other tissue sites, resulting in increased neurotoxicity.

Oral chelating agents are used to replace the painful dimercaprol injections when the patient is stable enough to tolerate oral therapy and prolonged chelation is necessary. **Succimer**, also known as *2,3-dimercaptosuccinic acid* (DMSA), is an orally administered water-soluble derivative of dimercaprol. DMSA is available in 100 mg capsules. The recommended regimen of DMSA for both arsenic and mercury poisoning is 10 mg/kg orally every 8 hours for 5 days followed by 10 mg/kg orally every 12 hours for 14 days. The DMSA–heavy metal complex is excreted in the urine and bile. A period of 2 weeks between courses of chelation is recommended. Mild adverse effects include nausea, vomiting, diarrhea, loss of appetite, and transient elevations in liver enzyme levels. DMSA also may cause hemolysis in glucose-6-phosphate dehydrogenase–deficient patients.

D-**Penicillamine** is an orally administered chelator that has been used in the past for less-severe mercury poisoning or as an adjunct to dimercaprol therapy in arsenic poisoning. Its use is largely restricted because of the potential for significant leukopenia, thrombocytopenia, and proteinuria along with the improved tolerability of succimer.

Patients with ingestion of elemental mercury require no follow-up unless there is an underlying disease that decreases the gastrointestinal transit time. Serial abdominal radiographs to document the progression of the metal are recommended. Acute inhalation of mercury fumes and ingestion of inorganic mercury require hospitalization to monitor the respiratory and gastrointestinal status, respectively. Therapeutic abortion may be considered in pregnant patients because of the teratogenic effect of mercury.

Strategies to reduce arsenic exposure in rice are noted in Table 760.4.

Table 760.4 Potential Strategies for Reducing Exposure of Arsenic in Rice

1. Diversify the diet
   - Eat a well-balanced diet and a variety of grains[†,‡,§]
   - Identify children at risk for high consumption of rice and rice products (e.g., gluten-free diets, highly allergic)
2. Consider alternatives to rice for first food
   - Start infants on barley, oats, or other grains[†,‡]
   - If rice cereal must be used for infants, limit to one serving per day[§]
3. Adopt strategies that help minimize exposure
   - Rinse rice in a colander before cooking[§]
   - Cook rice like pasta, with plenty of extra water[§]
   - Choose lower-arsenic varieties of rice (e.g., basmati)[§]
   - Avoid or limit use of rice milk or other rice beverages for infants[‡] and children under 5 yr old[§,¶]
   - Read labels of processed foods: choose alternatives to foods sweetened with brown rice syrup or thickened with rice products
4. Regulatory action
   - Federal agencies should establish regulatory limits for arsenic content in rice and rice products[§]

[†]U.S. Food and Drug Administration.
[‡]American Academy of Pediatrics.
[§]Consumer Reports.
[¶]United Kingdom Food Standard Agency.
From Lai PY, Cottingham KL, Steinmaus C, et al. Arsenic and rice: translating research to address health care providers' needs. *J Pediatr.* 2015;167(4):797–803.

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Chapter 761

Lead Poisoning

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Lead is a metal that exists in four isotopic forms. Clinically it is purely a toxicant; no organism has an essential function that is lead dependent. Chemically its low melting point and ability to form stable compounds have made it useful in the manufacture of hundreds of products; this commercial attractiveness has resulted in the processing of millions of tons of lead ore, leading to widespread dissemination of lead in the human environment.

The **blood lead level (BLL)** is the gold standard for determining risk of health effects. The threshold level at which lead begins to cause biochemical, subclinical, or clinical disturbance remains to be determined. In 2021, the Centers for Disease Control and Prevention (CDC) designated 3.5 μg/dL as the *"reference value based on the 97.5th percentile of the population of US children aged 1-5 years."* It is the BLL that identifies the 2.5% of children with the highest BLLs. As a measure of the distribution of BLLs in young American children rather than a toxicity threshold, this number will change in a manner dependent on the epidemiology of BLLs. Surveillance by the CDC has shown that the prevalence of elevated BLLs has declined markedly. Approximately 500,000 U.S. children ages 1-5 years currently have BLLs ≥3.5 μg/dL. Fortunately, children with levels high enough to be life-threatening (>100 μg/dL) are rarely seen in the United States, though deaths continue to occur in other areas of the world. Although BLL ≥3.5 μg/dL is stated as a reference value, it is likely that clinicians and departments of health will consider this a threshold for action.

PUBLIC HEALTH HISTORY

In the late 1970s, nearly all preschool-age children in the United States had BLLs above the current reference value of 3.5 μg/dL. Over the next 25 years, government regulations resulted in the significant reduction of three main contributors to lead exposure by means of (1) the elimination of the use of tetraethyl lead as a gasoline additive, (2) the banning of lead-containing solder to seal food- and beverage-containing cans, and (3) the application of a federal rule that limited the amount of lead allowed in paint intended for household use to less than 0.06% by weight (further reduced by the Consumer Product Safety Commission to 0.009% in 2008). Factors identified by the CDC in the late 1970s that indicate increased risk of lead poisoning, in addition to preschool age, include low socioeconomic status; living in older housing, built primarily before 1960; urban location; and Black race. Another high-risk group that has been identified consists of recent immigrants from less wealthy countries, including adoptees. These risk factors largely persist currently, as indicated by an analysis of over 1 million BLLs obtained from U.S. children between October 2018 and February 2020 and analyzed in a commercial lab. In addition, these data indicated that over half of the children still have measurable BLLs, i.e., ≥1 μg/dL.

Progress is also being made globally. In Mexico, the introduction of unleaded gasoline in 1990 was associated with a decline in BLLs among first-grade students, from 17 μg/dL in 1990 to 6.2 μg/dL in 1997. Algeria, the last country to use leaded gasoline for cars and trucks, phased out its use in 2021. In Malta, after the import of red lead paint was banned and the use of lead-treated wood for fuel in bakeries was prohibited, mean BLLs of pregnant women and newborns decreased by 45%. After it was documented that children living in the neighborhood of a battery factory in Nicaragua had a mean BLL of 17.2 μg/dL, but children in the control community had a mean BLL of 7.4 μg/dL, the factory was closed. Despite these advances, in 2021 the World Health Organization (WHO), citing research for UNICEF by the Institute for Health Metrics and Evaluation, estimated that 815 million children globally may have elevated BLLs above 5 mg/dL. The majority live in developing countries, where in some regions BLLs may be 10- to 20-fold higher than in developed countries.

Unfortunately, local lead-related harms continue to occur. When the water source for Flint, Michigan, was changed (2014) to the Flint River and utilized a water treatment plant with poor corrosion control, the lead level of Flint tap water increased, as did the BLLs of children <5 years of age. Flint is not unique; many other cities have lead pipes that can result in water contamination. In 2021 the US government allocated $15 billion for lead pipe removal.

In 2010, the CDC and WHO identified numerous lead-contaminated villages in northern Nigeria. The grinding of ore to extract gold caused widespread leaded dust dissemination. It is likely that hundreds of children died because of this activity, and all remaining children in some of the villages assessed were lead poisoned, with 97% having a BLL ≥45 μg/dL, the threshold for chelation therapy in the United States. Unfortunately, such disasters continue to occur in Nigeria and neighboring countries from similar metal extraction activities.

SOURCES OF EXPOSURE

Lead poisoning may occur in utero because lead readily crosses the placenta from maternal blood. The spectrum of toxicity is similar to that experienced by children after birth. The source of maternal blood lead content is either redistribution from endogenous stores (i.e., the mother's skeleton) or lead newly acquired from ongoing environmental exposure.

Several hundred products contain lead, including paint, batteries, cable sheathing, cosmetics, mineral supplements, plastics, toys (Table 761.1), and traditional medicines (Table 761.2). Major sources of exposure vary among and within countries; the major source of exposure in the United States remains old lead-based paint. Approximately 34.6 million homes, mainly built before 1950, have lead-based paint (2021 estimate), of which the CDC has estimated that 22.3 million are in a hazardous state. As paint deteriorates, it chalks, flakes, and turns to dust. Improper rehabilitation work of painted surfaces (e.g., sanding) can result in dissemination of lead-containing dust throughout a home. The dust can coat all surfaces, including children's hands. All of these forms of lead can be ingested. If heat is used to strip paint, then lead vapor concentrations in the room can reach levels sufficient to cause lead poisoning via inhalation. There is an increased awareness that tap water in both homes and schools may have substantial amounts of lead. The latter arose from the discovery of contaminated water in most New York City public schools. Moreover, this occurrence raised questions about the safety of the US Environmental Protection Agency (EPA) lead-in-water-standard of 15 parts per billion (ppb; μg of Pb/L of water) that water distribution companies must meet in at least 90% of homes in their service areas. This standard was not based on achieving health safety but rather on what the water companies felt was financially feasible. After review, in 2021 the EPA recommended lowering the "trigger" level to 10 ppb. Breaching this value requires water companies to prepare an intervention plan should the level subsequently go over 15 ppb. It does not require action to reduce the amount of lead in that water supply. Even 10 ppb is still much greater than the 1 ppb recommended by the American Academy of Pediatrics as the limit for allowable lead in drinking water. It should be noted that the EPA lead in water standard does not apply to schools, although many states have set their own standards.

In other parts of the world, especially in poorer countries, additional sources can be found. These include contaminated neighborhoods as the result of car/truck battery lead recycling, aluminum cookware made with recycled metals, spices, and traditional medicines.

METABOLISM

The nonnutritive hand-to-mouth activity of young children is the most common pathway for lead to enter the body. In most cases, lead is ingested either as a component of dust licked off of surfaces or in swallowed paint chips, through water contaminated by its flow through lead pipes or brass fixtures, or from otherwise contaminated foods or liquids. Cutaneous contamination with inorganic lead compounds, such as those found in pigments, does not result in a substantial amount of absorption. Organic lead compounds, such as tetraethyl lead, may penetrate through skin; however, these are rarely encountered.

The percentage of lead absorbed from the gut depends on several factors: particle size, pH, other material in the gut, and nutritional status of

Table 761.1 Sources of Lead

Paint chips
Dust
Soil
Parent's or household contact's occupational exposure (auto repair, smelting, construction, remodeling, plumbing, gun/bullet (firing range) exposure, painting, e-scrap)
Glazed ceramics
Herbal remedies (e.g., Ayurvedic medications)
Home remedies, including antiperspirants, deodorants (litargirio)
Jewelry (toys or parents')
Stored battery casings or recycling (or living near a battery smelter)
Lead-based gasoline (in aviation fuel for propeller planes)
Moonshine alcohol
Mexican candies; Ecuadorian chocolates
Ceremonial spices
Indoor firing ranges
Retained bullet fragments
Imported spices (svanuri marili, zafron, kuzhambu)
Lead-based cosmetics (kohl, surma, kajal)
Lead plumbing (water)
Imported foods in lead-containing cans
Domestic foods (applesauce pouches, others)
Imported toys
Home renovations
Antique toys or furniture
Kratom

Table 761.2 Cases of Lead Encephalopathy Associated with Traditional Medicines by Type of Medication

TRADITIONAL MEDICAL SYSTEM	NO. (%) CASES OF LEAD ENCEPHALOPATHY	NO. (%) PEDIATRIC CASES WITHIN CAM SYSTEM OR MEDICATION
Ayurveda	5 (7)	1 (20)
Ghasard	1 (1)	1 (100)
Traditional Middle Eastern practices	66 (87)	66 (100)
Azarcon and Greta	2 (3)	2 (100)
Traditional Chinese medicine	2 (3)	2 (100)
Total	76 (100)	72 (95)

CAM, Complementary and alternative medicines.
From Karri SK, Saper RB, Kales SN. Lead encephalopathy due to traditional medicines. *Curr Drug Saf.* 2008;3:54–59.

essential elements. Large paint chips are difficult to digest and are mainly excreted; this chemical characteristic of lead compounds is fortunate, as a single chip may contain a potentially lethal dose of lead. Fine dust can be dissolved more readily, especially in an acid medium. Lead eaten on an empty stomach is better absorbed than that taken with a meal. The presence of **calcium** and **iron** may decrease lead absorption by direct competition for binding sites; iron (and probably calcium) deficiency results in enhanced lead absorption, retention, and toxicity.

After absorption, lead is disseminated throughout the body via blood. It circulates bound to erythrocytes; approximately 97–99% of lead in blood is bound on or in the red blood cells. The plasma fraction is too small to be measured by conventional techniques employing atomic absorption spectroscopy or anodic stripping voltammetry; it is presumably the plasma portion that may leave the blood compartment to enter cells and induce toxicity. Thus clinical laboratories report the BLL, not the serum or plasma lead level. The increasing availability and decreasing cost of inductively coupled plasma mass spectrometry, which is capable of measuring lead in ng/dL quantities, may eventually result in clinical availability of tools to measure plasma lead, a more proximal measure to where toxicity is actually occurring.

Most retained lead accumulates in bone, where it resides for years. But in all cells, lead has multiple effects. It binds to enzymes, particularly those with available sulfhydryl groups, changing the contour and diminishing function. For example, three of eight enzymes in the ubiquitously distributed heme pathway are susceptible to lead inhibitory effects. The accumulation of excess amounts of heme precursors is also toxic. The last enzyme in this pathway, ferrochelatase, enables protoporphyrin to chelate iron, thus forming heme. **Erythrocyte protoporphyrin (EP)** levels higher than 35 μg/dL (laboratory dependent) are abnormal and are consistent with lead poisoning, iron deficiency, or recent inflammatory disease. Measurement of the EP level is thus a useful tool for monitoring biochemical lead toxicity. EP levels begin to rise several weeks after BLLs have reached 20 μg/dL in a susceptible portion of the population and are elevated in nearly all children with BLLs higher than 50 μg/dL. A drop in EP levels also lags behind a decline in BLLs by several weeks because it depends on both cell turnover and cessation of further overproduction by marrow red blood cell precursors. The test can be ordered either as the free EP or the zinc protoporphyrin. Results are reported in μg/dL. When reported in μmol/mmol this likely indicates that the analysis has been standardized to a hematocrit of 45, an unwarranted assumption in young children.

A second mechanism of lead toxicity works via its competition with calcium. Many calcium-binding proteins have a higher affinity for lead than for calcium. Lead bound to these proteins may alter function, resulting in abnormal intracellular and intercellular signaling. Neurotransmitter release is, in part, a calcium-dependent process that is adversely affected by lead.

Although these two mechanisms of toxicity may be reversible, a third mechanism prevents the development of the normal tertiary brain structure. In immature mammals the normal neuronal pruning process that results in elimination of multiple intercellular brain connections is affected by lead. Failure to construct the appropriate tertiary brain structure during infancy and childhood may result in a permanent abnormality. In a longitudinal study of childhood lead poisoning, MRI examinations of the participants when in their 20s found smaller areas of brain in the prefrontal cortex and hippocampus regions, areas involved in decision-making and memory formation.

CLINICAL EFFECTS

The BLL is the best-studied measure of the lead burden in children. Although subclinical and clinical findings correlate with BLLs in populations, there is considerable interindividual variability in this relationship. **Lead encephalopathy** is more likely to be observed in children with BLLs higher than 100 μg/dL; however, one child with a BLL of 300 μg/dL may have no symptoms, whereas another with the same level may be comatose. Susceptibility may be associated with polymorphisms in genes coding for lead-binding proteins, such as Δ-aminolevulinic acid dehydratase, an enzyme in the heme pathway.

Several **subclinical effects** of lead have been demonstrated in cross-sectional epidemiologic studies. Hearing and height are inversely related to BLLs in children; in neither case, however, does the lead effect reach a level that would bring an individual child to medical attention. As BLLs increase in the study populations, more sound (at all frequencies) is needed to reach the hearing threshold. Children with higher BLLs are shorter than those with lower levels; for every 10 μg increase in the BLL, the children are 1 cm shorter. Chronic lead exposure also may delay puberty.

Several longitudinal studies have followed cohorts of children for decades after birth and examined the relationship between BLLs and cognitive test scores over time. In general, there is agreement that BLLs, expressed either as levels obtained concurrently with cognitive testing or as a measure that integrates multiple BLLs drawn from subjects over time, are inversely related to cognitive test scores. From these studies, no BLL above 0 μg/dL appears safe. On average, for each 1 μg/dL elevation in BLL, the cognitive score is approximately 0.25-0.50 points lower, though the relationship is not linear across the BLL spectrum.

Because the BLLs from early childhood are predictors of the cognitive test results performed years later, this finding implies that the effects of lead can be permanent.

The effect of in utero lead exposure is less clear. Scores on the Bayley Scale of Mental Development were obtained repeatedly every 6 months for the first 2 years of life in a cohort of infants born to middle-class families. Results correlated inversely with cord BLLs, a measure of in utero exposure. However, after 2 years of age, all other cognitive tests performed on the cohort over the next 10 years correlated with the BLLs at age 2 years but not with cord BLLs, indicating that the effects of prenatal lead exposure on brain function were superseded by early childhood events and later BLLs. Later studies, performed in cohorts of Mexican children monitored from the prenatal period, confirm the association between in utero lead exposure and later cognitive outcomes. In these studies, maternal plasma lead levels, obtained especially during the first trimester, were more strongly associated with cognitive scores in the offspring than with the traditionally measured maternal whole BLLs.

Behavior also is adversely affected by lead exposure. Hyperactivity is noted in young school-age children with histories of lead poisoning or with concurrent elevations in BLL. Older children with higher bone lead content are more likely to be aggressive and to have behaviors that are predictive of later juvenile delinquency. One report supports the concept of long-term effects of early lead exposure. In this longitudinal study, the mothers of a cohort were enrolled during their pregnancies. BLLs were obtained early in pregnancy, at birth, and then multiple times in the offspring during the first 6 years. The investigators report that the later relative rate of arrests, especially for violent crimes, increased significantly in relationship to the presence of these BLLs early in life. For every 5 μg/dL increase in BLL, the adjusted arrest rate was 1.40 for prenatal BLLs and 1.27 for 6-year BLLs. Epidemiologic data support the findings in this observational study. In an analysis that combined two national datasets, total annual leaded gasoline use (U.S. Geological Survey) and total reported violent criminal acts (U.S. Department of Justice), the amount of leaded gasoline used yearly was found to be strongly associated with violent criminal behavior with a lag time of 23 years; that is, early childhood exposure was followed two decades later by violent behavior rising and falling in close tandem. A similar association was found, this time between urban air lead levels and later violent crime, with a similar best-fit model employing a lag of approximately 22 years.

An intervention study, in which children with moderate lead poisoning and initial BLLs of 20-55 μg/dL were aggressively managed over 6 months, addressed the issue of the effects of treatment on cognitive development. Components of treatment included education regarding sources of lead and its abatement, nutritional guidance, multiple home and clinic visits, and for a subset, chelation therapy. Average BLLs declined, and cognitive scores were inversely related to the change in BLLs. For every 1 μg/dL fall in BLLs, cognitive scores were 0.25 point higher. A randomized placebo-controlled treatment study of 2-year-old children with initial BLLs of 20-44 μg/dL that employed the chelating agent succimer administered over 6 months found no difference in mean cognitive scores at age 4 years. However, as in the earlier treatment study, regression analysis did find an inverse relation between *change* scores; that is, a change in BLLs was associated with an inverse change in cognitive scores.

Whether the behavioral effects of lead are reversible is unclear. In one small, short-term study, 7-year-old hyperactive children with BLLs in the 20s were randomly allocated to receive a chelating agent (penicillamine), methylphenidate, or placebo. Teacher and parent ratings of behavior improved for the first two groups but not the placebo group. BLLs declined only in the chelated group. Two-year-old lead-poisoned children enrolled in a placebo-controlled trial of the chelating agent succimer showed no mean difference in behavior at 4 or 7 years of age. However, mean BLLs were also not different in the two groups at those ages.

These studies support the concept that early exposure to lead can result in long-term deficits in cognition and behavior; they also hold out the possibility that reductions in lead burden may be associated with improvement in cognitive test scores.

CLINICAL SYMPTOMS

Gastrointestinal symptoms of lead poisoning include anorexia, abdominal pain, vomiting, and constipation, often occurring and recurring over a period of weeks. Children with BLLs higher than 20 μg/dL are twice as likely to have gastrointestinal complaints as those with lower BLLs. **Central nervous system** symptoms are related to worsening cerebral edema and increased intracranial pressure. Headaches, change in mentation, lethargy, papilledema, seizures, and coma leading to death are rarely seen at levels lower than 100 μg/dL but have been reported in children with a BLL as low as 70 μg/dL. The last-reported death directly attributable to lead toxicity in the United States was in 2006 in a child with a BLL of 180 μg/dL. There is no clear cutoff BLL value for the appearance of hyperactivity, but it is more likely to be observed in children who have levels higher than 20 μg/dL.

Other organs also may be affected by lead toxicity, but symptoms usually are not apparent in children. At high levels (>100 μg/dL), renal tubular dysfunction is observed. Lead may induce reversible Fanconi syndrome. In addition, at high BLLs, red blood cell survival is shortened, possibly contributing to a hemolytic anemia, although most cases of anemia in lead-poisoned children are a result of other factors, such as iron deficiency and hemoglobinopathies. Older patients may develop peripheral neuropathy leading to wrist drop and foot drop, as well as hypertension.

DIAGNOSIS

Screening

It is estimated that 99% of lead-poisoned children are identified by screening procedures rather than through clinical recognition of lead-related symptoms. Until 1997, universal screening by blood lead testing of all children at ages 12 and 24 months was the standard in the United States. Given the national decline in the prevalence of lead poisoning, the recommendations have been revised to target blood lead testing of high-risk populations. High risk is based on an evaluation of the likelihood of lead exposure. Departments of health are responsible for determining the local prevalence of lead poisoning, as well as the percentage of housing built before 1950, the period of peak leaded paint use. When this information is available, informed screening guidelines for practitioners can be issued. For instance, in New York State, where a large percentage of housing was built before 1950, the Department of Health mandates that all children be tested for lead poisoning via blood analyses. *In the absence of such data, the practitioner should continue to test all children at both 12 and 24 months*. In areas where the prevalence of lead poisoning and old housing is low, targeted screening may be performed on the basis of a risk assessment. Three questions form the basis of most published questionnaires (Table 761.3), and items that are pertinent to the locale or individual may be added. If there is a lead-based industry in the child's neighborhood, the child is a recent immigrant from a country that until recently still permitted the use of leaded gasoline, or the child has **pica** (pattern of eating non-food materials) or developmental delay, blood lead testing would be appropriate. All Medicaid-eligible children should be screened by blood lead testing. Venous sampling is preferred to capillary sampling because the chances of false-positive and false-negative results are less with the former. However, capillary screening can be performed rapidly in the office with a point of care (POC) instrument; use of such instruments in primary care offices substantially increases screening rates. Other screening guidelines vary by federal, state, and even local governmental agencies. Contacting your local Department of Health is one way to determine local primary care obligations.

The threshold for lead effects and the reference level for risk management purposes are not the same. Laboratory issues make the interpretation of values more difficult at low levels. Most labs achieve quality control of ±2 μg/dL for reports of BLL, but federal regulations allow laboratories that perform BLL testing to operate with an allowable error of ±4 μg/dL. A capillary screening value ≥3.5 μg/dL requires a venous sample for confirmation (Table 761.4). If the diagnostic (venous) test

Table 761.3 Minimum Personal Risk Questionnaire

1. Does the child live in or regularly visit a house that was built before 1950? (Include settings such as daycare, babysitter's, or relative's home.)
2. Does the child live in or regularly visit a house built before 1978 with recent (past 6 months) or ongoing renovations or remodeling?
3. Does the child have a sibling or playmate who has or did have lead poisoning?

From Screening young children for lead poisoning. Guidance for state and local public health officials. Atlanta: Centers for Disease Control and Prevention, 1997.

Table 761.4 Recommended Schedule for Obtaining a Confirmatory Venous Sample

BLOOD LEAD LEVEL (µg/dL)	TIME TO CONFIRMATION TESTING*
≥3.5-9	Within 3 mo
10-19	Within 1 mo
20-44	Within 2 wk
≥45	Within 48 hr

*The higher the blood lead level is on the initial screening capillary test, the more urgent it is to get a venous sample for confirmatory testing.
Courtesy Centers for Disease Control and Prevention, 2022. https://www.cdc.gov/nceh/lead/advisory/acclpp/actions-blls.htm#anchor_86654

confirms that the BLL is elevated, then further testing is required by the recommended schedule (Table 761.5). A confirmed venous BLL of 45 µg/dL or higher requires prompt chelation therapy.

Other Tools for Assessment

BLL determinations remain the gold standard for evaluating children because of ready availability and its correlation with health outcomes in populations. Techniques are available to measure lead in other tissues and body fluids. Experimentally, the method of x-ray fluorescence (XRF) allows direct and noninvasive assessment of bone lead stores. XRF methodology was used to evaluate a population that had long-term exposure to lead from a polluting battery-recycling factory. The study found that the school-age children had elevated lead levels in bone but not in venous blood, a finding that is consistent with our understanding of the slow turnover of lead in bone, which is measurable in years, in contrast to that in blood, which is measurable in weeks. It also indicates that children may have substantial lead in their bodies that is not detected by routine blood lead testing. This stored lead may be released to toxic levels if bone resorption rates suddenly increase, as occurs with prolonged immobilization of longer than a week and during pregnancy. Thus children with histories of elevated BLLs are potentially at risk for recrudescence of lead toxicity long after ingestion has stopped and may pass this lead to the next generation. XRF methodology is not available for clinical use in children.

Lead also can be measured in urine. Spontaneous excretion, even in children with high BLLs, is usually low. Lead excretion may be stimulated by treatment with chelating agents, and this property of these drugs forms the basis of their use as a component of lead treatment. It also has been used to develop a test that differentiates children with lead burdens responsive to chelation therapy, the **lead mobilization test**. In this test, a timed urine collection follows one or two doses of chelating agent, and the lead content is determined. However, this test is no longer recommended.

Lead in hair, nails, and saliva also is measurable but has problems of contamination and interpretability; thus these have no clinical utility. Radiographs of long bones may show dense bands at the metaphyses ("**lead lines**"), which may be difficult to distinguish from growth arrest

Table 761.5 Schedule for Follow-Up Blood Lead Testing

VENOUS BLOOD LEAD CONCENTRATIONS (µg/dL)	EARLY FOLLOW-UP TESTING (2-4 TESTS AFTER INITIAL TEST ABOVE SPECIFIC VENOUS BLLs)	LATER FOLLOW-UP TESTING AFTER BLL DECLINING
≥3.5-9	3 mo*	6-9 mo
10-19	1-3 mo*	3-6 mo
20-44	2 wk to 1 mo	1-3 mo
≥45	As soon as possible	As soon as possible

BLL, Blood lead level.
Courtesy Centers for Disease Control and Prevention, 2022. https://www.cdc.gov/nceh/lead/advisory/acclpp/actions-blls.htm

Fig. 761.1 Anteroposterior radiograph of the abdomen demonstrates retention of radiopaque lead-based paint chips within bowel, predominantly clustered in the ascending colon. Other etiologies resembling "paint chips" include certain medications, eggshells, other heavy metals including iron- and calcium-containing supplements. Dense "lead lines" are noted in the proximal femoral metaphyses. *(From Swenson DW, Walters MM. Musculoskeletal imaging. In: Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 7.50, p. 214.)*

lines but, if caused by lead, are indicative of months to years of exposure (Fig. 761.1). For children with acute symptoms, when a BLL result is not immediately available, a **kidneys-ureters-bladder (KUB) radiograph** may reveal **radiopaque flecks** in the intestinal tract, a finding that is consistent with recent ingestion of lead-containing plaster or paint chips (see Fig. 761.1). However, the absence of radiographic findings does not rule out lead poisoning.

Because BLLs reflect recent ingestion or redistribution from other tissues but do not necessarily correlate with the body burden of lead or lead toxicity in an individual child, tests of lead effects also may be useful. After several weeks of lead accumulation and a BLL higher than 20 µg/dL, increases in EP values to more than 35 µg/dL may occur. An elevated EP value that cannot be attributed to iron deficiency or recent inflammatory illness is both an indicator of lead effect and a useful means of assessing the success of the treatment; the EP level will begin to fall a few weeks after successful interventions that reduce lead ingestion and increase lead excretion. Because EP is light sensitive, whole blood samples should be covered in aluminum foil (or equivalent) until analyzed.

TREATMENT

All BLLs ≥3 μg/dL should be reported to state or local health departments. Once lead is in bone, it is released slowly and is difficult to remove even with chelating agents. Because the cognitive/behavioral effects of lead may be irreversible, the main effort in treating lead poisoning is to prevent it from occurring and to prevent further ingestion by already-poisoned children. The main components in the effort to eliminate lead poisoning are universally applicable to all children (and adults) and are as follows: (1) identification and elimination of environmental sources of lead exposure, (2) behavioral modification to reduce nonnutritive hand-to-mouth activity, and (3) dietary counseling to ensure sufficient intake of the essential elements calcium and iron and their supporting vitamins, D and C. For the small minority of children with more severe lead poisoning, drug treatment is available that enhances lead excretion. How effective these interventions may be at reducing BLLs or improving cognitive function remains unclear at the lower BLLs commonly observed currently in young children in the United States.

During health maintenance visits a limited risk assessment is warranted, which includes questions pertaining to the most common sources of lead exposure: the condition of old paint, secondary occupational exposure via an adult living in the home, and/or proximity to an industrial source of pollution. If such a source is identified, its elimination usually requires the assistance of public health and housing agencies as well as education for the parents. It would be safest for the family to move out of a lead-contaminated apartment until repairs are completed. During repairs, repeated washes of surfaces and the use of high-efficiency particle accumulator (HEPA) vacuum cleaners help reduce exposure to lead-containing dust. Careful selection of a contractor who is certified to perform lead abatement work is necessary. Sloppy work can cause dissemination of lead-containing dust and chips throughout a home or building and result in further elevation of a child's BLL. After the work is completed, dust wipe samples should be collected from floors and windowsills or wells to verify that the risk from lead has abated. The standards for what are considered acceptable lead dust levels have recently been modified by the EPA to lower limits that are more protective.

A single case of lead poisoning is often discovered in a household with multiple family members, including other young children, and even in a household with a common source of exposure such as peeling lead-based paint. The mere presence of lead in an environment does not produce lead poisoning. Parental efforts at reducing the hand-to-mouth activity of the affected child are necessary to reduce the risk of lead ingestion. Handwashing with soap and water effectively removes lead, but in a home with lead-containing dust, lead rapidly begins to reaccumulate on the child's hands after washing. Therefore handwashing is best limited to the period immediately before nutritive hand-to-mouth activity occurs.

Because there is competition between lead and essential metals, it is reasonable to promote a healthy diet that is sufficient in calcium and iron. The recommended daily intakes of these metals vary somewhat with age. In general, for children 1 year of age and up, a calcium intake of about 1 g/day is sufficient and convenient to remember (roughly the calcium content of a quart of milk [~1,200 mg/qt] or calcium-fortified orange juice). Calcium absorption is vitamin D dependent; milk is fortified with vitamin D, but other nutritional sources of calcium often are not. A multivitamin containing vitamin D may be prescribed for children who do not drink sufficient milk or who have inadequate sunlight exposure. Iron requirements also vary with age, ranging from 6 mg/day for infants to 12 mg/day for adolescents. For children identified biochemically as being iron deficient, therapeutic iron at a daily dose of up to 5-6 mg/kg/day for 3 months is appropriate. Iron absorption from vegetables is enhanced when iron is ingested with vitamin C (ascorbic acid), which is found in citrus juices. Giving additional calcium or iron above the recommended daily intake to mineral-sufficient children has not been shown to be of therapeutic benefit in the treatment of lead poisoning.

For children with BLLs of ≥20 μg/dL, an abdominal x-ray should be considered to check for lead-based paint chips or leaded foreign bodies, if not already obtained. If radiopaque fragments are visualized on imaging, bowel decontamination (typically with whole bowel irrigation) should be initiated (see Chapter 94).

Drug treatment to remove lead is lifesaving for children with lead encephalopathy. In nonencephalopathic children, it prevents symptom progression and further toxicity. Guidelines for **chelation** are based on the BLL. *A child with a venous BLL of 45 μg/dL or higher should be treated.* Four drugs have been used in the United States: 2,3-dimercaptosuccinic acid (DMSA [**succimer**]), $CaNa_2EDTA$ (versenate), British anti-lewisite (BAL [dimercaprol]), and penicillamine. DMSA and penicillamine can be given orally, whereas $CaNa_2EDTA$ and BAL can be administered only parenterally. The choice of agent is guided by the severity of the lead poisoning, the effectiveness of the drug, and the ease of administration (Table 761.6). Children with BLLs of 44-70 μg/dL may be treated with a single drug, preferably DMSA. Those with BLLs of 70 μg/dL or greater require two-drug treatment: $CaNa_2EDTA$ in combination with either DMSA or BAL for those without evidence of encephalopathy, or $CaNa_2EDTA$ and BAL for those with encephalopathy. Published data on the combined treatment with $CaNa_2EDTA$ and DMSA for children with BLLs higher than 100 μg/dL are very limited. However, anecdotal information derived from the treatment of hundreds of severely lead-poisoned children in northern Nigeria indicates that single-drug treatment with DMSA is lifesaving, although the degree of long-term residual damage in survivors has not been reported.

Drug-related toxicities are minor and reversible. These include gastrointestinal distress, transient elevations in transaminases, active urinary sediment, and neutropenia. These types of events are least common for $CaNa_2EDTA$ and DMSA, and more common for BAL and penicillamine. All of the drugs are effective in reducing BLLs when given in sufficient doses and for the prescribed time. These drugs also may increase lead absorption from the gut and should be administered to children in lead-free environments. Some authorities also recommend the administration of a cathartic immediately before or concomitant with the initiation of chelation to eliminate any lead already in the gut.

None of these agents removes all lead from the body. Within days to weeks after completion of a course of therapy, the BLL rises, even in the absence of new lead ingestion. The source of this rebound in the BLL is believed to be release from bone. Serial examinations of bone lead content have shown that chelation with $CaNa_2EDTA$ is associated with a decline in bone lead levels, but that residual bone lead remains detectable even after multiple courses of treatment.

Repeat chelation is indicated if the BLL rebounds to 45 μg/dL or higher. Children with initial BLLs higher than 70 μg/dL are likely to require more than one course. A minimum of 3 days between courses is recommended to prevent treatment-related toxicities, especially in the kidney.

The indication for chelation therapy for children with BLLs <45 μg/dL is less clear. Although use of these drugs in children with BLLs from 20-45 μg/dL will result in transiently lowered BLLs, and in some cases reversal of lead-induced enzyme inhibition, few such children increase their excretion of lead significantly during chelation, raising the question of whether any long-term benefit is achieved. A study of 2-year-old children with BLLs of 20-44 μg/dL who were randomized to receive either DMSA or placebo found that the drop in BLLs was greater in the first 6 months after enrollment in the DMSA-treated group, but the levels converged by 1 year of follow-up. Mean cognitive test scores obtained at 4 and 7 years of age were not statistically different between the groups. Chelation with DMSA (and $CaNa_2EDTA$) is not recommended for all children with BLLs <45 μg/dL. Further work needs to be done to determine whether there are subgroups of children with BLLs <45 μg/dL who might benefit from chelation. It also remains to be demonstrated whether other chelating agents available in the United States or elsewhere are effective at either substantially reducing body stores (bone) of lead or reversing the cognitive deficits attributable to lead at these BLLs.

Table 761.6 Chelators Used for Lead Poisoning

CHELATOR	DOSAGE	INDICATIONS	CONTRAINDICATIONS	ADVERSE EFFECTS
Succimer (DMSA)	1050 mg/m^2/day divided into 3 doses for 5 days, then 700 mg/m^2/day divided into 2 doses for 14 days (maximum 500 mg per dose for children)	BLL >45 µg/dL	None	Nausea, vomiting Diarrhea Metallic taste Transient increase in AST/ALT
$CaNa_2EDTA$	1,500 mg/mm^2/day continuous intravenous (IV) infusion for encephalopathy *Otherwise:* 1,000 mg/m^2/day divided in 2 to 4 doses for up to 5 days, IV or IM	BLL >70 µg/dL (starting after first dose of BAL or succimer) May substitute for succimer if that drug is not tolerated	Severe renal disease Hepatitis	Nephrotoxicity Transient increase in AST/ALT Arrythmia (bradycardia)
Dimercaprol (BAL)	4 mg/kg deep IM injection every 4 hours for 5 days in children and adults	BLL >70 µg/dL and encephalopathy Consider succimer as alternative	Peanut allergy Organic mercury poisoning Hepatic insufficiency	Pain at injection site Hypertension and tachycardia Nausea, vomiting Headache Fever (especially in children) Nephrotoxicity in the setting of an acidic urine
D-Penicillamine	1-1.5 g/day (children: 20-30 mg/kg/day), in 3 or 4 divided doses for 1-6 months To minimize adverse reactions, start at 250 mg/day (children: 10 mg/kg/day) and increase to 50% during week 2 and to a full dose by week 3 Maximum adult daily dose is 2 g	BLL of 45 to 69 µg/dL AND succimer not tolerated	Penicillin allergy	Leukopenia Thrombocytopenia Enuresis Abdominal pain Rashes

Note: Indications for chelation and dosing regimens may change. Consult with a medical toxicologist or regional poison center for the most up-to-date recommendations.
BAL, British antilewisite; BLL, blood lead level; $CaNa_2EDTA$, calcium disodium ethylenediaminetetraacetic acid; DMSA, 2,3-dimercaptosuccinic acid; IM, intramuscular; AST, alanine transaminase; ALT, aspartate transaminase.
Modified from Theobald JL, Mycyk MB. Iron and heavy metals. In: Walls RM, ed. *Rosen's Emergency Medicine*, 10th ed. Philadelphia: Elsevier; 2023: Table 146.5.

With successful intervention, BLLs decline, with the greatest fall in BLL occurring in the first 2 months after therapy is initiated. Subsequently, the rate of change in BLL declines slowly, so that by 6-12 months after identification, the BLL of the average child with moderate lead poisoning (BLL >20 µg/dL) will be 50% lower. Children with more markedly elevated BLLs may take years to reach the current CDC reference level, 3.5 µg/dL, even if all sources of lead exposure have been eliminated, behavior has been modified, and nutrition has been maximized. Early screening remains the best way of avoiding and therefore obviating the need for the treatment of lead poisoning.

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Chapter 762 Nonbacterial Food Poisoning

762.1 Mushroom Poisoning

Diane P. Calello and Katherine Baranowski

Mushrooms are an ideal food. They are low in calories, fat free, and high in protein, making them a great source of nutrition. Unfortunately, some are highly toxic if ingested. Picking (foraging) and consumption of wild mushrooms are increasingly popular in the United States. This rise in popularity has led to increased reports of severe and fatal mushroom poisonings.

The clinical syndromes produced by mushroom poisoning are divided according to the rapidity of onset of symptoms and the predominant system involved (Table 762.1). The symptoms are caused by the principal toxin present in the ingested mushrooms. The eight major toxins produced by mushrooms are categorized as cyclopeptide *(amatoxin and phallotoxin),* gyromitrin, muscarine, coprine, ibotenic acid and muscimol, psilocybin, orellanine, and gastrointestinal tract–specific irritants. The edible wild mushroom *Tricholoma equestre* is associated with delayed rhabdomyolysis, and *Clitocybe amoenolens* and *Clitocybe acromelalga* have been reported to cause erythromelalgia, although toxins responsible for these effects are unknown.

Symptoms after eating mushrooms may not be the direct effect of a toxin but may be an allergic reaction or a toxic effect of pesticides or other contaminants. In addition, all who ate the same mushroom may not become sick, or if they do, they may become sick at different intervals. Table 762.2 lists general principles of management. Wherever possible, identification of the implicated mushroom is encouraged via mycologist or regional Poison Control Center.

GASTROINTESTINAL

Rapid Onset

Many mushrooms from various genera (such as *Chlorophyllum* species) produce local gastrointestinal manifestations. The causative toxins are diverse and largely unknown. Within 1 hour of ingestion, patients experience acute abdominal pain, nausea, vomiting, and diarrhea. Symptoms may last hours to days, depending on the species of mushroom.

Treatment is mainly supportive. Children with large fluid losses may require parenteral fluid therapy. It is imperative to differentiate ingestion of mushrooms of this class from ingestion of *Amanita* and

Table 762.1 Summary of Common Mushroom-Associated Syndromes

TOXIN	SYNDROME	CLINICAL COURSE	TYPICAL CAUSATIVE MUSHROOM(S)
Cyclopeptides, principally amatoxins	Delayed gastroenteritis followed by hepatic failure	*Stage 1:* 6-24 hr after ingestion: onset of nausea, vomiting, profuse cholera-like diarrhea, abdominal pain, hematuria *Stage 2:* 12-48 hr after ingestion: apparent recovery; levels of hepatic enzymes are rising during this stage *Stage 3:* 24-72 hr after ingestion: progressive hepatic and renal failure, coagulopathy, cardiomyopathy, encephalopathy, convulsions, coma, death	"Deadly *Amanitas*," *(A. phalloides, A. bisporigera)* *Galerina* species
General gastrointestinal irritants	Early gastroenteritis, may be severe	30 min to 2 hr after ingestion: nausea, vomiting, abdominal cramping, diarrhea; may recover without treatment	*Chlorophyllum molybdites*, backyard mushrooms ("little brown mushrooms"), many others
Gyromitrin	Delayed gastroenteritis with central nervous system toxicity, seizures	6-24 hr after ingestion: nausea, vomiting, diarrhea, abdominal pain, muscle cramps, delirium, convulsions, coma; hemolysis, and methemoglobinemia may occur	*Gyromitra esculenta* ("false morel")
Orellanine	Delayed onset gastroenteritis and renal failure	Abdominal pain, anorexia, vomiting starting over 30 hr after ingestion, followed by progressive renal failure 3-14 days later	*Cortinarius* species
Muscarine	Cholinergic syndrome	30 min to 2 hr after ingestion: bradycardia, bronchorrhea, bronchospasm, salivation, perspiration, lacrimation, convulsions, coma	*Clitocybe* species, *Inocybe* species, *Boletus* species, some *Amanita* species
Coprine	Disulfiram-like reaction with ethanol	30 min after drinking ethanol (may occur up to 1 week after eating coprine-containing mushrooms): flushing of skin of face and trunk, hypotension, tachycardia, chest pain, dyspnea, nausea, vomiting, extreme apprehension	*Coprinus atramentarius*
Ibotenic acid and muscimol	Hyperactivity, delirium, coma	30 min to 2 hours after ingestion: delirium, hallucinations, and coma	*Amanita muscaria, Amanita pantherina*
Psilocybin	Hallucinations	30 min to 3 hr after ingestion: hallucinations, euphoria, drowsiness, compulsive behavior, agitation	*Psilocybe* species

Modified from Brent J, Palmer RB: Mushrooms. In: Shannon MW, Borron SW, Burns MJ, eds. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*, 4th ed. Philadelphia: WB Saunders; 2007: Table 23-1.

Table 762.2 General Management of Mushroom Ingestion

1. Determine history of ingestion: how many types of mushrooms ingested, what time, if anyone else ate them, and what symptoms are present.
2. Attempt to determine which of the possible syndromes (see Table 762.1) the patient may have. For example, gastrointestinal symptoms occurring more than 6 hr after ingestion strongly suggest cyclopeptide, gyromitrin, or *Cortinarius* poisoning.
3. Administer activated charcoal. If the patient has diarrhea, do not give a cathartic. If a cathartic is used, give it only with the first dose of activated charcoal. Use repeated doses of activated charcoal for suspected amatoxin poisonings.
4. If feasible and when indicated, send gastric aspirate or emesis, along with any remaining mushrooms, to a mycologist for identification.
5. Try to perform a preliminary identification of mushroom and spores. Start to develop a spore print as soon as possible.
6. Maintain supportive measures, including airway support, intravenous fluids, and vasopressors (if needed). Monitor volume status.
7. Avoid antispasmodics for gastrointestinal symptoms.
8. Anticipate the clinical course.

From Brent J, Palmer RB: Mushrooms. In: Shannon MW, Borron SW, Burns MJ, eds. *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*, 4th ed. Philadelphia: WB Saunders; 2007: Box 23.1.

Galerina species containing cyclopeptide toxins, which present with symptoms after 6 hours of ingestion.

Delayed Onset

Cyclopeptide (Amatoxin) Poisoning

Poisonings by species of *Amanita* (death cap mushroom) and *Galerina* account for 95% of the fatalities from mushroom intoxication; the mortality rate for this group is 5–10%. Most species produce two classes of **cyclopeptide toxins:** (1) **phallotoxins,** which are heptapeptides believed to be responsible for the early symptoms of *Amanita* poisoning, and (2) **amatoxins,** octapeptides that inhibit nuclear RNA polymerase II and subsequent production of messenger RNA leading to impaired protein synthesis and cell death. Cells with high turnover rates, such as those in the gastrointestinal mucosa, kidneys, and liver, are the most severely affected. Other suggested toxin effects are induction of apoptosis, glutathione depletion in the liver, and oxygen free radical formation. Acute yellow atrophy of the liver and necrosis of the proximal renal tubules are found in lethal cases.

The clinical course of poisoning with *Amanita* or *Galerina* species is biphasic. Nausea, vomiting, and severe abdominal pain ensue 6-24 hours after ingestion. Profuse watery diarrhea follows shortly thereafter and may last for 12-24 hours or longer. During this time, patients become severely dehydrated. From 24 to 48 hours

after poisoning, jaundice, hypertransaminasemia (peaking at 72-96 hours), renal failure, and coma occur. Death occurs 4-7 days after the ingestion. A prothrombin time less than 10% of control is a poor prognostic factor. Of note, there are species of Amanita mushrooms that may present with earlier onset of symptoms and confound diagnosis, such as *Amanita smithiana,* which grows in the Pacific Northwest.

Treatment

Treatment for *Amanita* poisoning is both supportive and specific. Fluid loss from severe diarrhea during the early course of the illness is profound, requiring aggressive correction of fluid loss, electrolytes, and acid-base disturbances. In the late phase of the disease, management of renal and hepatic failure is also necessary.

Specific therapy for *Amanita* poisoning is designed to remove the toxin rapidly and to block binding at its target site. Oral activated charcoal is recommended as part of the initial treatment for children with *Amanita* poisoning. For significant ingestions, intravenous silibinin or intravenous penicillin G may be considered after discussion with a toxicologist or Poison Control Center. Silibinin and penicillin G inhibit binding of both toxins, interrupt enterohepatic recirculation of amatoxin, and protect the liver from further injury, although their effectiveness is controversial. *N*-acetylcysteine should be given for hepatoprotective effect. Hemodialysis or hemoperfusion may be beneficial in removing toxin. Orthotopic liver transplantation may be required for children with severe hepatic failure.

Gyromitrin Poisoning

Species of *Gyromitra* contain **gyromitrin,** which decomposes in the stomach to form **monomethylhydrazine** (CH_3NHNH_2) and inhibits central nervous system (CNS) enzymatic production of γ-aminobutyric acid (GABA). Monomethylhydrazine also oxidizes iron in hemoglobin, resulting in methemoglobinemia. Children with *Gyromitra* poisoning often experience vomiting, diarrhea, and abdominal pain within 6-24 hours of ingestion of the toxin. CNS symptoms such as vertigo, diplopia, headache, ataxia, and seizures develop later in the clinical course. Hemolysis and methemoglobinemia (see Chapter 511.6) are rare but potential life-threatening complications of gyromitrin poisoning.

Treatment

Hypovolemia from gastrointestinal fluid losses and seizures require supportive intervention. **Pyridoxal phosphate,** the coenzyme that catalyzes the production of GABA, can reverse the effects of monomethylhydrazine when administered in high doses. Pyridoxine hydrochloride (25 mg/kg infused over 30 minutes) is given at a frequency that is dependent on clinical improvement. Diazepam is given for persistent seizures. Parenteral administration of methylene blue is indicated if the methemoglobin concentration exceeds 30%. Blood transfusions may be required for significant hemolysis.

RENAL

Orellanine Poisoning

Species of *Cortinarius* mushrooms contain the heat-stable toxin bipyridyl **orellanine,** which causes severe nonglomerular renal injury characterized by interstitial fibrosis and acute tubular necrosis. Although the exact mechanism of injury is not fully understood, a metabolite of orellanine is thought to inhibit renal protein synthesis. *Cortinarius* poisoning is characterized by delayed onset of nausea, vomiting, and diarrhea that manifest 36-48 hours after ingestion. Although the initial symptoms may be trivial, more serious renal toxicity occurs in several days. Acute renal failure occurs in 30–50% of those affected, beginning with polyuria and progressing to renal failure (see Chapter 572).

Treatment

Treatment for orellanine poisoning is supportive. Early presentation, within 4-6 hours after ingestion, can be treated with activated charcoal and gastric lavage. Hemodialysis may be needed in patients suffering from renal failure. Most patients recover within 1 month, but chronic renal insufficiency develops in one third to one half of patients who subsequently require renal transplantation.

AUTONOMIC NERVOUS SYSTEM

Muscarine Poisoning

Mushrooms of the genera *Inocybe* and, to a lesser degree, *Clitocybe* contain **muscarine** or muscarine-related compounds. These quaternary ammonium derivatives bind to postsynaptic receptors, producing an exaggerated cholinergic response.

The onset of symptoms is rapid (30 minutes to 2 hours after consumption), and intoxication is characterized by symptoms of cholinergic excess: diaphoresis, excessive lacrimation, salivation, miosis, bradycardia, hypotension, urinary and fecal incontinence, and vomiting. Respiratory distress caused by bronchospasm and increased bronchopulmonary secretions is the most serious complication. The symptoms subside spontaneously within 6-24 hours.

Treatment

Atropine sulfate, the specific antidote, is administered intravenously (0.01 mg/kg; maximum: 2 mg). This is repeated until the pulmonary symptoms resolve or the patient becomes overtly tachycardic.

Coprine Poisoning

Coprinus atramentarius and *Clitocybe clavipes* contain **coprine.** Like disulfiram (Antabuse; Odyssey Pharmaceuticals, Inc.), coprine inhibits the metabolism of acetaldehyde after ethanol ingestion. The clinical manifestations result from accumulation of acetaldehyde.

Coprine intoxication becomes apparent after ethanol ingestion and may be delayed up to 5 days after consumption of the mushroom. Hyperemia of the face and trunk, tingling of the hands, metallic taste, tachycardia, and vomiting occur acutely. Hypotension may result from intense peripheral vasodilation.

The syndrome typically is self-limited and lasts only several hours. No specific antidote is available. If hypotension is severe, vascular reexpansion with isotonic parenteral solutions may be required.

CENTRAL NERVOUS SYSTEM

Ibotenic acid and Muscimol Poisoning

Although *Amanita muscaria* and *Amanita pantherina* may contain muscarine, the toxins responsible for the CNS symptoms after ingestion of these mushrooms are primarily **muscimol** and **ibotenic acid,** the heat-stable derivatives of the isoxazoles. Muscimol, a hallucinogen, and ibotenic acid, an insecticide, act as GABA agonists. From 30 minutes to 3 hours after ingestion, CNS symptoms appear: obtundation, alternating lethargy and agitation, and occasionally seizures. Nausea and vomiting are uncommon. If large amounts of muscarine are contained in the mushroom, symptoms of cholinergic crisis also may occur.

Specific therapy must be carefully selected, and in most cases supportive care will suffice. If an exaggerated cholinergic response is observed, atropine should be administered. Conversely, because ingestions of *A. muscaria* or *A. pantherina* may cause anticholinergic findings, the acetylcholinesterase inhibitor physostigmine can be used to reverse the delirium and coma. Benzodiazepines also are used for the agitation and delirium. Seizures can be controlled with diazepam. In the majority of patients, however, early supportive care and close observation are all that is required.

Psilocybin Intoxication

Mushrooms belonging to the genus *Psilocybe* ("magic mushrooms") contain **psilocybin and psilocin,** two psychotropic compounds. Within 30 minutes after ingestion, patients experience euphoria and hallucinations, often accompanied by tachycardia and mydriasis. Fever and seizures have also been observed in children with psilocybin poisoning. These symptoms are short-lived, usually lasting for 6 hours after consumption of the mushroom. Treatment consists of rest and observation in a quiet environment. Severely agitated patients may respond to diazepam.

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762.2 Solanine Poisoning

Katherine Baranowski and Diane P. Calello

Solanine is an alkaloid found in plants of the nightshade family (Solanaceae), specifically tomatoes, eggplant, paprika and pepper-based spices, and most significantly, white potatoes. The majority of solanine poisoning reported has arisen from the ingestion of greened potatoes. When exposed to light and allowed to turn green and/or sprout, potatoes produce several alkaloid glycosides containing the cholesterol derivative *solanidine*. Two of these glycosides, α-solanine and α-chaconine, are found in highest concentration in the peels and sprouts. Some solanine can be removed by boiling but not by baking. The major effect of α-solanine and α-chaconine is the reversible inhibition of cholinesterase. Cardiotoxic and teratogenic effects have also been reported.

Clinical manifestations of solanine and chaconine poisoning occur within 7-19 hours after ingestion. The most common symptoms are vomiting, abdominal pain, and diarrhea; in more severe instances of poisoning, neurologic symptoms, including drowsiness, apathy, confusion, weakness, and vision disturbances, are rarely followed by coma or death.

Treatment of solanine poisoning is largely supportive. In the most severe cases, symptoms resolve within 1-2 weeks.

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762.3 Seafood Poisoning

Diane P. Calello and Katherine Baranowski

CIGUATERA FISH POISONING

The most frequently reported seafood toxin illness in the world is ciguatera fish poisoning. Grouper is the most commonly identified source of the toxin, followed by snapper, kingfish, amberjack, dolphin, eel, and barracuda. Poisoning has also been associated with farm-raised salmon.

The dinoflagellate ***Gambierdiscus toxicus,*** a microscopic unicellular organism found along coral reefs, produces high concentrations of **ciguatoxin** and **maitotoxin.** The toxins are passed along the food chain from small herbivorous fish that consume the dinoflagellate to larger predatory fish and then to humans. These toxins are harmless in fish but produce distinct clinical symptoms in humans.

Ciguatoxins are odorless, colorless, and tasteless and are not destroyed by cooking or freezing. Ciguatoxins increase the sodium ion permeability of excitable membranes and depolarize nerve cells, actions that are inhibited by calcium and tetrodotoxin.

Between 2 and 30 hours after ingestion, ciguatera fish poisoning typically produces a biphasic illness. The initial symptoms are nonspecific and are of gastrointestinal origin (diarrhea, vomiting, nausea, and abdominal pain). The second phase occurs within a few days of ingestion and consists of intense itching, anxiety, myalgias, painful intercourse, feeling of loose teeth, and rash on palms and soles; the neurologic symptoms of **circumoral dysesthesias** and **cold allodynia** (reversal of hot and cold sensation) are characteristic of this disease and may last for months. Tachycardia, bradycardia, hypotension, and death occur very infrequently. Eating fish organs, roe, or viscera is associated with greater symptom severity. The diagnosis of ciguatera fish poisoning is based on clinical presentation and a compatible epidemiologic history; the diagnosis is confirmed by testing the ingested fish for toxin. There is no human biomarker to confirm ciguatera fish poisoning.

Treatment

Treatment of ciguatera fish poisoning is supportive. Intravenous fluids may be required for severe diarrhea, and careful observation for hypovolemic shock is advised. Once adequate hydration is established, mannitol (0.5-1.0 g/kg intravenously over 30-45 minutes), given within 48-72 hours of the toxic fish ingestion, is recommended for reduction of acute symptoms (especially neurologic symptoms) and possible prevention of chronic neurologic symptoms. Various other medications and herbal remedies have been tried, with variable results. Most cases are self-limited with a favorable prognosis.

SCOMBROID (PSEUDOALLERGIC) FISH POISONING

Ingestion of members of the **Scombridae** families, including albacore, mackerel, tuna, bonito, and kingfish, have been linked to major outbreaks of pseudoallergic fish poisoning. Non-scombroid fish such as mahi-mahi (dolphin fish), swordfish, and bluefish also are associated with poisoning.

The bacterial transformation of histidine to histamine is responsible for the clinical syndrome. Histidine is found in high concentrations in the flesh of scombroid fish; if refrigeration is inadequate, the action of bacterial decarboxylases during putrefaction converts histidine to histamine. Fish containing more than 20 mg of histamine per 100 g of flesh are toxic. In patients receiving isoniazid, a potent histaminase blocker, ingestion of fish flesh containing a lower concentration of histamine may be toxic.

The onset of clinical manifestations is acute and occurs within 10 minutes to 2 hours of ingestion. The most common symptoms and signs are diarrhea, erythema, sweating, flushing, diaphoresis, urticaria, nausea, and headache (Fig. 762.1). Abdominal pain, tachycardia, oral burning or numbness, dizziness, respiratory distress, hives, and facial swelling also occur. The illness is usually self-limited, terminating within 8-24 hours.

Treatment

Treatment is mainly supportive. With severe diarrhea, fluid replacement may be necessary. Antihistamines and antiemetics have been variably successful.

PARALYTIC SHELLFISH POISONING

Mussels, clams, oysters, scallops, and other filter-feeding mollusks may become contaminated during dinoflagellate blooms or **"red tides."** During periods of contamination, water in coastal areas can be colored red by the algae; this sign is the origin of the term *red tide*. (Such discoloration does not necessarily indicate the presence of toxin, and toxin may be present in high quantities without discoloration. Nonetheless, discolored water should be regarded with suspicion.) The dinoflagellates *Alexandrium* spp. and *Gymnodinium catenatum* often are responsible for these red tides and contain several potent neurotoxins. Paralytic shellfish poisoning is a distinctive neurologic illness caused by 20 closely related heat-stable paralytic shellfish toxins, generally referred to as **saxitoxins.** These compounds prevent nerve conduction by inhibiting the sodium-potassium pump. Consumption of bivalves, such as mussels, scallops, and clams, is the usual pathway of intoxication, although crustaceans and fish have been implicated as well.

The onset of clinical manifestations of paralytic shellfish poisoning occurs rapidly, 30 minutes to 2 hours after ingestion. Abdominal pain and nausea are common. Paresthesias are common and occur circumorally or in a stocking-glove distribution, or both. Perioral numbness or tingling, diplopia, ataxia, dysarthria, and the sensation of floating are seen less commonly. In severe cases, respiratory failure from diaphragmatic paralysis may result. Swimming in the water during a red tide episode does not appear to have neurologic sequelae, although skin or mucosal irritation may result.

Treatment

No antidote for paralytic shellfish poisoning is known. Supportive care, including mechanical ventilation, may be needed. Although the symptoms are usually self-limited and short-lived, weakness and malaise may persist for weeks after ingestion.

NEUROTOXIC SHELLFISH POISONING

Neurotoxic shellfish poisoning is a rare disease that occurs after consumption of molluscan shellfish contaminated with brevetoxins. Shellfish harvested along the Gulf of Mexico during or right after a red tide are at risk of contamination with brevetoxins produced by the

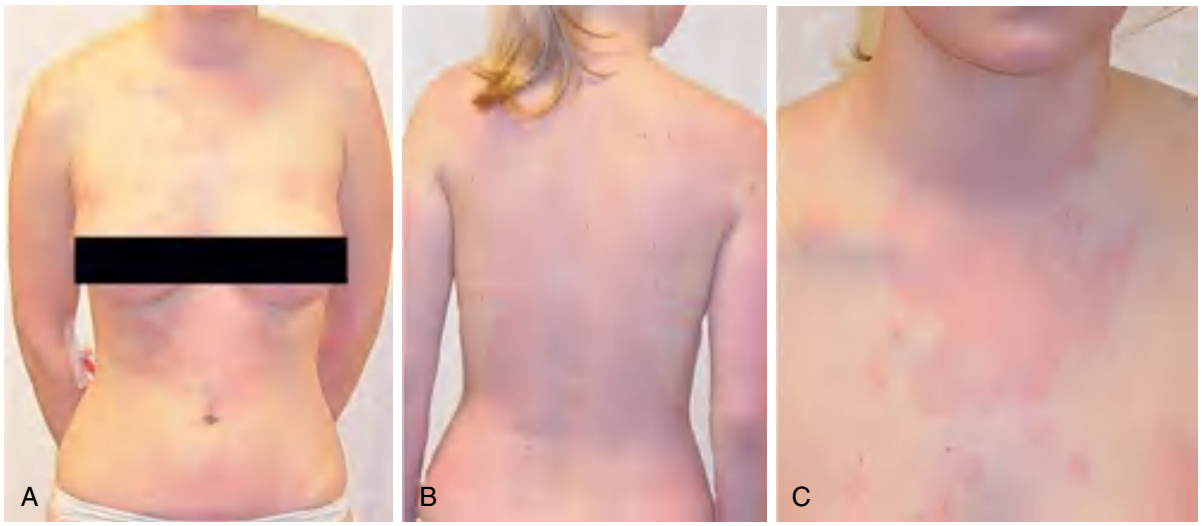

Fig. 762.1 Scombroid fish poisoning. A and B, Widespread erythematous rash predominantly on the face (not shown) and trunk of patient 1. C, Close-up view of the upper chest area. Note the absence of wheals. *(Modified from Jantschitsch C, Kinaciyan T, Manafi M, et al. Severe scombroid fish poisoning: an underrecognized dermatologic emergency. J Am Acad Dermatol. 2011;65[1]:246–247. Fig. 1.)*

dinoflagellate *Karenia brevis;* some raphidophytes (*Chattonella* spp.) also produce brevetoxins. **Brevetoxins** are a group of more than 10 lipid-soluble neurotoxins that activate sodium ion channels, causing nerve membrane depolarization. Shellfish are not affected by brevetoxins. Rinsing, cleaning, cooking, and freezing do not destroy the toxins, which also cannot be detected by taste or smell.

The onset of clinical manifestations of neurotoxic shellfish poisoning occurs from within a few minutes up to 18 hours after consumption. Most symptoms are gastrointestinal (nausea, vomiting, and diarrhea) or neurologic (numbness and tingling of the lips, mouth, face, and extremities, ataxia, partial limb paralysis, reversal of hot and cold sensation, slurred speech, headache, and fatigue). Neurotoxic shellfish poisoning is similar to a mild case of paralytic shellfish poisoning.

Treatment

There are no specific antidotes for brevetoxins. Treatment involves mostly supportive care. Brevenal, a natural antagonist of brevetoxin produced by *K. brevis,* may be used as a form of treatment in the future.

DIARRHETIC SHELLFISH POISONING

Several outbreaks of diarrhetic shellfish poisoning have been reported in Europe after consumption of mussels, cockles, and other shellfish. The dinoflagellates *Dinophysis* and *Prorocentrum* produce **okadaic acid** and its derivatives, the **dinophysistoxins.** These compounds inhibit protein phosphatases. The intracellular accumulation of phosphorylated proteins causes increased fluid secretion by gut cells via calcium influx, which is mediated by cyclic adenosine monophosphate and prostaglandins.

Patients have severe diarrhea. Care is supportive and directed at rehydration. The illness is self-limited, and recovery occurs in 3-4 days; few patients require hospitalization.

AMNESIC SHELLFISH POISONING

Amnesic shellfish poisoning has been identified after consumption of shellfish from the United States, Spain, and the United Kingdom. The responsible toxin, **domoic acid,** comes from a diatom, *Pseudonitzschia multiseries,* and is a potent glutamate agonist, disrupting neurochemical transmission in the brain. It also binds to glutamate receptors, which increase calcium influx, producing neuronal swelling in the hippocampal area of the brain and death.

The initial clinical manifestations are gastrointestinal with nausea, vomiting, diarrhea, and abdominal cramps within 24 hours of ingestion. Neurologic symptoms may follow including headache, confusion, and short-term memory loss. Memory loss is closely related to advanced age with those >50 years more likely to suffer from memory loss lasting months to years.

PUFFERFISH POISONING

The consumption of pufferfish (blowfish) in certain geographic areas such as Japan and the Indo-Pacific Ocean is associated with a lethal neurotoxic illness due to **tetrodotoxin**. Fugu, a Japanese delicacy, is sought after in part because of the subtle neurotoxic effects experienced upon eating, including perioral paresthesias and a dissociative feeling. While a trained fugu chef will remove the most toxic parts of the fish, the toxin is still found in varying degrees.

Tetrodotoxin, which is also found in the blue-ringed octopus, causes a paralytic illness due to the blockade of voltage-dependent sodium channels. Early symptoms include paresthesias, nausea, and dizziness, which progresses to weakness, numbness, and incoordination. Autonomic compromise may also occur with bradycardia and hypotension. In the most severe of cases, respiratory compromise requires assisted ventilation.

There is no specific antidote for tetrodotoxin pufferfish poisoning.

AZASPIRACID POISONING

The azaspiracids are a class of algal toxins associated with **harmful algal blooms (HABs).** Azaspiracid poisoning results from ingestion of contaminated bivalve shellfish, especially mussels. Azaspiracid toxins are distributed throughout the muscle tissue in the shellfish. Azaspiracid is cytotoxic to cells and an inhibitor of Ca^{2+} channels in plasma membranes. Symptoms start 6-18 hours after ingestion and include nausea, vomiting, severe stomach cramps, and diarrhea, which often persist up to 5 days.

Cyanobacteria (blue-green algae) also produce HABs; exposure is usually during recreational water sports and may be cutaneous or gastrointestinal. Symptoms include rash, cough, abdominal pain, diarrhea, nausea, emesis, muscle aches, watery eyes, weakness, or sore throat.

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762.4 Melamine Poisoning

Katherine Baranowski and Diane P. Calello

Melamine (1,3,5-triazine-2,4,6-triamine, or $C_3H_6N_6$) is found in many plastics, adhesives, laminated products, cement, cleansers, fire retardant paint, and more. Melamine poisoning from food products was unheard of until 2007, when melamine-tainted pet food caused the death of many dogs and cats in the United States. In 2008, feeding of melamine-tainted infant formula to more than 300,000 children resulted in urolithiasis and resultant kidney injuries, 50,000 hospitalizations, and 6 deaths in China. This was the first reported epidemic of melamine-tainted milk products.

Melamine contains 66% nitrogen by mass. The illegal addition of melamine to infant formula can give the formula a milky appearance and falsely raise the protein content as measured by nitrogen testing. Melamine, combined with cyanuric acid, forms cyanurate crystals in the kidneys. Along with protein, uric acid, and phosphate, melamine forms renal calculi. The melamine stones and gravel can be treated with hydration, alkalinization, or lithotripsy. Acute renal failure requires supportive care and dialysis if needed.

Clinical manifestations are initially subtle and nonspecific. The severity is dose related. The first symptoms in affected infants are unexplained crying (especially when urinating), vomiting, and discolored urine caused by the formation of stones and gravel in the urinary tract. Urinary obstruction and acute renal failure follow. In the absence of a specific diagnosis, death from renal failure may occur. Whether children with melamine-induced renal failure will have chronic renal sequelae is currently unknown.

In addition to the more well-known renal toxicity, cognitive defects can be seen after acute, chronic, or prenatal exposure. Dissolved and insoluble melamine and its insoluble metabolites all have the potential to cause neurotoxicity.

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Chapter 763

Biological and Chemical Terrorism

*Theodore J. Cieslak, Jonathan Newmark, and Mark G. Kortepeter**

In April of 2017, an attack on the town of Khan Shaykhun in Syria employed a poisonous "nerve agent" (likely sarin) that resulted in the deaths of at least 92 civilians, many of them young children. The attack intentionally targeted civilian neighborhoods at the time children were getting ready for school, which is strong evidence that its purpose was terror, not warfare. Terrorist actions targeting children are not novel. Brought to the forefront of American consciousness by Timothy McVeigh's references to child fatalities as "collateral damage" during the Oklahoma City bombing in April 1995, the intentional targeting of children became a global reality with the attack upon a school in Beslan, Russia, in September 2004. The attack, which left 334 dead (including 186 children), presaged additional attacks specifically directed against children. School shootings have become an all too frequent occurrence in the United States with over 175 children dying from mass shootings on school grounds since 1999.

Paralleling the targeting of children is an apparent trend toward the use of "unconventional" weapons of terror. In 1984, members of the Rajneeshee cult employed *Salmonella typhi* in a wave of intentional poisonings that affected 751 persons, including 142 teenage patrons of a popular pizza parlor. In 1995, the Aum Shinrikyo cult killed 12 and sickened thousands by intentionally releasing sarin nerve agent in the Tokyo subway system. A disgruntled scientist allegedly deployed anthrax spores via the U.S. mail in October 2001, killing 5 and injuring 17 in an attack upon a nation already reeling in the wake of the 9/11 attacks. Conflicts in Afghanistan, Syria, and Iraq from 2012 to 2016 led to another spike in chemical attacks.

These developments remind us that terrorists can strike at any time, utilizing any number of unconventional weapons, including biologic and chemical agents. Children will not be spared in these attacks on civilians, and indeed schools and daycare sites may be the targets of these actions.

ETIOLOGY

Although terrorists may choose to use **weapons of opportunity,** agents that are readily available to some member of the terrorist group, the motives of terrorists often are obscure and difficult to predict. Prevention and response strategies should thus concentrate not on those agents most likely to be used but, rather, on those agents that, if used, would constitute the gravest potential threats to public health and security.

Biologic threat agents, including pathogens and toxins, have been divided by the Centers for Disease Control and Prevention (CDC) into three categories, with **category A** including diseases caused by those six agents posing the greatest threat: anthrax, plague (see Chapter 249.3), tularemia (see Chapter 252), smallpox, botulism (see Chapter 256), and the viral hemorrhagic fevers, including Ebola (see Chapter 317).

Terrorists could also procure and release a vast array of potentially harmful chemicals. The Chemical Threat Risk Assessment prepared by the U.S. Department of Homeland Security lists over 170 chemical compounds as potential threats in accidental or deliberate scenarios. Tank cars full of flammable industrial gases and liquids, corrosive industrial acids and bases, poisonous compounds such as cyanides and nitrites, pesticides, dioxins, and explosives traverse our railways and roads daily. Four classes of "military-grade" chemicals with a history of use in warfare or manufactured specifically for use as weapons include the organophosphate-based nerve agents, vesicants, cyanides (misleadingly referred to as "blood agents"), and certain pulmonary irritants or "choking agents."

EPIDEMIOLOGY AND PEDIATRIC-SPECIFIC CONCERNS

Large-scale attacks on civilian targets will likely involve pediatric victims. Children may be more susceptible than adults to the effects of certain biologic and chemical agents (see Chapter 759). A thinner and less-keratinized epidermis makes dermally active agents, such as mustard or trichothecene mycotoxins, a greater risk to children than to adults. A larger surface area per unit volume further increases the problem. A small relative blood volume makes children more susceptible to the volume losses associated with enteric infections such as cholera and to gastrointestinal intoxications such as might be seen with exposure to the staphylococcal enterotoxins. The high minute ventilation of children, compared with that of adults, increases the threat of agents delivered via the inhalational route. The fact that children live "closer to the ground" compounds this effect when heavier-than-air chemicals are involved.

*The views expressed herein are those of the authors and do not necessarily reflect the position of the University of Nebraska, the U.S. Department of Defense, Health and Human Services, and Veterans' Affairs, or their component entities.

An immature blood-brain barrier may heighten the risk of central nervous system toxicity from nerve agents. Developmental considerations make it less likely that a child would readily flee an area of danger, thereby increasing exposure to these various adverse effects. Moreover, children are more likely to be terrified at the sight of responders in personal protective ensembles.

Children appear to have a unique susceptibility to certain agents that might be used by terrorists. Although adults generally suffer only a brief, self-limited incapacitating illness after infection with Venezuelan equine encephalitis virus, young children are more likely to experience seizures, permanent neurologic sequelae, and death. In the case of smallpox, waning herd immunity may disproportionately affect children. Vaccine-induced immunity to smallpox diminishes significantly after 3-10 years. Although most adults are considered susceptible to smallpox given that routine civilian immunization ceased in the early 1970s, older adults may have some residual protection from death, if not from the development of disease. Today's children are among the first to grow up in a world without any individual or herd immunity to smallpox.

Children also may experience unique disease manifestations not seen in adults. Suppurative parotitis is a common characteristic finding among children with melioidosis but is not generally seen in adults with *Burkholderia pseudomallei* infection (see Chapter 251.2). Seizures, often the presenting symptom of cyanide or nerve agent poisoning, may be much more difficult to recognize clinically in children than in adults, more likely presenting as unresponsiveness or change in mental status than tonic-clonic episodes.

Pediatricians are likely to experience unique problems in managing childhood victims of a biologic or chemical attack. Many of the drugs useful in treating such casualties are unfamiliar to pediatricians or have relative contraindications in childhood. The fluoroquinolones and tetracyclines are commonly cited as agents of choice in the treatment and prophylaxis of anthrax, plague, tularemia, brucellosis, and Q fever. Both drug classes are often avoided in children, although the risk of morbidity and mortality from diseases induced by agents of bioterrorism far outweighs the minor risk associated with short-term use of these agents. Ciprofloxacin received, as its first licensed pediatric indication, approval from the FDA for use in the prophylaxis of anthrax after inhalational exposure during a terrorist attack; doxycycline and levofloxacin are licensed specifically in children for the same indication. Levofloxacin is also licensed for postexposure prophylaxis of children against plague, and moxifloxacin is considered an acceptable alternative to first-line therapies for the treatment of plague in those less than 18 years of age. Immunizations potentially useful in preventing biologic agent–induced diseases are often not approved for use in pediatric patients. The available anthrax vaccine is licensed only for those between 18 and 65 years. The plague vaccine, currently out of production and probably ineffective against inhalational exposures, was approved only for individuals ages 18-61 years. The live replicating smallpox vaccine (ACAM2000), a live vaccine employing vaccinia virus, can cause fetal demise when given to pregnant women. A nonreplicating smallpox (and mpox) vaccine (Jynneos) was introduced in 2019.

Many otherwise useful pharmaceutical agents are not available in pediatric dosing regimens. The military distributes nerve agent antidote kits consisting of prefilled autoinjectors designed for the rapid administration of atropine and pralidoxime. Many emergency departments and some ambulances stock these kits. The doses of agents contained in the nerve agent antidote kit are calculated for soldiers and thus are inappropriate for young children, and pediatric pralidoxime autoinjectors are not yet available. Atropine autoinjectors specifically formulated for children are approved by the FDA, although their availability is limited. Unfortunately, there is no pediatric combination autoinjector containing atropine and pralidoxime, the backbone of acute nerve agent treatment in adults. Moreover, children smaller than 7 kg (15 pounds) are too small for safe use of atropine autoinjectors, while obtaining venous access may be time-consuming and extremely difficult in a contaminated environment.

Although physical protective measures and devices (e.g., "gas masks") are likely to be of little utility in a civilian terrorism setting, such commercially available devices are not often available in pediatric sizes. The Israeli experience during the first Gulf War suggests that frightened parents may improperly use such masks on their children, resulting in inadvertent suffocation.

In the event of a large-scale terrorist attack, there may be an insufficient number of pediatric hospital beds. In any large disaster, excess bed capacity might potentially be provided at civilian and veterans hospitals under the auspices of the National Disaster Medical System. Although that system now specifically tracks pediatric beds, none of these would be found in the Veterans Administration system and few are likely to exist elsewhere. The situation is even more dire regarding burn unit beds, which may be needed in an attack with vesicants such as sulfur mustard.

CLINICAL MANIFESTATIONS

Should a terrorist attack occur, clinicians may be called on to make prompt diagnoses and render rapid lifesaving treatments before the results of confirmatory diagnostic tests are available. Although each potential agent of terrorism produces its own unique clinical manifestations, it is useful for the frontline clinician to consider their effects in terms of a limited number of distinct clinical syndromes. This approach helps clinicians make prompt, rational decisions regarding empirical therapy. Casualties resulting from a terrorist attack would either experience symptoms immediately upon exposure to an agent (or within the first several hours after exposure) or would see their symptoms develop slowly over a period of days to weeks. In the former case, the sinister nature of the event is often obvious and the etiology more likely to be conventional or chemical in nature.

Biologic agents differ from conventional, chemical (see Chapter 759), and nuclear (see Chapter 758) weapons in that they have inherent incubation periods. Consequently, patients are likely to present distant in time and place from the point of an unannounced and unnoticed exposure to a biologic agent. Whereas traditional first responders, such as firefighters and paramedics, may be at the forefront of a conventional or chemical terrorism response, the primary care physician or emergency room is likely to constitute the first line of defense against the effects of a biologic agent.

Casualties can thus be categorized as either immediate or delayed in presentation. Within each of these categories, patients can be further classified as having primarily respiratory, neuromuscular, or dermatologic manifestations (Table 763.1). A limited number of agents may cause each particular syndrome, permitting institution of empiric therapy targeted at a short list of potential etiologies. The viral hemorrhagic fevers might manifest as fever and a bleeding diathesis; these agents are considered separately in Chapter 317. In most cases, supportive care is the mainstay of hemorrhagic fever treatment, although two drugs (Inmazeb, Ebanga) have recently been licensed for the treatment of adults and children with Ebola.

Sudden-Onset Neuromuscular Syndrome: Nerve Agents

The very rapid onset of neuromuscular symptoms after an exposure should lead the clinician to consider nerve agent intoxication. The nerve agents (*tabun, sarin, soman, and VX)* are **organophosphate** analogs of common pesticides that act as potent inhibitors of the enzyme acetylcholinesterase. The so-called "Novichok" agents, used in deliberate attacks upon Russian targets in Salisbury, UK (2018) and Tomsk, Russia (2020), also belong to this agent class. The nerve agents are hazardous via ingestion, inhalation, or cutaneous absorption (see Chapter 94).

The inhibition of cholinesterase by these compounds results in the accumulation of acetylcholine at neural and neuromuscular junctions, causing excess stimulation. The resultant **cholinergic**

Table 763.1 Diseases Caused by Agents of Chemical and Biologic Terrorism, Classified by Syndrome

	NEUROMUSCULAR SYMPTOMS PROMINENT	RESPIRATORY SYMPTOMS PROMINENT	DERMATOLOGIC FINDINGS PROMINENT
Sudden-onset or intermediate-onset	Nerve agents	Chlorine Phosgene Cyanide	Mustard Lewisite
Delayed-onset	Botulism	Anthrax Plague Tularemia Ricin	Smallpox

syndrome involves central, nicotinic, and muscarinic effects. Central effects are both muscarinically and nicotinically mediated and include altered mental status progressing rapidly to lethargy and coma, as well as ataxia, convulsions, and central respiratory depression. Studies on pesticide exposure suggest that children may be more prone to central neurologic dysfunction with organophosphate toxicity than adults. The most lethal effects are respiratory, which result not only from central effects but also from direct paralysis of the diaphragm and other respiratory muscles (nicotinic effects), as well as bronchospasm and bronchorrhea (muscarinic effects). Nicotinic effects include muscle fasciculations and twitching, followed by weakness, which can progress to flaccid paralysis as muscles fatigue. Importantly, flaccid paralysis is not present initially, as in a patient with botulinum toxin poisoning. In botulinum toxin poisoning, neurotransmitter cannot be released from the presynaptic terminal, whereas in nerve agent poisoning, excess neurotransmitter accumulates because acetylcholinesterase, the enzyme that turns off the transmitter, is inhibited. Muscarinic effects include miosis (the clinical hallmark of a patient who has suffered a non–life-threatening nerve agent challenge), visual blurring, profuse lacrimation, and watery rhinorrhea. Bronchospasm and increased bronchial secretions lead to cough, wheezing, dyspnea, and cyanosis. Cardiovascular manifestations include bradycardia, hypotension, and atrioventricular block. Flushing, sweating, salivation, nausea, vomiting, diarrhea, abdominal cramps, and urinary incontinence are also seen. In the absence of prompt intervention, death can quickly result from a combination of central effects and respiratory muscle paralysis.

The classic neuromuscular syndrome of extremely acute symptoms most commonly results from an aerosol or vapor exposure, the most likely route in a terrorist attack. But nerve agents are liquids at standard temperature and pressure and do not cause immediate irritation to skin. Liquid nerve agent may thus pass through the skin and enter the systemic circulation, causing cholinergic crisis. This can be delayed by minutes to hours, depending upon dose and body site. In children, because the stratum corneum of the skin forms only gradually, skin transit time will be reduced. Miosis may be a late development. *If the clinician suspects that the child may have been exposed to nerve agent via the cutaneous route, they should immediately treat, even if miosis has not yet developed.*

Cyanide poisoning is a major differential diagnosis of nerve agent poisoning in an attack scenario. Cyanide poisons cytochrome a3 in the mitochondrial electron transport chain and can cause an almost immediate and rather similar syndrome of loss of consciousness, immediate rapid breathing, status epilepticus, and rapid progression to cardiac arrest. Important clinical differential points include miosis, which is usually absent in cyanide poisoning, and the usual lack of cyanosis (ironically) due to the tissues' inability to use oxygen from the blood, causing venous blood to retain oxygen and remain red. In an emergency, it may be necessary to treat for both nerve agent and cyanide poisoning until the cause is definitively identified.

Delayed-Onset Neuromuscular Syndrome: Botulism

The delayed onset (hours to days after exposure) of neuromuscular symptoms is characteristic of botulism. Botulism, an intoxication rather than an infection, occurs after exposure to one of eight related neurotoxins produced by certain strains of *Clostridium botulinum,* a strictly anaerobic, spore-forming, gram-positive bacillus commonly found in soil. Naturally occurring botulism (see Chapter 256) usually follows ingestion of preformed toxin (food poisoning) or results from intestinal toxin production (infantile botulism). An aerosol exposure to the toxin would likely result in a case of clinical botulism indistinguishable from that caused by natural exposures.

Following exposure to botulinum toxin, clinical manifestations typically begin with bulbar palsies, causing patients to complain of ptosis, photophobia, and blurred vision resulting from difficulty in accommodation. Symptoms can progress to include dysarthria, dysphonia, dysphagia, and finally, a descending symmetric paralysis. Sensation and sensorium are typically not affected. In the absence of intervention, death often results from respiratory muscle failure. The mechanism of action of botulinum toxin is, in many ways, the opposite of that of nerve agent intoxication. Seizures, loss of consciousness, and peripheral twitching and fasciculations, typical of nerve agent poisoning, are not seen in botulism.

Sudden-Onset Respiratory Syndrome: Chlorine, Phosgene, and Cyanide

The acute onset of respiratory symptoms shortly after exposure should prompt the clinician to consider a range of potential chemical agents. Of note, nerve agents, discussed previously, may affect respiration via massive bronchial hypersecretion, bronchospasm, and respiratory muscle paresis. However, the nerve agent casualty will likely have generalized muscle involvement and central nervous system manifestations. In contrast, the toxic inhalants chlorine and phosgene produce respiratory distress without neuromuscular involvement or other features of cholinergic crisis. Several other pulmonary toxicants may produce similar clinical toxidromes.

Chlorine is a dense, acrid, yellow-green gas that is heavier than air. After mild to moderate exposure, ocular and nasal irritation occurs, followed by cough, a choking sensation, bronchospasm, and substernal chest tightness. Pulmonary edema, mediated by hydrochloric acid and free oxygen radical generation, follows moderate to severe exposures within 30 minutes to several hours. Hypoxemia and hypovolemia secondary to noncardiogenic pulmonary edema are the factors responsible for death.

Phosgene, like chlorine, is a common industrial compound that was used as a weapon on the battlefields of World War I. Its odor has been described as similar to "new-mown hay." Like chlorine, phosgene exposure also is thought to result in the generation of hydrochloric acid, contributing particularly to upper airway, nasal, and conjunctival irritation. Acylation reactions caused by the effects of phosgene on the pulmonary alveolar-capillary membrane lead to pulmonary edema. Phosgene lung injury also may be mediated, in part, by an inflammatory reaction associated with leukotriene production. Patients with mild to moderate exposures to phosgene

may be asymptomatic, a fact that may cause victims to remain in a contaminated area. Noncardiogenic pulmonary edema or "dry land drowning" occurs 4-24 hours after exposure and is dose dependent, with heavier exposures causing earlier symptoms. Dyspnea may precede radiologic findings. In severe exposures, pulmonary edema may be so marked as to result in hypovolemia and hypotension. As in the case of chlorine, death results from hypoxemia and asphyxia.

Cyanide, by contrast, is a cellular poison capable of causing protean clinical manifestations, not a pulmonary toxicant. Initially, cyanide toxicity is most likely to manifest as tachypnea and hyperpnea, progressing rapidly to apnea in cases with significant exposure (see Chapter 94). The efficacy of cyanide as a chemical terrorism agent is limited by its volatility in open air and relatively low lethality compared with nerve agents. Released in a closed room, however, cyanide could have devastating effects, as evidenced by its use in the Nazi gas chambers during World War II. Cyanide inhibits cytochrome a3, interfering with normal mitochondrial oxidative metabolism and leading to cellular anoxia and lactic acidosis. In addition to respiratory distress, early findings among cyanide victims include tachycardia, flushing, dizziness, headache, diaphoresis, nausea, and vomiting. With greater exposure, seizures, coma, apnea, and cardiac arrest may follow within minutes. An elevated anion gap metabolic acidosis is typically present and decreased peripheral oxygen utilization leads to an elevated mixed venous oxygen saturation value.

Delayed-Onset Respiratory Syndrome: Anthrax, Plague, Tularemia, and Ricin

A delayed onset of respiratory symptoms (days after exposure) is characteristic of several infectious diseases and at least one toxin that might be adapted for sinister purposes by terrorists. Among the most threatening and problematic of these are anthrax, plague, tularemia, and ricin.

Anthrax is caused by infection with the gram-positive spore-forming rod *Bacillus anthracis*. Its ability to form a spore enables the anthrax bacillus to survive for long periods in the environment and enhances its potential as a weapon.

The vast majority of naturally occurring anthrax cases are cutaneous, acquired by close contact with the hides, wool, bone, and other by-products of infected ruminants (principally cattle, sheep, and goats). Cutaneous anthrax is amenable to therapy with a variety of antibiotics and is readily recognizable to experienced clinicians in endemic areas; consequently, it is rarely fatal. Although it is common in parts of Asia and sub-Saharan Africa, only two cases of cutaneous anthrax had occurred in the United States in the 9 years that preceded the attacks of 2001 (when 11 cutaneous cases were seen). Gastrointestinal anthrax has been described only once in the United States, in a drum circle participant whose drum heads were made from imported animal hides. In general, however, it occurs after the ingestion of contaminated meat. In the past, inhalational anthrax, or **woolsorters' disease,** was an occupational hazard of abattoir and textile workers. Now eliminated as a naturally occurring disease in the United States, it is this inhalational form of anthrax that poses the greatest terror threat. Following an inadvertent release in 1979 from a bioweapons facility at Sverdlovsk in the former Soviet Union, 66 of 77 (86%) known adult victims of inhalational anthrax died. In the 2001 attacks involving contaminated mail in the United States, 5 of 11 (46%) patients with inhalational anthrax died. Whether better intensive care modalities, changes in antibiotic therapy, or earlier recognition accounted for this improved mortality rate remains unknown.

Symptomatic *inhalational* anthrax typically begins 1-6 days after exposure, although incubation periods of up to several weeks have been reported. The disease begins as a flulike illness, characterized by fever, myalgia, headache, and cough. A brief intervening period of improvement sometimes follows, but rapid deterioration then ensues; high fever, dyspnea, cyanosis, and shock mark this second phase. Hemorrhagic meningitis occurs in up to 50% of cases. Chest radiographs obtained late in the course of illness may reveal a widened mediastinum or prominent mediastinal lymphadenopathy; pleural effusions also may be seen. Bacteremia is often so profound that Gram stains of peripheral blood may demonstrate the organism at this stage. Prompt treatment is imperative. Death occurs in as many as 95% of inhalational anthrax cases if such treatment is begun more than 48 hours after the onset of symptoms.

Whereas inhalational anthrax is a disease primarily of mediastinal lymphatic tissue, exposure to aerosolized plague bacilli typically leads to a primary pneumonia. Endemic **plague** is usually transmitted via the bites of fleas and is discussed in Chapter 249.3. The causative organism of all forms of human plague, *Yersinia pestis,* is a bipolar-staining, gram-negative facultative intracellular bacillus. An ability to survive within the macrophage aids its dissemination to distant sites following inoculation or inhalation. "Buboes," markedly swollen, exquisitely tender regional lymph nodes in the distribution of a bite, are the hallmark feature of bubonic plague. Fever and malaise are typically present, and septicemia often develops as bacteria gain access to the circulation. Petechiae, purpura, and overwhelming disseminated intravascular coagulopathy commonly occur, and 80% of bubonic plague victims ultimately have positive blood cultures. Plague is extremely lethal, as illustrated by the fact that the "Black Death" eliminated one-third of the population of Europe during the Middle Ages.

Intentional aerosol dissemination of *Y. pestis* would likely result in a preponderance of pneumonic plague cases. Pneumonic plague may also arise secondarily after seeding of the lungs of septicemic patients. Symptoms include fever, chills, malaise, headache, and cough. Chest radiographs may reveal a patchy consolidation, and the classic clinical finding is blood-streaked sputum. Disseminated intravascular coagulation and overwhelming sepsis typically develop as the disease progresses. Untreated pneumonic plague has a fatality rate approaching 100%.

Tularemia is a highly infectious disease caused by the gram-negative coccobacillus *Francisella tularensis.* Naturally occurring tularemia is discussed in Chapter 252. The high degree of infectivity of *F. tularensis* (<10 organisms are thought to be necessary to produce infection via inhalation), as well as its survivability in the environment, contributes to its inclusion on the CDC's list of Category A agents. Several clinical forms of endemic tularemia are known, but inhalational exposure resulting from a terrorist attack would likely lead to a plaguelike primary pneumonia or to typhoidal tularemia, manifesting as a variety of nonspecific symptoms, including fever, malaise, and abdominal pain.

Ricin is a protein toxin derived from the castor bean plant *(Ricinus communis)* that inhibits ribosomal protein synthesis. It is highly toxic in animal studies when inhaled and may result in the delayed onset of respiratory distress, pulmonary edema, and acute respiratory failure. If injected, it may cause a sepsis-like syndrome that may progress to multiorgan system failure; ingestion can lead to severe gastroenteritis. Ricin-containing letters were mailed to a U.S. Senate office building in 2004, to President Obama and New York City Mayor Bloomberg in 2013, and to President Trump in 2020, although no persons were sickened in any of the attacks.

Intermediate-Onset Dermatologic Syndrome: Mustard and Lewisite

The development of skin lesions within hours to days of exposure is characteristic of the chemical vesicants. These compounds, often referred to as **blistering agents**, are cellular poisons and include the alkylating agent mustard and the organic arsenical agent lewisite. Injury to rapidly reproducing cells begins within minutes of contact with these agents. Clinical effects typically become evident several hours after exposure to mustard, whereas patients exposed to lewisite feel immediate pain. Both mustard and lewisite affect the eyes and respiratory tract, and their inadvertent ingestion may produce significant gastrointestinal symptoms. Mustard exposure may lead, several days later, to bone marrow suppression. With

a large inhalational challenge, mustard may also cause an acute respiratory syndrome, particularly affecting the upper airway and presenting with laryngospasm and stridor.

Delayed-Onset Dermatologic Syndrome: Smallpox

The appearance of an exanthem days to weeks after exposure is likely to be a presenting feature of smallpox. Caused by infection with variola virus, a member of the *Orthopoxvirus* family, smallpox has an incubation period of 7-17 days. This would likely permit the wide dispersal of asymptomatic exposed persons, thus contributing to the spread of an outbreak. During the incubation period, the virus replicates in the upper respiratory tract. A primary viremia ensues, during which time seeding of the liver and spleen occurs. A secondary viremia then develops, the skin is seeded, and the classic exanthem of smallpox appears.

Symptoms of smallpox begin abruptly during the phase of secondary viremia and include fever, rigors, vomiting, headache, backache, and extreme malaise. Within 2-4 days, macules appear on the face and extremities and then progress in synchronous fashion to papules, pustules, and finally scabs. As the scabs separate, survivors often are left with disfiguring, depigmented scars. The synchronous nature of the rash and its centrifugal distribution distinguish smallpox from chickenpox, which has a centripetal distribution. Historically, smallpox had a 30% mortality rate, with death typically resulting from visceral organ involvement.

DIAGNOSIS

In some cases, the terrorist nature of a chemical or biologic attack may be obvious; for example, a chemical attack in which victims succumb in close temporal and geographic proximity to a dispersal device or when terrorists announce their attack. In other instances, the clinician may need to rely on epidemiologic clues to suspect an intentional release of chemical or biologic agents. The presence of large numbers of victims clustered in time and space should raise the index of suspicion, as should cases of unexpected death or unexpectedly severe disease. Diseases unusual in a given locale, in a given age group, or during a certain season likewise may warrant further investigation. Simultaneous outbreaks of a disease in noncontiguous areas should cause one to consider an intentional release (as in the 2001 mail-borne anthrax attacks), as should outbreaks of multiple diseases in the same area. Even a single case of a rare disorder such as anthrax or certain viral hemorrhagic fevers would be suspicious, and a single case of smallpox would almost certainly be the result of an intentional dissemination. Large numbers of dying animals might provide evidence of an unnatural aerosol release, as would evidence of disparate attack rates between those known to be indoors and outdoors at a given time.

In a mass casualty setting, diagnoses may be made largely on clinical grounds. The diagnosis of nerve agent intoxication is based primarily on clinical recognition and patient response to antidotal therapy. Several simple rapid detection devices developed for military use can detect the presence of nerve agents in the environment. Some of these are now commercially available and are stocked in certain emergency departments and public safety vehicles. Measurements of acetylcholinesterase in plasma or erythrocytes of nerve agent victims may be helpful in long-term prognostication, but the correlation between cholinesterase levels and clinical effects is often poor, and the test is rarely available on an emergency basis.

Botulism should be suspected clinically among patients presenting with a symmetric, descending, flaccid paralysis. Although the differential diagnosis of botulism includes other uncommon neurologic disorders, such as myasthenia gravis and the Guillain-Barré syndrome, the presence of multiple casualties with similar symptoms should aid in the determination of a botulism outbreak. Electromyography is useful in supporting the diagnosis.

Initially the diagnosis of cyanide poisoning also will likely be made on clinical grounds in the presence of the appropriate toxidrome. An unusually high anion gap metabolic acidosis with elevated serum lactate and an oxygen concentration greater than expected in mixed venous blood lend support to the clinical diagnosis. Elevated blood cyanide concentrations can confirm the clinical suspicion.

Of all the chemical and biological agents, the only ones for which immediate therapy without waiting for definitive diagnosis is potentially lifesaving and mandatory are nerve agents and cyanide poisoning. If these are suspected, they should be treated before waiting for further diagnostic certainty.

Anthrax should be suspected upon finding gram-positive bacilli in skin biopsy material (in the case of cutaneous disease), blood smears, pleural fluid, or spinal fluid. Chest radiographs demonstrating a widened mediastinum in the context of fever and constitutional signs and, in the absence of another obvious explanation (e.g., blunt trauma or postsurgical infection), should also lead one to consider the diagnosis. Confirmation can be obtained by blood culture.

A diagnosis of plague can be suspected on finding bipolar "safety-pin"–staining bacilli in Gram or Wayson stains of sputum or aspirated lymph node material; confirmation is obtained by culturing *Y. pestis* from blood, sputum, or lymph node aspirate. The organism grows on standard blood or MacConkey TRA agars, but it is often misidentified by automated systems. *F. tularensis,* the causative agent of tularemia, grows poorly on standard media; its growth is enhanced on media containing cysteine. Because of its extreme infectivity, however, many laboratories prefer to make a diagnosis via polymerase chain reaction or serologically using an enzyme-linked immunosorbent assay or serum agglutination assay.

Smallpox should be suspected on clinical grounds and can be confirmed by culture or electron microscopy of scabs or vesicular fluid, although the manipulation of clinical material from suspected smallpox victims should be attempted only at public health laboratories able to employ maximum biocontainment (Biosafety Level 4) precautions. Similar caution should be exercised with specimens from patients with various viral hemorrhagic fevers.

PREVENTION

Preventive measures can be considered in both a preexposure and a postexposure context. **Preexposure protection** against a chemical or biologic attack may consist of physical, chemical, or immunologic measures. **Physical protection** against primary attack often involves gas masks and protective suits; such equipment is used by the military and by certain hazardous materials response teams, but it is unlikely to be available to civilians at the precise moment that a release occurs. Medical personnel need to understand the principles of physical protection as they apply to infection control and the spread of contamination.

Pneumonic plague is spread through respiratory droplets. Droplet precautions, including the use of simple surgical masks, are thus warranted for providers caring for patients with plague. Smallpox is transmitted by droplet nuclei. Airborne precautions, including (ideally) a high-efficiency particulate air filter mask, are thus warranted with smallpox victims. Patients with certain viral hemorrhagic fevers, such as those caused by filoviruses (Ebola, Marburg) and arenaviruses, should be managed using a combination of droplet and contact precautions, ideally in a specialized biocontainment unit. Most other biologic agent victims can be safely cared for with the use of standard precautions. In the case of chemical agents, residual mustard or nerve agent on the skin or clothing of victims might potentially pose a hazard to medical personnel. For such victims, whenever possible, clothing should be removed, and the patients decontaminated using copious amounts of water before extensive medical care is rendered. Most other chemical agents are volatile enough that spread of an agent among patients or from patient to caregiver is unlikely.

Preexposure chemical prophylaxis might be used on the basis of credible intelligence reports. Should officials deem that the threatened release of a specific biologic agent appears imminent, antibiotics might be distributed to a population before exposure. Opportunities to employ such a strategy are likely to be limited, although federal and state officials are examining various mechanisms for such employment. In military settings, pyridostigmine is FDA-approved as pretreatment against expected nerve agent attack. It is not approved for use in children, and it is not likely to be recommended in civilian settings.

Although licensed vaccines **(preexposure immunologic measures)** against anthrax and smallpox have been developed, widespread use of either vaccine is likely to be problematic, especially in children. The anthrax vaccine is licensed only for those persons age 18 years and older, is given as a five-dose series over 18 months, and requires annual booster doses. These considerations make civilian employment of the current anthrax vaccine on a large scale unlikely, although recombinant anthrax vaccines requiring fewer doses are in development.

Significant obstacles to the widespread employment of smallpox vaccine also exist, although public health officials have contemplated the resumption of a smallpox vaccination campaign. Whereas in the past, the live replicating smallpox vaccine (prepared from vaccinia virus, an *Orthopoxvirus* related to variola) was used safely and successfully in young infants, it has a relatively high rate of serious complications in certain patients. *Fetal vaccinia* and demise can occur when pregnant women are vaccinated. *Vaccinia gangrenosa*, an often fatal complication, can occur when immunocompromised persons are vaccinated. *Eczema vaccinatum* occurs in those with preexisting dermatoses (atopic dermatitis). Severe vaccine-related encephalitis was well known during the era of widespread vaccination; because it occurs only in primary vaccines, it would disproportionately affect pediatric patients. Autoinoculation can occur when the virus present at the site of vaccination is manually transferred to other areas of skin or to the eye. Young children would presumably be at greater risk for such inadvertent transmission. Myocarditis has been reported following vaccinations of military recruits. A new nonreplicating vaccine may alleviate some of these concerns.

To manage complications associated with use of the replicating vaccine, vaccinia immune globulin should be available when one is undertaking a vaccination campaign. Vaccinia immune globulin (6000 U/kg intravenously) may be given to vaccine recipients who experience severe complications or to significantly immunocompromised individuals exposed to smallpox and in whom vaccination would be unsafe. In 2018, tecovirimat was approved by the FDA for the treatment of persons (including children) experiencing severe complications from vaccine. Vaccine, as well as vaccinia immune globulin and tecovirimat, can be obtained as needed upon consultation with officials at the CDC. In addition to a potential role in preexposure prophylaxis, vaccination may be effective in postexposure prophylaxis if given within the first 4 days after exposure.

Anthrax vaccine might similarly be employed in a postexposure setting. Some authorities recommend three doses of this vaccine as an adjunct to postexposure chemoprophylaxis after documented exposure to aerosolized anthrax spores. Nonetheless, postexposure administration of oral antibiotics constitutes the mainstay of management for asymptomatic victims believed to have been exposed to anthrax as well as to other bacterial agents such as plague and tularemia. Table 763.2 lists appropriate prophylactic regimens for various biologic exposures.

TREATMENT

Although Tables 763.2, 763.3, and 763.4 provide recommended therapies for overt diseases caused by various chemical and biologic agents, it is likely that the clinician attending to victims will need to make therapeutic decisions before the results of confirmatory diagnostic tests are available and in situations in which the diagnosis is not known with certainty. In particular, decontamination by hospital personnel in appropriate personal protective equipment is required for patients exposed to chemical agents who have not been adequately decontaminated in the prehospital setting (see Table 763.4). In such cases, it is useful to note that many diseases and symptoms caused by chemical and biologic agents will resolve with supportive care. Most cases of chlorine or phosgene exposure can be successfully managed by providing meticulous attention to oxygenation and fluid balance. Mustard victims may require intensive multisystem support, but no specific antidote or therapy is available. Many viral diseases, including most viral hemorrhagic fevers, as well as equine encephalitides, are also managed supportively.

In addition to ensuring adequate oxygenation, ventilation, and hydration, the clinician may need to provide specific empiric therapies on an urgent basis. Patients suffering from the sudden onset of severe neuromuscular symptoms may have nerve agent intoxication and should be given atropine (0.05-0.1 mg/kg) promptly for its antimuscarinic effects. Although atropine relieves bronchospasm and bradycardia, reduces bronchial secretions, and ameliorates the gastrointestinal effects of nausea, vomiting, and diarrhea, it does not improve skeletal muscle paralysis. 2-Pralidoxime chloride (*2-PAM*) cleaves the organophosphate moiety from cholinesterase and regenerates intact enzyme if "aging" has not occurred. The effect is most prominent at the neuromuscular junction and leads to improved muscle strength. Its prompt use (at a dose of 25-50 mg/kg) as an adjunct to atropine is recommended in all serious cases.

Ideally, both atropine and pralidoxime should be administered intravenously (IV) in severe cases, although the intraosseous route is acceptable. In the field, as time is of the essence in treating nerve agent poisoning, first responders are trained to administer atropine IM via autoinjector. Some experts also recommend that atropine be given IM in the presence of hypoxia to avoid arrhythmias associated with IV administration. Many emergency management services stock military-style autoinjector kits consisting of atropine and 2-PAM for IM injection. Pediatric atropine autoinjectors containing 0.5 or 1 mg of atropine are licensed and held in the Strategic National Stockpile, although kits intended for adults (with 2 mg of atropine and 600 mg of pralidoxime) may be used in children >2-3 years of age (Table 763.5). Autoinjectors cannot easily be used in the smallest infants.

Animal studies support the routine prophylactic administration of anticonvulsant doses of benzodiazepines, even in the absence of observable convulsive activity. Although diazepam has long been employed for this purpose, midazolam was recently granted FDA approval, and animal studies have shown it to have superior efficacy in treating acute nerve agent poisoning. Military and civilian stocks of diazepam autoinjectors are being replaced by midazolam autoinjectors.

Delayed neuromuscular symptoms in the setting of terrorism might be due to botulism. Supportive care, with meticulous attention to ventilatory support, is the mainstay of botulism treatment. Such support may be necessary for several months, making the management of a large-scale botulism outbreak especially problematic in terms of medical resources. A licensed heptavalent antitoxin (types A-G) is available through the CDC (1-800-232-4636). Administration of this antitoxin is unlikely to reverse disease in symptomatic patients but may prevent further progression. In addition, a pentavalent product (containing antibody against toxin types A-E but licensed only for treatment of type A or B intoxication), Botulism Immune Globulin Intravenous (Human; BabyBIG), is available through the California Department of Health Services (1-510-231-7600) specifically for the treatment of infant botulism.

The *rapid onset of respiratory symptoms* may signal an exposure to chlorine, phosgene, cyanide, or a number of other toxic industrial chemicals. Although the mainstay of therapy in virtually all of these exposures consists of removal to fresh air and intensive supportive care, cyanide intoxication often requires the administration of specific antidotes.

Table 763.2 CDC Category A Agents of Bioterrorism

DISEASE	CLINICAL FINDINGS	INCUBATION PERIOD (DAYS)	ISOLATION PRECAUTIONS	INITIAL TREATMENT	PROPHYLAXIS
Anthrax (inhalational) Patients who are clinically stable after 14 days can be switched to a single oral agent (as described in the prophylaxis section of this table) to complete a 60-day course	Febrile prodrome with rapid progression to mediastinal lymphadenitis and mediastinitis, sepsis, shock, and meningitis	1-5	Standard	See Table 763.3.	**Ciprofloxacin 30 mg/kg/day PO divided q12h*** (max 500 mg/dose) *or* **doxycycline 4.4 mg/kg/day PO divided q12h** (max 100 mg/dose) *or* clindamycin 30 mg/kg/day PO divided q8h (max 900 mg/dose) *or* levofloxacin 16 mg/kg/day PO divided q12h (max 250 mg/dose) *or* **amoxicillin 75 mg/kg/day PO divided q8h†** (max 1 g/dose) or penicillin VK 50-75 mg/kg/day divided q6-8h
Plague (pneumonic)	Febrile prodrome with rapid progression to fulminant pneumonia, hemoptysis, sepsis, disseminated intravascular coagulation	2-3	Droplet (for first 3 days of therapy)	Gentamicin** 1.25- 2.5 mg/kg IV q8h *or* doxycycline 2.2 mg/kg IV q12h *or* ciprofloxacin 15 mg/kg IV q12h *or* levofloxacin 8 mg/kg IV/PO q12h	Doxycycline 2.2 mg/kg PO q12h *or* ciprofloxacin 20 mg/kg PO q12h *or* levofloxacin 8 mg/kg PO q12h
Tularemia	Pneumonic: abrupt onset of fever with fulminant pneumonia Typhoidal: fever, malaise, abdominal pain	2-10	Standard	Options same as for plague‡, gentamicin preferred	Same as for plague‡
Smallpox	Febrile prodrome with synchronous, centrifugal, vesiculopustular exanthema	7-17	Airborne (+ contact)	Tecovirimat *Oral dosage by body weight:* 13 kg to <25 kg: 200 mg q12h 25 kg to <40 kg: 400 mg q12h 40 kg to <120 kg: 600 mg q12h ≥120 kg: 600 mg q8h *Intravenous infusion dosage by body weight:* 3 kg to <35 kg: 6 mg/kg q12h by IV infusion over 6 hr 35 kg to <120 kg: 200 mg q12h by IV infusion over 6 hr ≥120 kg: 300 mg q12h by IV infusion over 6 hr	Vaccination may be effective if given within the first several days after exposure
Botulism	Afebrile descending symmetric flaccid paralysis with cranial nerve palsies	1-5	Standard	Supportive care; antitoxin (see text) may halt the progression of symptoms but is unlikely to reverse them	No licensed preexposure prophylaxis is available; postexposure administration of antitoxin may prevent the development of symptoms
Viral hemorrhagic fevers	Febrile prodrome with rapid progression to shock, purpura, and bleeding diatheses	4-21	Contact (consider airborne in cases of massive hemorrhage)	Supportive care; ribavirin may be beneficial in treating Lassa fever, and perhaps other arenaviral hemorrhagic fevers	Ribavirin has been shown to be efficacious in the postexposure prophylaxis of Lassa fever

*Preferred drugs are shown in **bold**.
**Some experts say 4.5-7.5 mg/kg/day.
†Penicillin and amoxicillin should only be used when the strain of *Bacillus anthracis* is known to be susceptible.
‡Levofloxacin (as well as moxifloxacin) is licensed by the U.S. Food and Drug Administration for the prophylaxis and treatment of plague in the setting of a bioterror attack, but not tularemia.
PO, By mouth; IV, intravenously.

Table 763.3 Treatment of Inhalational Anthrax in Children

WHEN MENINGITIS PRESENT OR HAS NOT RULED OUT*	WHEN MENINGITIS CAN BE RULED OUT*
1. A bactericidal fluoroquinolone: **Ciprofloxacin 30 mg/kg/day IV divided q8h**† (max 400 mg/dose) *or* Levofloxacin 24 mg/kg/day IV divided q12h (max 250 mg/dose) *or* Moxifloxacin 12 mg/kg/day IV divided q12h (max 200 mg/dose; for children 3 mo to 2 yr); 10 mg/kg/day IV divided q12h (for children 2-5 yr); 8 mg/kg/day IV divided q12h (for children 6-11 yr); 400 mg IV qd (for children >12 yr and >45 kg)	1. A bactericidal antimicrobial: **Ciprofloxacin 30 mg/kg/day IV divided q8h** (max 400 mg/dose) *or* Levofloxacin 20 mg/kg/day IV divided q12h (max 250 mg/dose) *or* Imipenem 100 mg/kg/day IV divided q6h (max 1 g/dose) *or* Vancomycin 60 mg/kg/day IV divided q8h *or* **Penicillin G 400,000 U/kg/day IV divided q4h** (max 4 MU/dose) [if PCN sensitive] *or* Ampicillin 200 mg/kg/day IV divided q6h (max 3 g/dose)
2. A second bactericidal antimicrobial: **Meropenem 120 mg/kg/day IV divided q8h** (max 2 g/dose) *or* Imipenem 100 mg/kg/day IV divided q6h (max 1 g/dose) *or* Doripenem 120 mg/kg/day IV divided q8h (max 1 g/dose) *or* Vancomycin 60 mg/kg/day IV divided q8h *or* **Penicillin G** 400,000 U/kg/day IV divided q4h**‡ (max 4 MU/dose) [if PCN sensitive] *or* Ampicillin 400 mg/kg/day IV divided q6h (max 3 g/dose)	
3. A protein synthesis inhibitor: **Linezolid 30 mg/kg/day IV divided q8h** (for children <12 yr); 30 mg/kg/day IV divided q12h (for children >12 yr; max 600 mg/dose) *or* Clindamycin 40 mg/kg/day IV divided q8h (max 900 mg/dose) *or* Rifampin 20/mg/kg/day IV divided q12h (max 300 mg/dose) *or* Chloramphenicol 100 mg/kg/day IV divided q6h	2. A protein synthesis inhibitor: **Clindamycin 40 mg/kg/day IV divided q8h (max 900 mg/dose)** *or* Linezolid 30 mg/kg/day IV divided q8h (for children <12 yr); 30 mg/kg/day IV divided q12h (for children >12 yr; max 600 mg/dose) *or* Rifampin 20/mg/kg/day IV divided q12h (max 300 mg/dose) *or* Doxycycline 4.4 mg/kg/day IV loading dose (for children <45 kg; max 200 mg), followed by 4.4 mg/kg/day IV divided q12h; 200 mg IV loading dose, followed by 100 mg IV q12h (for children >45 kg)

*Meningitis occurs in approximately 50% of patients with inhalational anthrax.
**Some experts provide a range of 400,000–600,000 U/kg/d.
†Preferred drugs are shown in **bold**.
‡Penicillin and amoxicillin should only be used when the strain of *Bacillus anthracis* is known to be susceptible.
IV, Intravenous; qd, every day; PCN, penicillin.
Data from Bradley JS, Peacock G, Krug SE, et al. Pediatric anthrax clinical management. *Pediatrics*. 2014;133:e1411–e1436. Appendices 3 & 4.

The classic **cyanide antidote** utilizes a nitrite along with sodium thiosulfate and is given in two stages. The methemoglobin-forming agent (e.g., sodium nitrite) is administered first, because methemoglobin has a high affinity for cyanide and causes it to dissociate from cytochrome oxidase. Nitrite dosing in children should be based on body weight to avoid excessive methemoglobin formation and nitrite-induced hypotension. For the same reasons, nitrites should be infused slowly over 5-10 minutes. A sulfur donor, such as sodium thiosulfate, is given next. This compound is used as a substrate by the hepatic enzyme rhodanese, which converts cyanide to thiocyanate, a less toxic compound excreted in the urine. Thiosulfate treatment itself is efficacious and relatively benign and may be used alone for mild to moderate cases. Sodium nitrite and sodium thiosulfate are packaged together in standard antidote kits, along with amyl nitrite, a sodium nitrite substitute that can be inhaled in prehospital settings in which IV access is not available.

Many first responder agencies in the United States have replaced the traditional two-part cyanide antidote kit with hydroxocobalamin, which exchanges its hydroxy group for cyanide, forming harmless cyanocobalamin (vitamin B_{12}) that is subsequently excreted by the kidneys. Hydroxocobalamin use is not complicated by the potential for nitrite-induced hypotension or methemoglobinemia, and it has low toxicity. The recommended dose is 5 g in adults or 70 mg/kg in children, administered IV over 15 minutes. A second dose (5 g in adults; 70 mg/kg in children) may be repeated in severely affected patients. Side effects include modest hypertension and reddening of skin, mucous membranes, and urine that may last several days. Although no human controlled trials are currently available to compare hydroxocobalamin with nitrite/thiosulfate-based therapies, many authorities believe that hydroxocobalamin's efficacy and safety profile favor it as the cyanide antidote of choice, especially for children in the mass casualty context. To use hydroxocobalamin, however, the solution must be mixed immediately before use, in the field if need be, so first responders need to be properly trained to employ it.

Animal research suggests a modest benefit of steroid therapy in mitigating lung injury after chlorine inhalation; thus steroids may be considered for patients with chlorine exposure, especially as an adjunct to bronchodilators in those with bronchospasm and/or a history of asthma. Symptomatic relief has also been reported following chlorine exposure with nebulized 3.75% sodium bicarbonate therapy, though the impact of this regimen on pulmonary damage is unknown. Animal models have also suggested a benefit from antiinflammatory agents, including ibuprofen and *N*-acetylcysteine, which appear to ameliorate phosgene-induced pulmonary edema, as well as the utilization of low tidal volume ventilation (protective ventilation), although the results of such interventions have not yet been reported in clinical trials.

In cases in which the delayed onset of respiratory symptoms may be the result of a terrorist attack, consideration should be given to the empirical administration of an antibiotic effective against anthrax, plague, and tularemia. Ciprofloxacin (10-15 mg/kg IV q12 hours), levofloxacin (8 mg/kg IV q12 hours), or doxycycline (2.2 mg/kg IV q12 hours) is a reasonable choice. Although naturally occurring strains of *B. anthracis* usually are quite sensitive to penicillin G, these agents are chosen because penicillin-resistant strains of *B. anthracis* exist. Moreover, ciprofloxacin and doxycycline are effective against almost all known strains of *Y. pestis* and *F. tularensis*. Concerns about inducible β-lactamases in *B. anthracis* have led experts to recommend one to two additional antibiotics in patients with inhalational anthrax. Rifampin, vancomycin, penicillin or ampicillin, clindamycin, and imipenem are reasonable choices based on in vitro sensitivity data. Because *B. anthracis* relies on the production of two protein toxins, edema toxin and lethal toxin, for its virulence, drugs that act at the ribosome to disrupt protein synthesis (e.g., clindamycin, the macrolides) provide a theoretical advantage. Frequent meningeal involvement among inhalational anthrax victims makes agents with superior central nervous system penetration desirable. The treatment of anthrax is detailed in Table 763.3.

Table 763.4 Critical Chemical Agents of Terrorism

AGENT	TOXICITY	CLINICAL FINDINGS	ONSET	DECONTAMINATION*	MANAGEMENT
NERVE AGENTS					
Tabun, sarin, soman, VX	Anticholinesterase: muscarinic, nicotinic, central nervous system effects	Vapor: miosis, rhinorrhea, dyspnea Liquid: diaphoresis, vomiting Both: coma, paralysis, seizures, apnea	Seconds: vapor Minutes to hours: liquid	Vapor: fresh air, remove clothes, wash hair Liquid: remove clothes, wash skin, hair with copious soap and water, ocular irrigation	ABCs. Atropine: 0.05-0.1 mg/kg IV†, IM‡ (min: 0.1 mg, max: 5 mg), repeat q2-5 min prn for marked secretions, bronchospasm AND Pralidoxime: 25-50 mg/kg IV, IM§ (max: 1 g IV; 2 g IM), may repeat within 30-60 min prn, then again q1h for one or two doses prn for persistent weakness, high atropine requirement AND Diazepam: 0.3 mg/kg (max: 10 mg) IV *or* Lorazepam: 0.1 mg/kg IV, IM (max: 4 mg) *or* Midazolam: 0.2 mg/kg (max: 10 mg) IM prn for seizures or severe exposure
VESICANTS					
Mustard	Alkylation	Skin: erythema, vesicles Eye: inflammation Respiratory tract: inflammation	Hours	Skin: soap and water Eyes: water (effective only if done within minutes of exposure)	Symptomatic care
Lewisite	Arsenical		Immediate pain	Skin: soap and water Eyes: water (effective only if done within minutes of exposure)	Possibly British antilewisite (BAL) 3 mg/kg IM q4-6h for systemic effects of lewisite in severe cases
PULMONARY AGENTS					
Chlorine, phosgene	Liberate hydrochloric acid, alkylation	Eye, nose, and throat irritation (especially chlorine) Respiratory: bronchospasm, pulmonary edema (especially phosgene)	Minutes: eye, nose, and throat irritation, bronchospasm Hours: pulmonary edema	Fresh air Skin: water	Symptomatic care (see text)
CYANIDE					
	Cytochrome oxidase	Tachypnea, coma, seizures, apnea	Seconds	Fresh air	ABCs, 100% oxygen
	Inhibition: cellular anoxia, lactic acidosis			Skin: soap and water	Na bicarbonate prn metabolic acidosis; hydroxocobalamin 70 mg/kg IV (max: 5 g) *or* nitrite/thiosulfate, given as follows (see text): *Na nitrite (3%): dose (mL/kg)* (max: 10 mL) — *Estimated hemoglobin concentration (g/dL)* 0.27 — 10 0.33 — 12 (estimated for average child) 0.39 — 14 Followed by Na thiosulfate (25%): 1.65 mL/kg (max: 50 mL)

*Decontamination, especially for patients with significant nerve agent or vesicant exposure, should be performed by healthcare providers garbed in adequate personal protective equipment. For emergency department staff, this equipment consists of a nonencapsulated, chemically resistant body suit, boots, and gloves with a full-face air-purifier mask/hood.
†Intraosseous route is likely equivalent to intravenous.
‡Atropine might have some benefit via endotracheal tube or inhalation, as might aerosolized ipratropium. See also Table 741.5.
§Pralidoxime is reconstituted to 50 mg/mL (1 g in 20 mL water) for IV administration, and the total dose infused over 30 min, or may be given by continuous infusion (loading dose 25 mg/kg over 30 min, and then 10 mg/kg/hr). For IM use, it might be diluted to a concentration of 300 mg/mL (1 g added to 3 mL water—by analogy to the U.S. Army's Mark 1 autoinjector concentration) to effect a reasonable volume for injection. See also Table 741.5.
ABCs, Airway, breathing, and circulatory support; IM, intramuscularly; IV, intravenously; max, maximum; min, minimum; prn, as needed.
Adapted from Henretig FH, Cieslak TJ, Eitzen EM. Biological and chemical terrorism. *J Pediatr.* 2002;141:311–326.

Table 763.5 Pediatric Autoinjector Recommendations for Mass Casualties or Prehospital Care*

ATROPINE AUTOINJECTOR THERAPY		
APPROXIMATE AGE	**APPROXIMATE WEIGHT (KG)**	**AUTOINJECTOR SIZE (MG)**
<6 mo	<7.5	0.25
6 mo to 4 years	7.5-18	0.5
5-10 years	18-30	1.0
>10 years	>30	2.0

PRALIDOXIME AUTOINJECTOR THERAPY			
APPROXIMATE AGE (YEARS)	**APPROXIMATE WEIGHT (KG)**	**NUMBER OF AUTOINJECTORS**	**PRALIDOXIME DOSE (MG/KG)**
3-7	13-25	1	24-46
8-14	26-50	2	24-46
>14	>50	3	<35

*Consider adult pralidoxime autoinjector use for severely affected mass casualties when intravenous (IV) access or more precise mg/kg intramuscular (IM) dosing is logistically impractical. The initial dose using atropine autoinjectors is one autoinjector of each recommended size. The initial dose using pralidoxime autoinjectors is the recommended number of (adult-intended, 600 mg) autoinjectors. These latter may also be injected into an empty sterile vile; the contents redrawn through a filter needle into a small syringe may then provide a ready source of concentrated (300 mg/mL) pralidoxime solution for IM injection to infants. Autoinjectors may become available that provide adult doses of both atropine and pralidoxime in one injector; these could be used in children ≥3 years in lieu of two individual injectors and dosed as noted above for pralidoxime alone.

Raxibacumab, a monoclonal antibody that inhibits anthrax antigen binding to cell receptors, thus preventing toxins from entering cells, is approved for the treatment of inhalation anthrax in combination with antibiotics, as is obiltoxaximab, which neutralizes anthrax toxins. The adult dose of raxibacumab is 40 mg/kg given IV over 2 hours and 15 minutes. The dose for children is weight based: ≤15 kg, 80 mg/kg; >15-50 kg, 60 mg/kg; >50 kg, 40 mg/kg. Premedication with diphenhydramine IV or by mouth (PO) is recommended 1 hour before the infusion.

In patients with an established diagnosis of tularemia, gentamicin (5 mg/kg IV/IM divided 2 or 3 times/day) is the preferred choice for therapy due to the limited availability of streptomycin (15 mg/kg IM q12 hours). Bioterrorism-related plague should be treated with two distinct antibiotic classes until sensitivity patterns are known; gentamicin, streptomycin, ciprofloxacin, and levofloxacin are all approved agents for treatment of pneumonic plague in children (see Table 763.2). To be effective, therapy for pneumonic plague must be initiated within 24 hours of the onset of symptoms. There is little clinical experience with ricin-induced pulmonary injury. The mainstay of therapy is expected to be supportive care.

The management of **vesicant-induced injury** is similar to that for burn victims and is largely symptomatic (see Chapter 89). The major difference between thermal burns and vesicant burns is that vesicant casualties do not need the large volumes of fluid required by thermal burn victims, as their epidermis remains intact. These patients are at risk of overhydration if treated using thermal burn protocols. Mustard victims will benefit from the application of soothing skin lotions such as calamine and the administration of analgesics. Early intubation of severely exposed patients is warranted to guard against edematous airway compromise. Oxygen and mechanical ventilation may be needed, and meticulous attention to hydration is of paramount importance. Ongoing research suggests a role for oral *N*-acetylcysteine in mitigating chronic pulmonary effects due to mustard injury. Lewisite victims can be managed in much the same manner as mustard victims. Dimercaprol (British antilewisite) in peanut oil, given IM, may help ameliorate the systemic effects of lewisite, although few hospitals or pharmacies are likely to have this drug on hand.

The management of symptomatic smallpox victims also is largely supportive, with attention to pain control, hydration status, and respiratory sufficiency of primary importance. The parenteral antiviral compound cidofovir, licensed for the treatment of cytomegalovirus retinitis in HIV-infected patients, has in vitro efficacy against variola and other orthopoxviruses. Its utility in treating smallpox victims is untested. Moreover, in the face of a large outbreak of disease, wide parenteral use of this drug would be problematic. Tecovirimat demonstrates excellent in vitro activity against orthopoxviruses, but its utility in treating patients with smallpox is likewise untested.

In all chemical casualties, but especially if a liquid agent such as VX or mustard is suspected, decontamination is crucial and should be considered a primary medical intervention. Although this has been part of casualty doctrine in the civilian and military environments for decades, a 2016 study showed that disrobing eliminated 90% of contamination in normal volunteers; following this with showering using water or soap and water eliminated 99% of contamination. This has huge implications for the hospital management of possibly contaminated casualties, including children, and hospitals must plan to execute the decontamination mission at all levels.

For those faced with an acute chemical emergency, especially a mass casualty situation, a useful resource is the Chemical Hazard Emergency Medical Management website (https://chemm.hhs.gov), maintained by the Assistant Secretary for Preparedness and Response within the U.S. Department of Health and Human Services. Among its features is a decision support tool, CHEMM-IST, which aids in identification of the chemical a patient was exposed to.

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Chapter 764

Mass Psychogenic Illness

Jonathan W. Mink

Mass psychogenic illness refers to the rapid spread of illness signs and symptoms affecting members of a cohesive group, originating from a nervous system disturbance involving excitation, loss, or alteration of function, whereby physical complaints that are exhibited unconsciously have no corresponding organic etiology. Mass psychogenic illness shares features in common with **conversion disorder (functional neurologic system disorder)** (see Chapter 35) in that the symptoms are not consciously produced and are typically sensorimotor in nature. The physical symptoms are associated with significant distress and impairment; they commonly interfere with function at school or home and affect peer relationships. Some experts have argued that "functional" is a better used term than "psychogenic" because it does not imply etiology and does not reinforce dualist thinking about the mind being separate from the brain.

Much less is known about the biologic underpinnings and clinical features of mass psychogenic illness than is known about conversion disorder and other somatic symptom disorders. However, there are some important features in common with conversion disorder. These include sudden abrupt onset, inconsistency with known anatomy and physiology, atypical features, and inconsistency of symptoms over time. Specific features of mass psychogenic illness are the occurrence of these symptoms in a cohesive group; the presence of increased anxiety; spread of symptoms via sight, sound, or oral communication (including social media); and a high female:male ratio.

CLINICAL FEATURES AND DIAGNOSIS

There are many examples of mass psychogenic illness throughout history. The best known is perhaps that of the Salem "witches." Most widely reported examples of mass psychogenic illness are in adults, but there are several reports in children as well. In 2004, 10 teenage females from a school in rural North Carolina developed paroxysmal episodes resembling epilepsy or syncope. These females were from a cohesive social group (school-age students in a small school) and had similar symptoms. The symptoms were shown not to be consistent with either syncope or epilepsy, and they eventually resolved after a two-week holiday break from school. Another episode in Le Roy, New York, was an outbreak of a "tic-like" illness among high school students. The symptoms were atypical for tics because they were not preceded by a premonitory urge and could not be suppressed with effort. In addition, the symptoms were remarkably similar across the affected patients. Symptoms resolved over time. In the Le Roy example, there was likely an exacerbating role of both social media and mass media, which amplified the cohesiveness of the group. There has been a surge of cases of "tic-like" symptoms in adolescents during the COVID-19 pandemic. It has been suggested that social media, especially videos presented on the TikTok platform, has played an important role in the spread of these symptoms.

In a study of 280 environmental chemical incidents in the United Kingdom between 2007 and 2008, 7% were classified as mass psychogenic illness according to five diagnostic criteria: (1) presence of somatic (bodily) symptoms, (2) preexisting social connection between two or more of the affected people, (3) epidemic spread of symptoms, (4) attribution of symptoms by affected individuals (or by their parents or caregivers) to a threatening external agent of a physical (usually chemical, biologic, or radiologic) or spiritual nature, and (5) symptoms and signs that are not compatible with the environmental exposure specified by the affected individuals nor with any other environmental exposure that could reasonably be expected to have been present at the time of (or shortly before) the onset of symptoms.

One study has examined experimentally induced mass psychogenic illness. In a randomized controlled experiment, participants were assigned to one of three groups to study the effects of a simulated biologic threat and elements of social contagion. The three groups were (1) no-intervention control group, (2) psychogenic illness induction group, and (3) psychogenic illness induction plus media group. Groups 2 and 3 were told that the purpose of the study was to test the side effects of a carrier compound for an antiinfluenza medication. They were told that the compound did not produce serious side effects but was being evaluated with regard to mild side effects. In groups 2 and 3, professional actors were placed among the participants to feign illness during the study with symptoms of nausea, dizziness, and headache. Group 3 was also shown a documentary about the 1918 flu pandemic. The video contained interviews with survivors and vivid images of death and illness. The two psychogenic induction groups had 11 times more symptoms than did the control group. If a subject had a lifetime history of a traumatic event or depression, he or she was more likely to have symptoms. The documentary viewing was not associated with a higher rate of symptoms. This study confirmed the role of **"social contagion"** in mass psychogenic illness and provided a model for future studies of factors leading to such contagion.

TREATMENT STRATEGIES

Mass psychogenic illness is usually self-limited, but treatment requires careful reassurance and communication between physician and patient. Explanation models should be communicated in a sensitive manner so as not to appear dismissive of symptoms. When doctors and patients do not agree on the "reality" of the illness, the prognosis is worse. Thus media attention, medical and scientific disagreement, and legal proceedings must be managed in a way that does not exacerbate the symptoms or the illness.

In the Le Roy illness, treatment varied across individuals. The treatment strategies included cognitive-behavioral therapy, supportive psychotherapy, education, pharmacotherapy for coexisting anxiety, and alteration of social setting. Many of the patients sought multiple medical opinions. There were frequent discussions among public health and other medical officials and the local media outlets. Reduced media attention seemed to lead to more rapid improvement of symptoms in some patients.

It is helpful for healthcare providers to avoid the dichotomy of approaching illness using a medical model in which diseases are considered as being either physically *or* psychologically based. In contrast, a biobehavioral continuum of disease better characterizes illness as occurring across a spectrum ranging from a predominantly biologic etiology on one end to a predominantly psychosocial etiology on the other. It is beneficial to the patient for the treating physician to try to shift the emphasis from understanding the etiology to a path toward recovery.

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Chapter 765

Animal and Human Bites

David A. Hunstad

Many animals, besides domestic and stray dogs and cats, inflict bites on humans. The profile of such bites varies by country and region, based on community and living conditions, indigenous species, and opportunity for encounter.

EPIDEMIOLOGY

Worldwide there are tens of millions of dog bites each year, resulting in nearly 60,000 deaths annually from rabies (see Chapter 320). **Dog bites** represent approximately 80–90% of all bites in the United States, while 5–15% are from cats, 2–5% from rodents, and the remainder from rabbits, ferrets, farm animals, monkeys, and reptiles. An estimated 4.5 million persons in the United States are bitten by dogs annually; over 800,000 of those seek medical care. Bites from dogs are also most common in Bangladesh, India, Pakistan, and Myanmar, whereas in Nepal cattle and buffalo account for more than half of bites, followed by dogs, pigs, and horses. Approximately 1% of dog bite wounds and 6% of cat bite wounds in the United States require hospitalization. During the past three decades, there have been several dozen deaths per year in the United States from dog-inflicted injuries; the majority of these occurred in children under 11 years of age. Various studies have examined the incidence of dog bite injuries by dog breed. Compared with other breeds, bites by pit bull terriers and mixed-breed dogs account for higher rates of hospital admission, lower Glasgow Coma Scores at admission, and an increased risk of death. Unaltered male dogs account for approximately 75% of attacks, while nursing female dogs may inflict injury when humans attempt to handle their puppies.

The majority of dog attacks on children in the United States occur between the ages of 6 and 11 years, with a slight predominance in males. Approximately 65% of attacks occur around the home, 75% of biting animals are known by the children, and 50% of attacks are said to be unprovoked. Similar statistics apply in Canada, where 70% of all bites reported in one study were sustained by children age 2-14 years; 65% of dogs involved in biting were part of the family or extended family.

Of the approximately 450,000 reported **cat bites** per year occurring in the United States, nearly all are inflicted by known household animals. Because rodent bites (rat, mouse, gerbil) do not represent reportable conditions, little is known about the epidemiology of these injuries or the incidence of infection after rodent-inflicted bites or scratches.

Few data exist on the incidence and demographics of **human bite** injuries in pediatric patients; however, preschool and early school-age children appear to be at greatest risk of sustaining an injury from a human bite, often in daycare or preschool settings. In some series, the proportion of human bites is highest among adolescents, an age group in which fist-to-teeth injuries (so-called "fight bites") become more common.

CLINICAL MANIFESTATIONS

Dog bite–related injuries can be divided into three categories of almost equal incidence: abrasions, puncture wounds, and lacerations with or without an associated avulsion of tissue. Bites from larger dogs may also involve crush injury to tissues. In contrast, the most common type of injury from cat bites is a puncture wound, often penetrating deep into tissue or joint spaces. Human bite injuries are of two types: an occlusion injury that is incurred when the upper and lower teeth come together on a body part, or a clenched-fist injury that occurs when the injured fist, usually on the dominant hand, strikes the teeth of another individual.

DIAGNOSIS

Management of the bite victim should begin with a thorough history and physical examination. Careful attention should be paid to the circumstances surrounding the bite event (e.g., species and number of animals, type of animal [domestic or wild], whether the attack was provoked or unprovoked, location of the attack), a history of drug allergies, and the immunization status of the child (tetanus) and animal (rabies). During physical examination, meticulous attention should be paid to the type, size, and depth of the injury; the presence of any foreign material in the wound; the status of underlying structures; and, when the bite is on an extremity, the exact location of the injury, an assessment of possibly involved structures, and the range of motion of the affected area. Photographs of the injury should be recorded in the patient's medical record. Radiographs of the affected part should be considered if it is likely that a bone or joint was penetrated or fractured or if foreign material is present in the wound. The possibility of a fracture or penetrating injury of the skull should particularly be considered in infants who have sustained dog bite injuries to the face or head.

COMPLICATIONS

Infection is the most common complication of bite injuries regardless of the species of biting animal. In most cases, culture specimens from a fresh dog bite wound are not likely to be clinically useful. Although potentially pathogenic bacteria have been isolated from up to 80% of dog bite wounds that are brought to medical attention within 8 hours of the bite, the infection rate for wounds receiving medical attention in <8 hours is relatively low (2.5–20%). Cultures should be obtained from the wound if there is clinical evidence of infection or if the patient is immunocompromised. *Capnocytophaga canimorsus* is isolated from approximately 5% of infected wounds in immunocompromised patients (especially asplenia) and can cause serious systemic infection in these individuals. In contrast to dogs, the infection rate in cat bite wounds, even those that receive prompt medical attention, is >50%; therefore cat bites should be closely monitored for signs of infection.

The rate of infection after rodent bite injuries is not known. Most of the oral flora of rats is similar to that of other mammals; however, up to 50% of rats, depending on worldwide geography, may harbor strains of *Streptobacillus moniliformis* and *Spirillum minus,* both of which cause rat bite fever (see Chapter 766).

All human bite wounds, regardless of the mechanism of injury, should be considered high risk for infection. Current recommendations do not support obtaining cultures at the time of the bite as it does not change empiric antibiotic therapy; however, any infected wounds should be cultured.

Table 765.1 lists common causes of soft tissue bacterial infections after dog, cat, or other animal bites. Bites of humans or cats, those in which treatment is delayed, those in immunocompromised patients, and those associated with deep puncture wounds or significant crush injury carry a higher risk for infection. An elevated risk for infection is also present if the bite is to certain anatomic regions (e.g., hand, foot, or genitals) or there is penetration of bone or tendons.

TREATMENT

Table 765.2 outlines the management of human or animal bite wounds to reduce risk for infection. The wound should be anesthetized, cleaned, and irrigated with sterile saline using moderate pressure. Irrigation with antibiotic-containing solutions provides no advantage over saline alone and may cause local irritation of the tissues. Puncture wounds should be thoroughly cleansed and

Table 765.1 Microorganisms Associated with Animal Bites

DOG BITES
Staphylococcus species
Streptococcus species
Eikenella species
Pasteurella species
Proteus species
Klebsiella species
Haemophilus species
Enterobacter species
Capnocytophaga canimorsus
Bacteroides species
Moraxella species
Corynebacterium species
Neisseria species
Fusobacterium species
Prevotella species
Porphyromonas species

CAT BITES
Pasteurella species
Actinomyces species
Propionibacterium species
Bacteroides species
Fusobacterium species
Clostridium species
Wolinella species
Peptostreptococcus species
Staphylococcus species
Streptococcus species

HERBIVORE BITES
Actinobacillus lignieresii
Actinobacillus suis
Pasteurella multocida
Pasteurella caballi

SWINE BITES
Pasteurella aerogenes
Pasteurella multocida
Bacteroides species
Proteus species
Actinobacillus suis
Streptococcus species
Flavobacterium species
Mycoplasma species

RODENT BITES
Streptobacillus moniliformis
Spirillum minus (in Asia)

PRIMATE BITES
Bacteroides species
Fusobacterium species
Eikenella corrodens
Streptococcus species
Enterococcus species
Staphylococcus species
Enterobacterales
Herpes B virus

LARGE REPTILE (CROCODILE, ALLIGATOR) BITES
Aeromonas hydrophila
Pseudomonas pseudomallei (in Asia)
Pseudomonas aeruginosa
Proteus species
Enterococcus species
Clostridium species

Adapted from Perkins Garth A, Harris NS, Spanierman CS. Animal bites in emergency medicine. Available at: http://emedicine.medscape.com/article/768875-overview, updated October 7, 2021; accessed November 27, 2021. Reprinted with permission from eMedicine.com.

Table 765.2 Initial Management of Bite Wounds

HISTORY
Animal bite: Ascertain the type of animal, whether the bite was provoked or unprovoked, and the situation/environment in which the bite occurred. Follow rabies guidelines (see Chapter 320) for details on management of bites that carry a risk of rabies.
Patient: Obtain information on antimicrobial allergies, current medications, splenectomy, liver disease, or immunosuppressive conditions.

PHYSICAL EXAMINATION
If possible, photograph the wound and record its location, type, and approximate depth; range of motion; possibility of joint penetration; presence of edema or crush injury; nerve and tendon function; and signs of infection.

CULTURE
Aerobic and anaerobic cultures should be taken from infected wounds (not from fresh wounds).

IRRIGATION AND DEBRIDEMENT
Irrigate with water or sterile saline and debride devitalized or necrotic tissue.

RADIOGRAPHS
Plain radiographs should be obtained if bony penetration is possible or suspected; radiographs can also provide a baseline for future evaluation of osteomyelitis.

WOUND CLOSURE
Primary wound closure is usually not advocated unless wounds are extensive and closure is necessary for cosmetic or functional reasons, especially large facial or neck wounds or those overlying the joints. When possible, delayed primary closure or allowing the wound to close by secondary intention is recommended.

ANTIMICROBIAL THERAPY
Early presenting (uninfected) wounds: provide prophylactic antimicrobials for (1) moderate-to-severe injuries, especially if preexisting edema or significant crush injury is present; (2) bone or joint space penetration; (3) deep hand wounds; (4) immunocompromised patients; (5) wounds adjacent to prosthetic material; and (6) wounds in close proximity to the genital area. In most cases, coverage should include *Pasteurella* (*Eikenella* in human bites), *Staphylococcus, Streptococcus,* and anaerobes including *Fusobacterium, Porphyromonas, Prevotella,* and *Bacteroides* spp. See Table 765.3 for recommended antibiotics.
Infected wounds: See Table 765.3 for oral antibiotic recommendations. In cases where intravenous antibiotics are deemed necessary, antimicrobial choices include ampicillin/sulbactam, piperacillin-tazobactam, cefoxitin, or ertapenem.

HOSPITALIZATION
Indications include signs and symptoms of systemic toxicity and worsening infection.

IMMUNIZATIONS
Provide tetanus and rabies immunization, if indicated.

ELEVATION
Elevation may be required if edema is present. Lack of elevation is a common cause of therapeutic failure.

IMMOBILIZATION
For significant injuries, immobilize the extremity, especially the hands, with a splint.

FOLLOW-UP
Patients should be reminded to follow up within 48 hours or sooner for worsening or unresolved infections and continued pain.

REPORTING
Reporting the incident to a local health department may be required.

Adapted from Goldstein EJC, Abrahamian FM. Bites. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th ed. Philadelphia: Elsevier; 2020: Table 315-3.

Table 765.3 Recommended Empirical Oral Antibiotics for Bite Wound Prophylaxis and Treatment

ANTIBIOTIC	RECOMMENDED ADULT DOSE	RECOMMENDED CHILD DOSE*
AGENT OF CHOICE (A) Amoxicillin-clavulanate	875/125 mg twice daily	45 mg/kg per dose (amoxicillin component) twice daily
ALTERNATE COMBINATION THERAPY: B OR C (WITH ANAEROBIC ACTIVITY) PLUS E, F, G, H, OR I		
(B) Metronidazole	500 mg three times daily	10 mg/kg per dose three times daily
Or:		
(C) Clindamycin	450 mg three times daily	10 mg/kg per dose three times daily
PLUS, ONE OF THE FOLLOWING: (D) Doxycycline	100 mg twice daily	Not for use in children <8 yr old
(E) Trimethoprim-sulfamethoxazole	160/800 mg (1 DS tab) twice daily	4 to 5 mg/kg (trimethoprim component) per dose* twice daily
(F) Penicillin V potassium	500 mg four times daily	12.5 mg/kg per dose four times daily
(G) Cefuroxime	500 mg twice daily	10 mg/kg per dose twice daily
(H) Moxifloxacin	400 mg once daily	Use with caution in children

*Child dose should not exceed recommended adult dose.
From Phillips LL, Semple J: Bites and injuries inflicted by wild and domestic animals. In Auerbach PS, Cushing TA, Harris NS (editors): *Auerbach's Wilderness Medicine*, 7th ed, vol 1. Philadelphia: Elsevier, 2017; Table 30.3, p. 623.

gently irrigated with a catheter or blunt-tipped needle; blind, high-pressure irrigation should not be employed. Avulsed or devitalized tissue should be debrided and any fluctuant areas incised and drained.

Surgical approaches to management of bite wounds may include primary closure, delayed primary closure (i.e., in 3-5 days), or healing by secondary intention. Factors to be considered are the type, size, and depth of the wound; the anatomic location; the presence of infection; the time since the injury; and the potential for cosmetic disfigurement. Appropriate surgical consultation (e.g., general pediatric surgery; plastic, hand, or orthopedic surgery) should be obtained promptly for all patients with deep or extensive wounds; wounds involving the hands, face, or bones and joints; and infected wounds that require open drainage. Although there is general agreement that visibly infected wounds and those that are more than 24 hours old should not be sutured, there is a spectrum of practice regarding the closing of wounds <8 hours old with no evidence of infection. Because all bite wounds to the hand are at high risk for infection, particularly if there has been disruption of the tendons or penetration of the bones, surgical consultation is almost always indicated, and delayed primary closure is recommended for many bite wounds of the hands. Facial lacerations are at lower risk for secondary infection because of the excellent blood supply to this region. Given this fact and cosmetic considerations, many plastic surgeons advocate primary closure of facial bite wounds that have been brought to medical attention within 8 hours.

Similarly, there are few comparative trials addressing the efficacy and selection of antimicrobial agents for **prophylaxis** of bite injuries. The bacteriology of bite wound infections is more often a reflection of the oral flora of the biting animal than the skin flora of the victim (see Table 765.1). Because many aerobic and anaerobic bacterial species colonizing the oral cavity of the biting animal have the potential to invade local tissue, multiply, and cause tissue destruction, most bite wound infections are polymicrobial.

Despite substantial homology in the oral bacterial flora of humans, dogs, and cats, important differences exist among the biting species, reflected in the types of wound infections that occur. The predominant bacterial species isolated from infected dog bite wounds are *Staphylococcus aureus* (20–30%), *Pasteurella multocida* (20–30%), *Staphylococcus intermedius* (25%), and *C. canimorsus;* approximately one-half of dog bite wound infections also contain mixed anaerobes. Similar species are isolated from infected cat bite wounds; however, *P. multocida* is the predominant species in at least 50% of cat bite wound infections. At least 50% of rats harbor *S. moniliformis* in the oropharynx, and approximately 25% in Asia harbor *S. minus,* a small, uncultivatable gram-negative organism. In infected human bite wounds, nontypable strains of *Haemophilus influenzae, Eikenella corrodens, S. aureus,* α-hemolytic streptococci, and β-lactamase–producing aerobes (~50%) are the predominant species. Clenched-fist injuries are particularly prone to infection by *Eikenella* spp. (25%) and other anaerobes (50%).

The choice between oral and parenteral antimicrobial therapy should be based on the severity of the wound, the presence and degree of overt infection, signs of systemic toxicity, and the patient's immune status. **Amoxicillin-clavulanate is an excellent choice for empiric oral therapy** for human and animal bite wounds because of its activity against most bacteria that are isolated from infected bites (Table 765.3). Similarly, **ampicillin-sulbactam or piperacillin-tazobactam is preferred for patients who will receive empiric parenteral therapy**. Penicillin G is the drug of choice for prophylaxis and treatment of rat bite injuries, as this agent has excellent activity against *S. moniliformis* and *S. minus*. Because first-generation cephalosporins have limited activity against *P. multocida* and *E. corrodens,* they should not be used for prophylaxis or empiric therapy of bite wound infections. Therapeutic alternatives for bite wound infections in penicillin-allergic patients are limited; clindamycin plus trimethoprim-sulfamethoxazole is the most commonly suggested regimen for these patients. Tetracycline is the drug of choice for penicillin-allergic patients who have sustained rat bite injuries.

Although **tetanus** occurs only rarely after human or animal bite injuries, it is important to obtain a detailed immunization history and to provide tetanus toxoid to all patients who are incompletely immunized or who received their most recent tetanus immunization more than five years prior. The need for postexposure **rabies** vaccination in victims of dog and cat bites depends on whether the biting animal is known to have been vaccinated and, most importantly, on local experience with rabid animals in the community. Bites from bats, foxes, skunks, and raccoons should be considered

high risk for rabies, and postexposure prophylaxis is uniformly indicated. For dogs, cats, and other animals that are known or captured, observation for 7-10 days by the local animal control department is indicated, and rabies prophylaxis can be delayed as long as the animal remains asymptomatic. If a biting dog or cat has escaped, a decision about rabies prophylaxis can be based on the circumstances surrounding the bite and advice from local infectious disease specialists and/or health department officials. Worldwide, animal bites and contacts result annually in more than 10 million courses of rabies postexposure prophylaxis.

In human bites where the biter's blood may have contaminated the wound, risk for hepatitis B, hepatitis C, and HIV infections should be considered (see Chapters 322 and 406).

PREVENTION

It is possible to reduce the risk of animal bite injury with anticipatory guidance. Parents should be routinely counseled during prenatal visits and routine health maintenance examinations about the risks of having potentially biting pets in the household. All patients should be cautioned against harboring exotic animals as pets. All young children should be closely supervised, particularly when in the presence of animals, and from a very early age should be taught to respect animals and to be aware of their potential to inflict injury. Reduction of the rate of human bite injuries, particularly in daycare centers and schools, can be achieved by good surveillance of the children and adequate teacher-to-child ratios.

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Chapter 766

Rat Bite Fever

David A. Hunstad

ETIOLOGY

Rat bite fever is a generic term that has been applied to at least two distinct clinical syndromes, each caused by a different microbial agent. Rat bite fever caused by *Streptobacillus moniliformis* is most commonly reported in the United States as well as in Brazil, Canada, Mexico, Paraguay, Great Britain, and France; it has been identified elsewhere in Europe and in Australia. *S. moniliformis* is a gram-negative bacillus that is present in the nasopharyngeal flora of many laboratory and wild rats. Infection with *S. moniliformis* most commonly occurs following the bite of a rat; however, infection has also been reported in individuals who have been scratched by rats, in those who have handled dead rats, and in those who have ingested milk contaminated with the bacterium (termed **Haverhill fever**). Rat bite fever may also be transmitted by bites from wild mice. Rat bite fever caused by *Spirillum minus,* called **sodoku** (after the Japanese for "rat" and "poison"), is most commonly reported in Asia. *S. minus* is a small, spiral, aerobic gram-negative organism. Reports of rat bite fever from Africa are rare, suggesting under recognition rather than absence of the disease.

CLINICAL COURSE

The incubation period for the streptobacillary form of rat bite fever is variable, ranging from 3-10 days. The illness is characterized by an *abrupt* onset of fever up to 41°C (105.8°F) in over 90% of reported cases, as well as severe throbbing headache, intense myalgias, chills, and vomiting. In virtually all instances, the lesion at the cutaneous inoculation site has healed by the time that systemic systems first appear. Shortly after the onset of the fever, a polymorphous rash occurs in up to 75% of patients. In most patients, the rash consists of blotchy red maculopapular lesions that often have a petechial component; the distribution of the rash is variable, but it is typically most dense on the extremities (Fig. 766.1). Hemorrhagic vesicles may develop on the hands and feet and are very tender to palpation (Fig. 766.2).

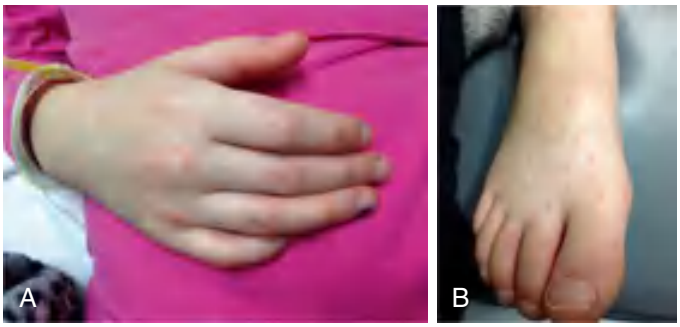

Fig. 766.1 Morbilliform rash on the hands/palms (A) and feet (B) of a patient with rat bite fever. *(From Vetter NM, Feder HM Jr, Ratzan RM. Rat bite fever caused by a kiss. Am J Emer Med. 2015;34:1190.e3–1190.e4. Figs. 1 and 3.)*

Fig. 766.2 Hemorrhagic vesicles on the first and third toes of a patient with advanced rat bite fever. *(From Elliott SP. Rat bite fever and Streptobacillus moniliformis. Clin Microbiol Rev. 22007;20:13–22. Fig. 3.)*

Approximately 50% of patients have arthritis, which first manifests toward the end of the first week of disease; early on, the arthritis may be migratory. If untreated, fever, rash, and arthritis last from 14-21 days, often with a biphasic pattern to the fever and arthritis. A wide range of complications are reported in patients with rat bite fever, the most common being pneumonia, persistent arthritis, brain and soft tissue abscesses, and, less commonly, myocarditis or endocarditis. The mortality rate in untreated rat bite fever is estimated to be 10–15%.

The incubation period of sodoku is longer (14-21 days) than that of the streptobacillary form of disease. The hallmark of *Spirillum*-induced disease is fever associated with an indurated, often suppurative, nonhealing lesion at the bite site. Lymphadenitis and lymphadenopathy are invariably present in the regional nodes that drain the inoculation site, and many patients have a generalized macular rash most prominent

when fever is present. In untreated patients, sodoku has a relapsing and remitting course; symptoms abate after 5-7 days of chills and fever but recur 7-10 days later. There may be multiple cycles if the disease is not recognized and treated.

DIAGNOSIS

Diagnosis of the streptobacillary form of rat bite fever is difficult because the disease is uncommon and can be confused with Rocky Mountain spotted fever or (less commonly) meningococcemia. Furthermore, *S. moniliformis* is difficult both to isolate and to identify with classic bacteriologic techniques. The organism is fastidious and is inhibited by sodium polyanethol sulfonate, an additive present in many commercial blood culture bottles. Therefore the clinical microbiology laboratory should be notified when this infection is suspected so that additional media can be inoculated. A definitive diagnosis is made when *S. moniliformis* is recovered from blood or joint fluid or is identified in human samples by polymerase chain reaction (PCR), which has been used successfully in humans.

Diagnosis of sodoku is made on clinical grounds because there are no diagnostic serologic tests and culture of *S. minus* has not been achieved in laboratory media. Rarely, the organism may be visualized in Gram-stained smears of pus from the inoculation site. Approximately 50% of patients exhibit a false-positive Venereal Disease Research Laboratory (VDRL) test.

TREATMENT

Penicillin is the drug of choice for both forms of rat bite fever. Intravenous penicillin G or intramuscular penicillin G procaine is recommended for 7-10 days; a regimen of IV penicillin G for 5-7 days followed by oral penicillin V for an additional 7 days has also been used. Doxycycline, gentamicin, or streptomycin represent effective alternatives for penicillin-allergic patients. Patients with endocarditis caused by *S. moniliformis* require high-dose penicillin G for 4 weeks; the addition of streptomycin or gentamicin might be helpful.

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Chapter 767

Mpox (Monkeypox)

David A. Hunstad

Since the eradication of **smallpox** (variola), mpox (formerly known as monkeypox) virus has, for humans, become the most important member of the genus ***Orthopoxvirus***. Monkeys are the predominant host for the virus; however, it may be endemic in African rainforest squirrels and is present in African rats, mice, domestic pigs, hedgehogs, and opossums. It has also been identified in and transmitted by imported prairie dogs in the United States and has affected elephants in zoos. Severity of infection varies by viral strain and by host; for example, disease is relatively mild in cynomolgus monkeys but severe in orangutans.

Mpox was first observed in humans from West and Central Africa in the 1970s at the time that smallpox had been eradicated from the area. In the 1970s, the secondary attack rate was around 3% (a stark comparison to the 80% seen in unvaccinated smallpox contacts). Few cases were observed over the next 2 decades; however, during a subsequent outbreak in the 1990s, when immunity to smallpox was no longer prevalent in the population, the secondary attack rate exceeded 75%. Mpox was introduced into the United States in 2003, presumably through rodents from Ghana that infected prairie dogs that were subsequently distributed as pets. Before 2022, primary transmission of the disease was from infected animal to human by bite or by human contact with an infected animal's blood, wound discharge, or other body fluids. Human-to-human transmission was previously thought to be uncommon, but a global outbreak in 2022 was linked to a shift to human-to-human transmission.

As of early 2023, nearly 87,000 cases were documented globally. Although children have comprised up to 40% of cases in previous outbreaks, the epidemiology of the current outbreak is different; less than 700 cases (<2%) have been reported in children and adolescents ≤20 years old. Mpox is currently spread predominantly through close human-to-human contact. The most recent outbreak has affected mostly gay, bisexual, and other men who have sex with men. Patients living with advanced HIV (with low CD4 counts) are at increased risk for severe disease. Although children typically acquire mpox from household contact, sexual contact is the primary route of transmission for adolescents. Mpox virus can persist on surfaces in households with an affected person.

CLINICAL COURSE

The classic clinical signs, symptoms, and course of mpox are similar to those of smallpox, although typically milder. After an incubation period of 10-14 days, during which the mpox virus replicates in lymphoid tissues, humans experience an abrupt onset of malaise, fever, myalgia, headache, and severe backache. Nonproductive cough, nausea, vomiting, and abdominal pain may be present. Generalized lymphadenopathy, a finding unusual in smallpox, is invariably present during the acute stages of mpox illness. After a prodrome of 2-4 days, an exanthem appears on the face and progresses inferiorly, including the palms and soles. As the rash spreads, fevers begin to abate. The rash is initially macular but transforms within hours to firm papules that rapidly vesiculate and become pustular over 2-3 days (Table 767.1). Unlike smallpox lesions but similar to chickenpox lesions, the lesions of mpox tend to occur in crops (Fig. 767.1). Late into the second week of illness, the lesions begin to desiccate, crust, scab, and fall off. During the 2022 global outbreak, lesions often occurred in the genital and anorectal areas and in the mouth (Fig. 767.2); cutaneous lesions are

Table 767.1 Mpox: Lesion Progression Through the Scab Stage

STAGE	STAGE DURATION (DAYS)*	CHARACTERISTICS
Enanthem		Sometimes, lesions first form on the tongue and in the mouth.
Macules	1-2	Macular lesions appear.
Papules	1-2	Lesions typically progress from macular (flat) to papular (raised).
Vesicles	1-2	Lesions then typically become vesicular (raised and filled with clear fluid).
Pustules	5-7	Lesions then typically become pustular (filled with opaque fluid) – sharply raised, usually round, and firm to the touch (deep seated). Finally, lesions typically develop a depression in the center (umbilication). The pustules will remain for approximately 5-7 days before beginning to crust.
Scabs	7-14	By the end of the second week, pustules have crusted and scabbed over. Scabs will remain for about a week before beginning to fall off.

*This is a typical timeline, but timelines can vary.
From Centers for Disease Control and Prevention. Key Characteristics for identifying Mpox. https://www.cdc.gov/poxvirus/mpox/clinicians/clinical-recognition.html

Fig. 767.1 A, Legs and feet of an mpox (endemic) patient. B, Legs and feet of a smallpox patient at an analogous stage of rash (pustular). *(A, Courtesy Joseph M. Harvey, MD. B, Courtesy J. Nobel, Jr., MD, Centers for Disease Control and Prevention.)*

Fig. 767.2 Clinical presentation of mpox. A, Pustules in the genital and pubic region, in which the initial umbilication has progressed to necrotic crust with central depression. B, Three semiconfluent pustular lesions with a depressed center located on the left side of the tongue dorsum. C, Pearly acral vesicles embedded in the thick stratum corneum of the palmar skin, shotty on palpation. D, Scattered papules, pustules, and umbilicated pustules surrounded by an erythematous halo on the lateral aspect of the chest and left arm. E, Pustules circumferentially distributed on the anal margin and perianal skin. F, A pustular lesion with a crusted center on the semimucosa of the lower lip, close to the right oral commissure. G, Primary inoculation site with a large, crusted lesion on the right cheek. H, The right palatine tonsil is reddened and enlarged and has a fibrin-covered ulcer. I, The penile glans and foreskin have lesions of varying sizes and stages of evolution, with edema surrounding the larger ulcer. *(From Tarín-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. Lancet. 2022;400[10353]:661–669. Fig. 1; Photos A–C, E–G, I taken by Eloy José Tarín-Vicente, MD; Photos D, H by Maria Ubals, MD.)*

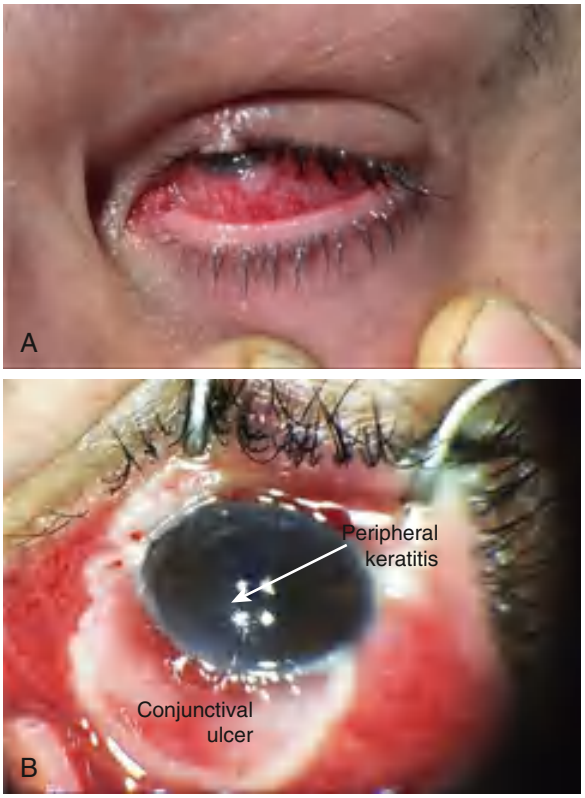

Fig. 767.3 Left eye in a patient with HIV-associated immunocompromise and ocular mpox, with conjunctivitis and conjunctival lesion earlier in the course of mpox illness (**A**), and with conjunctival ulcer and peripheral keratitis later in the course of mpox illness (**B**) — United States, August–September 2022. (*A courtesy Nathanael Adjei-Kyeremeh. B courtesy Dharmendra R. Patel; From Cash-Goldwasser S, Labuda SM, McCormick DW, et al. Ocular monkeypox – United States, July–September 2020. MMWR. 2022;71:1343–1347. Fig. 2.)*

less often disseminated with occasionally only a single lesion noted. Additionally, fever and other systemic symptoms may occur before the rash, *after* the rash, or *not at all*. Disseminated systemic or focal disease may include encephalitis, pharyngitis, myocarditis, arthritis, proctitis, lymphadenopathy, pneumonia, and ocular involvement (Fig. 767.3).

Mpox should be suspected in any child or adolescent who has the characteristic prodrome associated with a poxlike eruption and a history of close contact with someone who has been diagnosed with mpox, residence in Africa, or contact with prairie dogs or exotic mammals such as Gambian rats and rope squirrels. Diagnosis is by isolation of mpox viral DNA by polymerase chain reaction (PCR) from a skin lesion, including exudate or lesion crust. Oropharyngeal swabs may be considered in high-risk contacts of known or probable cases who have not yet developed a rash that can be swabbed (Table 767.2).

Cowpox, another *Orthopoxvirus*, often acquired from a pet rat, may produce similar cutaneous lesions. Regional lymphadenopathy and mild system features may also be present. Diagnosis is confirmed by a specific cowpox virus PCR.

PREVENTION AND TREATMENT

In 2019, the U.S. Food and Drug Administration (FDA) approved a new live-attenuated, replication-deficient vaccinia virus vaccine (branded Jynneos in the United States and Imvamune in the European Union [EU]; Bavarian Nordic) for use in patients ≥18 years old who are at risk for mpox acquisition. Despite evidence that preexposure administration of classical smallpox vaccine is 85% effective in preventing or attenuating mpox disease, the rarity of mpox infection does not warrant universal vaccination. However, following the recent 2022 outbreak, the U.S. Centers for Disease Control and Prevention recommends vaccinating high-risk patients (Table 767.3). This vaccine has a very low side effect profile and can be safely used in immunocompromised individuals, a significant advantage over classical (replication-competent) live smallpox vaccines.

For most immunocompetent patients with mild to moderate disease, supportive care is recommended. However, treatment should be considered for those with severe disease (hemorrhagic disease, large number of confluent lesions, necrotic lesions, severe lymphadenopathy that is necrotic or obstructing, involvement of multiple organ systems and comorbidities, or those who require hospitalization) or those with involvement of anatomic areas where scarring or stricture might cause serious sequelae (Fig. 767.4). In addition, treatment may be considered in patients at high risk for severe disease, including children less than 1 year old, immunocompromised or pregnant patients, or those with reduced skin integrity (e.g., eczema). Treatment options include tecovirimat, brincidofovir, cidofovir, or trifluridine ophthalmic solution; these medications were originally developed for treatment of other viral infections and

Table 767.2 Mpox Case Definitions

CLINICAL AND LABORATORY CLASSIFICATION	CRITERIA
Suspected	New characteristic rash* **OR** Meets one of the epidemiologic criteria and has high clinical suspicion† for mpox
Probable	No suspicion of other recent *Orthopoxvirus* exposure (e.g., vaccinia virus in ACAM2000 vaccination) AND demonstration of the presence of • *Orthopoxvirus* DNA by polymerase chain reaction testing of a clinical specimen **OR** • *Orthopoxvirus* using immunohistochemical or electron microscopy testing methods **OR** • Demonstration of detectable levels of anti-*Orthopoxvirus* IgM antibody during the period of 4-56 days after rash onset
Confirmed	Demonstration of the presence of mpox virus DNA by polymerase chain reaction testing or next-generation sequencing of a clinical specimen **OR** Isolation of mpox virus in culture from a clinical specimen
EPIDEMIOLOGIC CLASSIFICATION	
Within 21 days of illness onset:	Reports having contact with a person or persons with a similar appearing rash or with a person who has received a diagnosis of confirmed or probable mpox **OR** Had close or intimate in-person contact with persons in a social network experiencing mpox infections. This includes MSM who meet partners through an online website, digital application ("app"), or social event (e.g., a bar or party) **OR** Traveled, within 21 days of illness onset outside the United States to a country with confirmed cases of mpox or where mpox virus is endemic **OR** Had contact with a dead or live wild animal or exotic pet that is an African endemic species, or used a product derived from such animals (e.g., game meat, creams, lotions, powders, etc.)
EXCLUSIONS	
A case might be excluded as a suspected, probable or confirmed case if:	An alternative diagnosis* can fully explain the illness **OR** A person with symptoms consistent with mpox does not develop a rash within 5 days of illness onset **OR** A case where high-quality specimens do not demonstrate the presence of *Orthopoxvirus* or mpox virus or antibodies to *Orthopoxvirus*

*The characteristic rash associated with mpox lesions involves the following: deep-seated and well-circumscribed lesions, often with central umbilication; and lesion progression through specific sequential stages: macules, papules, vesicles, pustules, and scabs. The rash can sometimes be confused with other diseases that are more commonly encountered in clinical practice (e.g., syphilis, herpes, and varicella-zoster). Historically, sporadic accounts of patients co-infected with mpox virus and other infectious agents (e.g., varicella-zoster, syphilis) have been reported; so patients with a characteristic rash should be considered for *Mpox virus* testing, even if tests for other infectious agents are positive.

†Clinical suspicion may exist if lesions consistent with those from more common infections (e.g., syphilis, herpes, and varicella-zoster) coexist with lesions that may be characteristic of mpox.

From Centers for Disease Control and Prevention. Updated case-finding guidance: Mpox outbreak – United States, 2022. https://emergency.cdc.gov/han/2022/han00468.asp#:~text

Table 767.3 Mpox Vaccination Basics

Centers for Disease Control and Prevention recommends vaccination against mpox if:

- You had known or suspected exposure to someone with mpox
- You had a sex partner in the past 2 weeks who was diagnosed with mpox
- You are a gay, bisexual, or other man who has sex with men or a transgender, nonbinary, or gender-diverse person who in the past 6 months has had any of the following:
  - A new diagnosis of one or more sexually transmitted diseases (e.g., chlamydia, gonorrhea, or syphilis)
  - More than one sex partner
- You have had any of the following in the past 6 months:
  - Sex at a commercial sex venue (like a sex club or bathhouse)
  - Sex related to a large commercial event or in a geographic area (city or county for example) where mpox virus transmission is occurring
  - Sex in exchange for money or other items
- You have a sex partner with any of the above risks
- You anticipate experiencing any of the above scenarios
- You have HIV or other causes of immune suppression and have had recent or anticipate future risk of mpox exposure from any of the above scenarios
- You work in settings where you may be exposed to mpox:
  - You work with orthopoxviruses in a laboratory
  - You are part of an *Orthopoxvirus* and healthcare worker response team

From Centers for Disease Control and Prevention. Mpox Vaccination Basics. https://www.cdc.gov/poxvirus/mpox/vaccines/index.html

are thought to complement the immune response by reducing replication, maturation, and spread of mpox. Vaccinia immune globulin intravenous (VIGIV) may be considered in immunocompromised patients who cannot mount an appropriate immune response to clear the virus. In addition to antiviral medications, careful attention should be paid to skin hygiene, maintenance of adequate nutrition and hydration, and prompt implementation of local or systemic therapy for secondary bacterial infection that may occur. Pain management is a common reason for hospitalization because both cutaneous and mucosal lesions can be very painful. For prevention of human-to-human spread of disease, a combination of contact, droplet, and airborne infection control procedures should be implemented.

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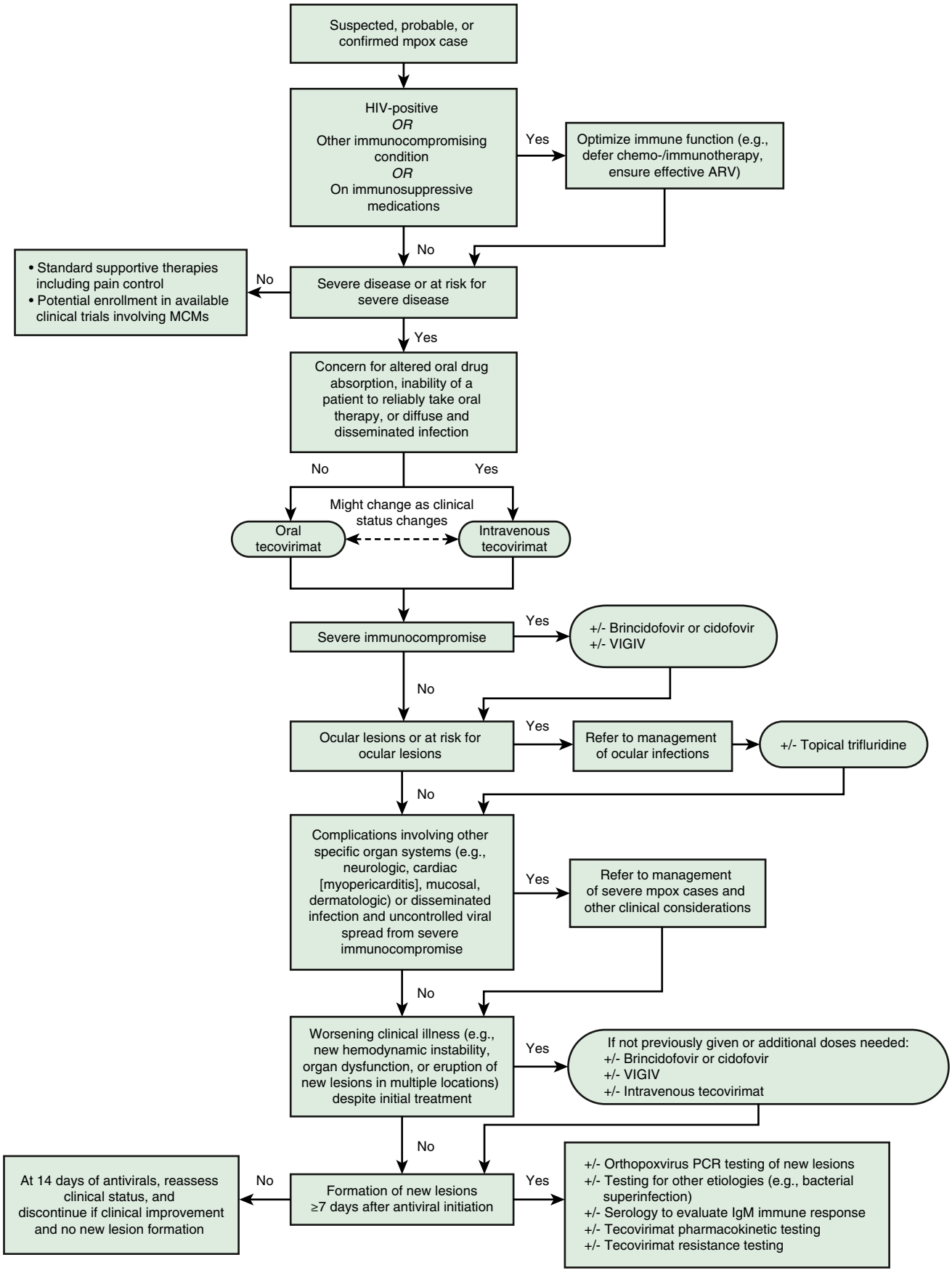
Suspected, probable, or confirmed mpox case
HIV-positive
OR
Other immunocompromising condition
OR
On immunosuppressive medications
Yes
Optimize immune function (e.g., defer chemo-/immunotherapy, ensure effective ARV)
No
Severe disease or at risk for severe disease
No
• Standard supportive therapies including pain control
• Potential enrollment in available clinical trials involving MCMs
Yes
Concern for altered oral drug absorption, inability of a patient to reliably take oral therapy, or diffuse and disseminated infection
No
Yes
Might change as clinical status changes
Oral tecovirimat
Intravenous tecovirimat
Severe immunocompromise
Yes
+/- Brincidofovir or cidofovir
+/- VIGIV
No
Ocular lesions or at risk for ocular lesions
Yes
Refer to management of ocular infections
+/- Topical trifluridine
No
Complications involving other specific organ systems (e.g., neurologic, cardiac [myopericarditis], mucosal, dermatologic) or disseminated infection and uncontrolled viral spread from severe immunocompromise
Yes
Refer to management of severe mpox cases and other clinical considerations
No
Worsening clinical illness (e.g., new hemodynamic instability, organ dysfunction, or eruption of new lesions in multiple locations) despite initial treatment
Yes
If not previously given or additional doses needed:
+/- Brincidofovir or cidofovir
+/- VIGIV
+/- Intravenous tecovirimat
No
Formation of new lesions ≥7 days after antiviral initiation
No
At 14 days of antivirals, reassess clinical status, and discontinue if clinical improvement and no new lesion formation
Yes
+/- Orthopoxvirus PCR testing of new lesions
+/- Testing for other etiologies (e.g., bacterial superinfection)
+/- Serology to evaluate IgM immune response
+/- Tecovirimat pharmacokinetic testing
+/- Tecovirimat resistance testing

Fig. 767.4 Algorithmic approach to treatment*,†,‡ of patients with severe§ or at risk¶ for severe manifestations of mpox** : United States, February 2023.††

* Treatment includes MCMs (i.e., tecovirimat, brincidofovir, cidofovir, VIGIV, and trifluridine) and supportive therapies, including pain management. https://www.cdc.gov/poxvirus/monkeypox/clinicians/pain-management.html

† Most immunocompetent patients should display signs of clinical improvement within 4 days of antiviral initiation (i.e., tecovirimat, brincidofovir, cidofovir, and trifluridine). Tecovirimat is expected to reach steady-state concentrations by day 6 of dosing in healthy volunteers; therefore worsening clinical illness after 7 days of treatment in patients with severe illness could prompt additional evaluations.

‡ Concern for altered drug absorption includes the inability to tolerate or take oral therapy (e.g., nothing by mouth), or possibility that the oral drug absorption might be altered because of inability to consume a high-fat meal, severity of symptoms (e.g., systemic illness), comorbidities (e.g., history of gastric bypass or underlying GI disease), or other factors that might alter oral drug absorption.

§ Hemorrhagic disease, a large number of confluent or necrotic lesions, severe lymphadenopathy that is necrotizing or obstructing (e.g., of the upper airway causing airway compromise or of the GI tract necessitating parenteral feeding), edema that is obstructing (e.g., of the lower GI tract), extradermatologic manifestations (e.g., pulmonary nodules, encephalitis, myopericarditis, or ocular infections), and sepsis. Detailed characteristics of severe disease are available at https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html#anchor_1655488137245.

¶ Persons with underlying medical conditions (e.g., severe or moderate immunocompromise [https://www.cdc.gov/poxvirus/monkeypox/clinicians/people-with-HIV.html]); bacterial superinfections; or complications, including strictures, edema, and infections of the penile foreskin, vulva, urethral meatus, or anorectum, which could require procedural intervention (e.g., urethral catheterization, colostomy, or surgical debridement). This also includes those with or at risk for ocular lesions (i.e., presence of eyelid lesions, facial lesions near the eyes, or finger or hand lesions in patients unable to avoid touching their eyes [for whom autoinoculation is a concern]). Detailed characteristics of persons at risk for severe disease are available at https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html#anchor_1655488137245.

** https://www.cdc.gov/poxvirus/monkeypox/clinicians/case-definition.html

†† This figure is a comprehensive synthesis of heterogeneous evidence and is intended to foster strategic decision-making rather than serve as a prescriptive treatment guideline.

ARV, Antiretroviral medications; GI, gastrointestinal; IgM, immunoglobulin M; MCM, medical countermeasure; PCR, polymerase chain reaction; VIGIV, vaccinia immune globulin intravenous. *(From Rao AK, Schrodt CA, Minhaj FS, et al. Interim clinical treatment considerations of severe manifestations of Mpox – United States, February 2023. MMWR. 2023;72:232–243.)*

Chapter 768

Envenomations

Sing-Yi Feng

Envenomations due to snakes, spiders, scorpions, and other venomous animals can cause significant morbidity and mortality, although the majority cause only localized pain and swelling. In the 2020 report of the American Association of Poison Control Centers, approximately 42,800 out of 2.1 million phone consultations were related to bites and stings of various creatures, with approximately 14,000 involving children <20 years of age.

Not every bite from a venomous creature is harmful. In many cases, no venom is injected; these are called **dry bites**. A dry bite may occur for many reasons, including failure of the venom delivery mechanism and depletion of venom. Up to 20% of pit viper, 80% of coral snake, and approximately 50% of all venomous snake bites are dry.

GENERAL APPROACH TO THE ENVENOMATED CHILD

Children may be bitten or stung as they play and explore their environment. The evaluation may be hampered by an unclear history of the circumstances and the possible offending organism, particularly with preverbal children. The overall effects of some venomous bites and stings may be relatively more severe in children than in adults because children generally receive a similar venom load from the offending animal yet have less circulating blood volume to dilute its effects.

General Management

The majority of envenomations require local wound care, pain control, and reassurance. However, the severely envenomated child may require advanced life support interventions including endotracheal intubation and mechanical ventilation. Intravenous access should be obtained in an unaffected extremity if possible (see Chapters 91 and 92) to provide fluids and vasopressors as needed. Early hypotension is usually due to vasodilation and should be treated with volume expansion using appropriate infusion of intravenous crystalloid solution (normal saline boluses of 20 mL/kg; repeated as needed up to three times). Shock unresponsive to volume repletion may require addition of a vasopressive agent such as epinephrine or norepinephrine (in addition to antivenom administration if appropriate). If the presentation is suspicious for an anaphylactic reaction to venom, treatment (including epinephrine) should be initiated as soon as possible (see Chapter 190) along with the appropriate **antivenom**.

The affected body part should be immobilized in a position of function and any areas of edema should be marked, measured, and monitored. If antivenom is available for the envenomation, efforts should be initiated to locate and secure an adequate amount to treat the patient. In the United States, regional poison control centers are available via the national phone number 1-800-222-1222 to facilitate this effort, especially if the species is exotic. Guidance in dosing the antivenom should be obtained from experienced toxicologists via the regional poison center.

General Wound Care

Bites and stings require basic wound care, including copious tap water or normal saline irrigation under pressure when possible. For small puncture wounds, this is impractical, but the skin should still be thoroughly cleansed with soap and water. Tetanus immunization should be updated as needed. Intact bullae should be left to act as a natural sterile dressing to prevent infection, whereas ruptured bullae should be debrided. Exposed tissue should be covered with wet to dry dressings. Necrotic wounds, as seen in some snake and spider bites, should be judiciously debrided, with removal of only clearly necrotic tissue. Reconstructive surgery with skin grafts or muscle/tendon grafts may be necessary later. Prophylactic antibiotics are usually not necessary because venom is bacteriostatic. Antibiotics should generally be reserved for signs of established secondary infection.

SNAKE BITES

Most snake bites are inflicted by nonvenomous species and are of no more consequence than a potentially contaminated puncture wound. Anatomic features including head shape, pupil shape, and anal plate arrangement can be used to differentiate venomous and nonvenomous snakes (Fig. 768.1). Medically important venomous snakes in the United States belong to two families: **Crotalinae** and **Elapidae** (Table 768.1). Most snakebites occur

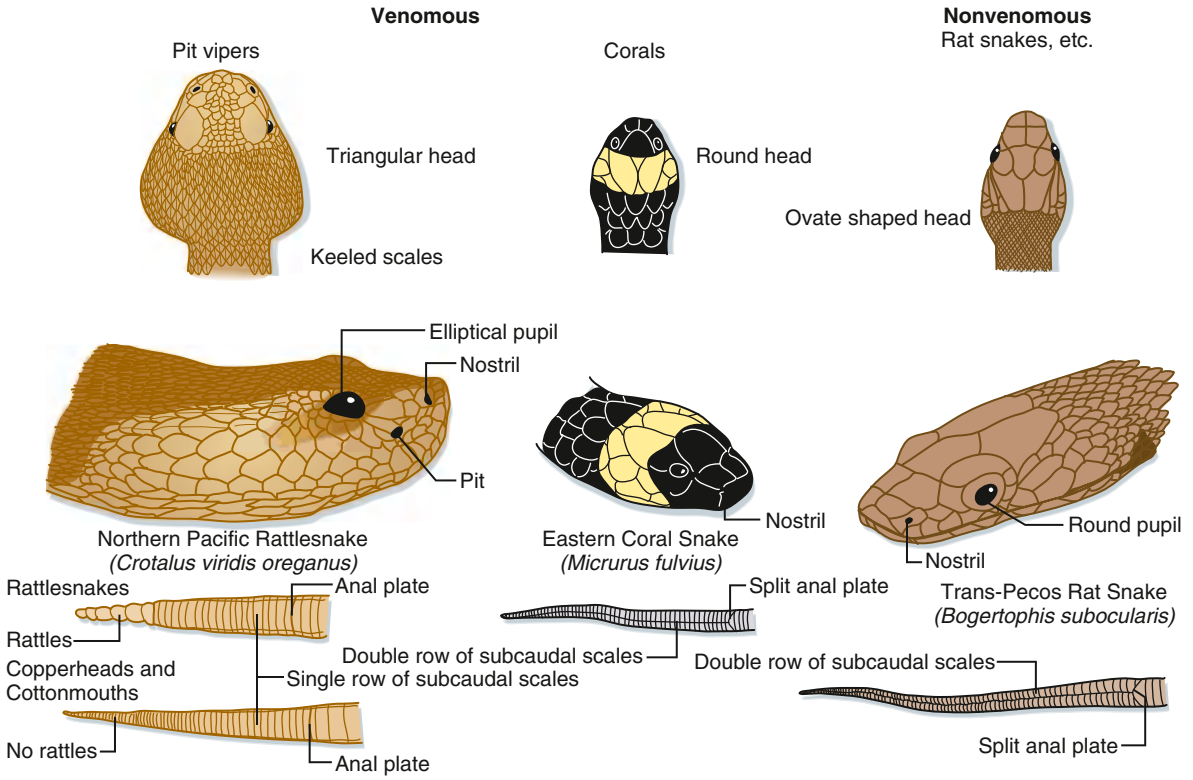

Fig. 768.1 Anatomic comparison of pit vipers, coral snakes, and nonvenomous snakes of the United States. *(Modified from Adams JG, ed. Emergency Medicine. Philadelphia: WB Saunders; 2008. Drawing by Marlin Sawyer.)*

Table 768.1 Important Venomous Snake Families in the United States

FAMILY	EXAMPLES	TOXIN EFFECTS/OTHER COMMENTS	ANTIVENOM
Crotalinae (pit vipers)	Rattlesnakes (*Crotalus* and *Sistrurus* spp.), cottonmouths and copperheads (*Agkistrodon* spp.)	Heat-sensing "pit" between each eye and nostril Toxins cause tissue damage, coagulopathy, cardiovascular collapse Exception: Mojave rattlesnake (*Crotalus scutulatus*) – neurotoxic venom	*Crotalinae* polyvalent immune Fab
Elapidae	Coral snakes (*Micrurus* spp.)	Venom is neurotoxic	Antivenin *(Micrurus fulvius)*

from April through September, when snakes are at their most active. Males sustain 75% of bites and children <5 years of age account for 10–15%. Bites are usually located on extremities, although other parts of the body have been reported. In the United States, approximately 98% of venomous snake bites are inflicted by pit vipers (Crotalinae). A small fraction of bites are caused by coral snakes (Elapidae) in the southern and southwestern states and by exotic pet snakes that have been imported.

Venoms and Effects

Snake venoms are complex mixtures of proteins including enzymes that cause local tissue destruction and other enzymes that have potentially lethal systemic effects including coagulopathy and neurotoxicity. The symptoms and severity of an envenomation vary according to the type of snake, the amount of venom injected, and the location of the bite. About 25% of snakebites are **"dry bites,"** where the patient has fang marks and puncture wounds but no pain, swelling, or systemic effects as no venom was injected. Most pit viper bites cause significant local pain, swelling, and ecchymosis and may result in necrosis of the affected extremity (Fig. 768.2). Pain and swelling typically begin quickly after the bite and may progress over hours to days. Serious envenomation may result in a consumptive coagulopathy, hypotension, and respiratory distress. In contrast, venom from the Elapidae is neurotoxic with little or no local tissue damage. These bites cause variable local pain, and the onset of systemic effects can be delayed for hours. Manifestations of neurotoxicity generally are caused by curare-like blockade at the neuromuscular junction. Symptoms usually begin with cranial nerve palsies such as ptosis, dysarthria, and dysphagia and may progress to respiratory failure and complete paralysis. Some pit vipers, including the Southern Pacific rattlesnake *(Crotalus oreganus helleri),* western diamondback rattlesnake *(Crotalus atrox),* timber rattlesnake *(Crotalus horridus),* and Mojave rattlesnake *(Crotalus scutulatus),* can also cause significant neurotoxicity, like the Elapidae. Regional poison control centers and toxicologists should be consulted early in the course of treatment.

Management

Prehospital care should focus on rapid transport to the emergency department while providing supportive care. Constrictive clothing, jewelry, and watches should be removed, and the injured body part should be immobilized in a position of function at the level of the heart. Many popularized field treatments for snake bites, such as

Fig. 768.2 Southern Pacific rattlesnake bite *(Crotalus oreganus helleri)* in a 2-yr-old child. Note the fang marks, swelling, and bruising of the tissues (photograph taken 2 hours following the bite). *(Courtesy Sean Bush, MD.)*

tourniquets, ice, electric shock, incision, and suction, have proven ineffective or deleterious.

At the hospital, supportive care should be continued as an effort is made to identify the offending snake and secure the appropriate antivenom (if applicable). In severe envenomations, advanced respiratory support may be required, including endotracheal intubation and mechanical ventilation. Intravenous access should be established in an unaffected extremity, intravenous fluids administered as needed, and standard laboratory specimens obtained, including complete blood count, coagulation studies, fibrinogen concentration, and serum chemistry analysis including total creatine kinase. Laboratory studies should initially be repeated every 4-6 hours to monitor the patient's progress and response to therapy. If tourniquets are placed in the field, they should be cautiously removed after venous access is obtained due to possible adverse effects that may follow from a sudden release of venom into the systemic circulation. The bitten extremity should be marked with the leading edge of the erythema and edema as well as the time to monitor progression of the swelling.

Assessment of the severity of the envenomation in the field and at the hospital is essential in determining the appropriateness of antivenom therapy for the snakebite victim (Table 768.2). Antivenoms are relatively specific for the genus of snake whose venom they are designed to neutralize. If it is determined that the patient requires antivenom, appropriating the correct antivenom should begin as soon as possible by discussing the matter with the hospital pharmacy, regional poison control center, and perhaps local zoos and museums that keep captive snakes because they often stock exotic snake antivenom.

Table 768.3 lists the indications for administering antivenom. CroFab, a Crotalinae polyvalent immune Fab antivenom (FabAV), is approved by the U.S. Food and Drug Administration (FDA) for use in crotalid envenomations. FabAV is derived from sheep (ovine) antibodies to crotalid snake venom, and side effects include both immediate and delayed hypersensitivity reactions. FabAV is derived from four snakes, three from the genus *Crotalus* (the eastern diamondback rattlesnake, the western diamondback rattlesnake, and the Mojave rattlesnake) and one from the genus *Agkistrodon* (the cottonmouth or water moccasin). It is effective against the venoms of all Crotalinae snakes in the United States. There is cross reactivity with FabAV against venom from copperhead snakes *(Agkistrodon contortrix)*. However, copperhead bites often do not require treatment with antivenom because they cause fewer systemic effects and less severe local tissue damage. Most copperhead envenomations cause only local tissue swelling, ecchymosis, and pain and generally do well with good supportive care and pain control. Any child with evidence of systemic toxicity should receive FabAV.

Initial dosing of FabAV is aimed at control of symptoms (progressive tissue swelling, thrombocytopenia, coagulopathy, neurotoxicity, or systemic toxicity). The dose is repeated until initial control of toxicity is achieved (see Table 768.3). Subsequent maintenance dosing may be needed to prevent or treat recurrence of venom effects because, due to its small molecular size, the half-life of FabAV is considerably shorter than that of crotalid venom constituents. Patients with significant envenomation should be followed for late hematologic abnormalities (coagulopathy) that can occur up to 2 weeks after the bite. Although these tend to be mild laboratory coagulopathies without clinical bleeding, rare cases of severe delayed bleeding have been reported. Further antivenom therapy should be considered for such delayed or recurrent coagulopathy as outlined in Table 768.4.

In April 2021, the U.S. FDA approved a crotaline immune Fab2 antivenin (Fab2AV) to treat adult and pediatric patients with North American Crotaline envenomations marketed as AnaVIP. This antidote is an equine-derived antivenin and, due to it being a Fab2 fragment, has a longer half-life than the FabAV. It has a similar side effect profile as the FabAV including anaphylactoid and hypersensitivity reactions. Initial dosing is 10 vials given intravenously over 60 minutes. If the symptoms continue to progress, then 10 vials can be given every hour until there is no further progression of symptoms. Patients should be observed for a minimum of 18 hours after the Fab2AV infusion. If a patient has reemerging symptoms including coagulopathies, then an additional four vials of the Fab2AV can be infused (Table 768.5).

Envenomation of the extremities can mimic compartment syndrome, with severe pain and swelling. It is important to treat these patients aggressively with FabAV or Fab2AV and pain control to control the severe pain and swelling. Although fasciotomy was once advocated for the treatment of crotalid snakebites of the extremities, it is now a treatment of last resort only if aggressive FabAV or Fab2AV treatment is unable to stop the progression of pain and swelling and true compartment syndrome is documented with measurement of intracompartmental pressure.

The antivenom for coral snakes *(Micrurus fulvius)* has been the recommended treatment for envenomation by the eastern coral snake *(M. fulvius)* and the Texas coral snake *(Micrurus tener)*. Indications for this antivenom are the development of any neurologic signs and symptoms of coral snake envenomation including paresthesias, slurred speech, respiratory difficulties, muscle weakness, and fasciculations. Due to it being equine in origin, its side effect profile includes anaphylaxis and allergic reactions. Most hospitals do not carry this antivenom and local poison centers should be notified to help locate supplies. Respiratory supportive care including endotracheal intubation and mechanical ventilation for respiratory failure remains the mainstay of treatment.

Disposition

If, after observation for 6-8 hours, a patient exhibits only fang-induced puncture marks with no local or systemic symptoms, the wounds can be considered dry bites and the patient can be safely discharged home. Patients with significant toxicity and those requiring treatment with antivenom should be admitted to the hospital. Patients with a history of eastern or Texas coral snakebite should be admitted to a monitored setting for 24 hours to observe for neurologic toxicity so that respiratory support can be provided as needed. Children should be admitted to an intensive care setting if they develop severe and progressive local tissue toxicity or evidence of systemic toxicity including coagulopathy, neurotoxicity, hemodynamic instability, or respiratory difficulties.

SPIDER BITES

In the United States, 18 genera of spiders have been identified that cause clinically significant envenomation. The spiders of importance in the United States include the *Latrodectus* species (the widow spiders) and the *Loxosceles* species (the recluse spiders).

Table 768.2 Pit Viper Envenomation Classification

GRADE	CLINICAL FEATURES	ANTIVENOM	DISPOSITION
0 (None)	No evidence of envenomation. A fang wound may be present. Pain is minimal, with less than 1 inch of surrounding edema and erythema. No systemic manifestations are present during the first 12 hr after the bite. No laboratory changes occur.	No	Observe for 8-12 hr. May be discharged if repeat labs are normal and no signs of envenomation develop.
I (Minimal)	Pain is moderate or throbbing and localized to the fang wound, surrounded by 1-5 inches of edema and erythema. No evidence of systemic involvement is present after 12 hr of observation. No laboratory changes occur.	No	Admission for 12-24 hr. Repeat labs every 6 hr. May be discharged if repeat labs are normal and no signs of envenomation develop.
II (Moderate)	There is more severe and widely distributed pain, edema spreading toward the trunk, and petechiae and ecchymoses limited to the area of edema. Nausea, vomiting, and a mild elevation in temperature are usually present.	Yes	Admission to intensive care unit.
III (Severe)	This may initially resemble a grade I or II; however, within 12 hr, edema spreads up the extremity and may involve part of the trunk. Petechiae and ecchymoses may be generalized. Systemic manifestations may include tachycardia and hypotension. Laboratory abnormalities may include an elevated white blood cell count, creatine phosphokinase, prothrombin time, and partial thromboplastin time, as well as elevated fibrin degradation products and D-dimer. Decreased platelets and fibrinogen are common. Hematuria, myoglobinuria, increased bleeding time, and renal or hepatic abnormalities may also occur.	Yes	Admission to intensive care unit.
IV (Very severe)	Sudden pain, rapidly progressive swelling that may reach and involve the trunk within a few hours, ecchymoses, bleb formation, and necrosis. Systemic manifestations, often commencing within 15 min of the bite, usually include weakness, nausea, vomiting, vertigo, and numbness or tingling of the lips or face. Muscle fasciculations, painful muscular cramping, pallor, sweating, cold and clammy skin, rapid and weak pulse, incontinence, convulsions, and coma may also be observed. An intravenous bite may result in cardiopulmonary arrest soon after the bite.	Yes	Admission to intensive care unit.

From Curtis AM, Erickson TB. Venomous animal injuries. Walls RM, ed. *Rosen's Emergency Medicine*, 10th ed. Philadelphia: Elsevier; 2023: Table 53.2, p. 696.

Table 768.3 Crotaline Fab Antivenom Dosing Guidelines

DOSE	RECOMMENDATIONS
Initial dose: four to six vials IV	• Reconstitute each vial of FabAV in 18 mL normal saline for injection and mix with continuous manual inversion at the rate of one to two inversions per second until no solid material is visible in the vial. • Further dilute four to six vials of reconstituted FabAV in 250 mL normal saline. • Infuse FabAV over 1 hr IV. • Start with slow infusion rate of 25-50 mL/hr for 10 min. • If no acute allergic reaction occurs, increase rate to 250 mL/hr to complete infusion. • The volume of the infusion may be decreased for the very small child or volume-sensitive patient. • Observe 1 hr after initial dose to assess for control of envenomation. • Repeat four to six vials of FabAV as needed to gain initial control.
Maintenance dose: two vials IV every 6 hr × 3 doses	• Monitor for delayed or recurrent toxicity requiring additional FabAV. • Antivenom dose requirements vary depending on the individual patient's response and clinical course. • Patients with mild envenomation may not require maintenance dosing beyond the initial dose.

Adapted from Goto CS, Feng SY. Crotalidae polyvalent immune Fab for the treatment of pediatric crotaline envenomations. *Ped Emerg Care*. 2009;25(4):273–279; and from Crofab Package Insert (revised 2018).

Table 768.4 Indications for Administration of Additional Antivenom in Patients with Recurrent Coagulopathy or Thrombocytopenia After Initial Control

- Evidence of clinically significant bleeding
- Platelet count below 25,000/mm^3
- International normalized ratio (INR) >3
- Activated partial thromboplastin time (aPTT) >50 seconds
- Fibrinogen <50 mg/dL
- Presence of multicomponent coagulopathy
- Worsening trend in a patient with prior severe coagulopathy
- High-risk behavior for trauma
- Certain comorbid conditions (e.g., systemic vasculitis, seizure disorders, prior stroke)

From Norris RL, Bush SP, Cardwell MD. Bites by venomous reptiles in Canada, the U.S. and Mexico. In: Auerbach PS, ed. *Wilderness Medicine*, 7th ed. Philadelphia: Elsevier; 2017.

Latrodectus Spiders

The *Latrodectus* species are found throughout the United States and include *L. mactans* (Fig. 768.3; **black widow** spider), *L. hesperus* (western black widow), *L. bishop* (red widow spider), *L. variolus,* and *L. geometricus* (brown widow spider). They are indigenous to every state except Alaska. The classic hourglass-shape marking is found only in *L. mactans*. They like to live close to the ground in secluded and dimly lit areas such as barns, sheds, and garages.

Venoms and Effects

Latrodectus spiders possess venoms that act at neuromuscular and autonomic nervous system synapses, resulting in excessive release of

Table 768.5	Crotaline Fab2 Antivenom Dosing Guidelines
Initial Dose: 10 vials (*no known maximum dose of Crotaline Fab2 antivenom)	• Reconstitute 10 vials for less than 1 min each using 10 mL sterile normal saline per vial • Combine all vials and dilute to a total volume of 250 mL sterile normal saline • Infuse at 25-50 mL/hr for 10 min; if tolerated at 250 mL/hr to completion
Evaluate for control	60 minutes after infusion, check for: • Local injury not progressing • Coagulation parameters improving • Systemic effects resolved
Observe	• Observe for at least 18 hr after initial control • If symptoms reemerge, can administer four vials in 250 mL

Adapted from AnaVIP package insert.

Fig. 768.3 Female black widow spider *(Latrodectus mactans).* Note the red hourglass-shaped marking on the underside of her abdomen. *(From The Centers for Disease Control and Prevention Public Health Image Library, Image #5449.)*

neurotransmitters. All of the widow spiders possess similar venoms, with the most important neurotoxin being α-latrotoxin.

Bites by the neurotoxic spiders tend to be very painful, and the offending spider is often seen. Systemic effects may include hypertension, tachycardia, bradycardia, hypersalivation, diaphoresis, and diffuse muscle spasm. Nausea, vomiting, abdominal pain, and abdominal rigidity may mimic appendicitis or another acute abdominal emergency.

Management

The management of a neurotoxic spider envenomation centers on sound supportive care. Generous doses of opioid analgesics and benzodiazepines should be utilized to ease severe pain and muscle spasm. *Latrodectus* antivenom (Wyeth) is equine-derived and may be considered to reverse severe systemic effects of widow spider envenomation. Although effective, it is associated with anaphylaxis, serum sickness, and anaphylactoid reactions and should be reserved for high-risk patients such as pregnant women at risk of spontaneous abortion due to the severe pain. One vial is administered via intravenous infusion. Efficacy is usually noted within 1 hour of administration, with reversal of systemic toxicity and relief of pain. Occasionally a second vial is necessary. Due to the possibility of severe or life-threatening reactions, the risks and benefits should be carefully considered and the antivenom infused slowly with continuous monitoring and preparation to treat anaphylaxis should it occur.

Fig. 768.4 Male recluse spider (*Loxosceles* spp.). Note the distinct violin-shaped marking on the dorsum of the cephalothorax. *(Courtesy Michael Cardwell/Extreme Wildlife Photography)*

Loxosceles Spiders

Venoms and Effects

The spiders most notorious for their dermonecrotic potential are the recluse spiders of the genus *Loxosceles*. The best-known member of this genus is the **brown recluse** (*Loxosceles reclusa*; Fig. 768.4), found in the midwestern and southern regions of the United States. The venom of *Loxosceles* spiders contains a phospholipase enzyme, sphingomyelinase D, as well as hyaluronidase. Hyaluronidase is the spreading factor that enables the venom to penetrate tissues, but it does not induce tissue damage. Sphingomyelinase D causes necrosis, red blood cell hemolysis, and platelet serotonin release. The bite of this spider is generally painless and initially goes unnoticed. A few hours after the bite, the area begins to blister and bleed and become painful. Within a day or two, the site will ulcerate and develop violaceous necrosis with surrounding ecchymosis and a rim of pale ischemia ("red, white, and blue" reaction). The lesion may gradually expand over a period of days to weeks until necrotic tissue sloughs and healing begins (Fig. 768.5).

Rare cases of systemic loxoscelism appear to be more common in young children. Patients present with systemic toxicity, including fever, chills, nausea, malaise, diffuse macular rash, and petechiae; they may experience hemolysis, coagulopathy, and renal failure.

In cases of necrotic dermal lesions with no identified spider as the culprit, a broad differential diagnosis must be considered to ensure appropriate management. The differential diagnosis includes skin infections (particularly methicillin-resistant *Staphylococcus aureus;* see Chapter 227), pyoderma gangrenosum, or ecthyma gangrenosum.

Management

The management of necrotizing spider bites includes good wound care, updating of tetanus status, and administration of antibiotics if there is secondary bacterial infection. Daily wound cleansing and splinting of the affected area should be provided until the wound has healed.

No therapy has been definitively proven effective in limiting the extent of necrosis after a recluse spider bite, including steroids, dapsone, colchicine, cyproheptadine, nitroglycerin, hyperbaric oxygen, and early excision of tissue. Meticulous wound care is the mainstay of treatment, and large lesions may require delayed secondary closure with skin grafting after clear tissue demarcation has occurred.

Patients with signs and symptoms of systemic loxoscelism should be admitted to the hospital for supportive treatment of hypovolemia, coagulopathy, hemolysis, and acute kidney injury. There is no commercially available antivenom in the United States for the management of necrotizing spider bites such as those from *Loxosceles* species.

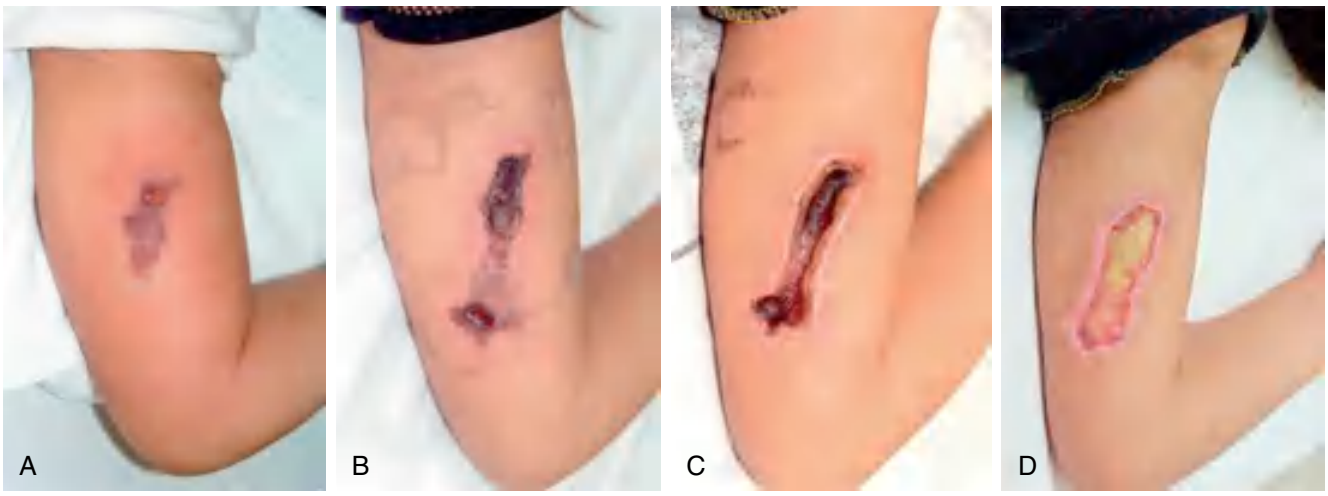

Fig. 768.5 Progression of cutaneous loxoscelism in a Brazilian patient who was bitten inside a house while putting on a shirt. Ulceration and necrosis at day 1 (A), day 9 (B), day 16 (C), and day 25 (D). *(From Isbister G, Fan HW. Spider bite. Lancet. 2011;378:2039–2046. Fig. 3. Photographs by Ceila MS Malaque.)*

Disposition

Victims with necrotic skin lesions should be monitored with frequent outpatient wound checks to determine progression of the lesion. Children with rapidly progressive dermonecrosis or systemic toxicity should be admitted to the hospital for supportive therapy, which may include intensive care admission for hemolysis, coagulopathy, renal failure, or hypotension.

SCORPION STINGS

There are more than 650 species of scorpions worldwide, some of which are capable of causing severe or lethal envenomation. In the United States, there are two clinically significant scorpions: ***Centruroides exilicauda*** (the bark scorpion) and ***Centruroides vittatus.*** Most scorpion envenomations occur in the southwestern United States, and fatalities are rare. In other regions of the world, especially Latin America, Africa, the Middle East, and Asia, a number of scorpions regularly cause fatalities.

Venoms and Effects

Centruroides scorpion venom contains phospholipase, acetylcholinesterase, hyaluronidase, serotonin, and neurotoxins, resulting in severe pain and paresthesia as well as systemic symptoms of excessive nerve depolarization and release of acetylcholine and catecholamines. The manifestations of scorpion stings in children vary from mild to severe and can include autonomic and somatic toxicity. Autonomic toxicity includes hypertension, tachycardia, hypersalivation, emesis, diaphoresis, and bronchoconstriction, although respiratory failure is rare. Somatic motor toxicity includes ataxia, fasciculations, myoclonus, and opsoclonus. Patients are often restless or agitated, and cranial nerve dysfunction may occur.

Management

Most scorpion stings do not produce severe effects and require only wound care and orally administered pain medications. However, patients with more severe symptoms may require intravenous opioids for analgesia and benzodiazepines for severe muscle spasm or agitation.

A bark scorpion–specific antivenom, Anascorp (Bioclon, Mexico), is approved by the FDA. This antivenom is recommended for critically ill patients with neurotoxicity or other severe symptoms, including intractable pain that is not responsive to adequate doses of opioid analgesics. Small children are more likely than adults to develop such severe symptoms. It is best to discuss antivenom therapy with the regional poison control center for guidance.

Disposition

Patients who have had mild scorpion stings with only local effects can be safely discharged home with wound care instructions, analgesics, and close outpatient follow-up. Patients with evolving symptoms, intractable pain, neurotoxicity, or other systemic toxicity should be admitted to the hospital, especially if scorpion antivenom is being considered. Those with severe toxicity should be admitted to an intensive care unit.

HYMENOPTERA STINGS

The insect order Hymenoptera includes the stinging ants, bees, and wasps, which are characterized by the presence of a modified ovipositor (the "sting" or "stinger") at the end of the abdomen through which venom is injected. Various members of the order can be found throughout the world.

Venoms and Effects

Hymenoptera venom is a complex mixture of proteins, enzymes, and vasoactive substances that result in local tissue injury and inflammation. Most stings cause only local pain, redness, and swelling followed by itching and resolution. Some patients experience a large local reaction in which swelling progresses beyond the sting site, possibly involving the entire extremity. Approximately 0.4–0.8% of children and 3% of adults are at risk for acute, life-threatening allergic reactions as a result of Hymenoptera venom sensitivity; anaphylaxis due to Hymenoptera envenomation causes an average of 62 deaths annually in the United States (see Chapter 187). Rare cases of delayed serum sickness can follow Hymenoptera stings (see Chapter 191). Africanized honeybees *(Apis mellifera scutellata)*, an aggressive hybrid of western honeybee species with African bee species, can cause massive stinging episodes resulting in systemic venom toxicity with hypotension, respiratory failure, shock, hemolysis, and renal failure.

Management

Patients with typical local reactions can be treated with supportive care including analgesics and antihistamines as needed. Patients with large local reactions should also receive a course of oral corticosteroids and a prescription for an epinephrine autoinjection kit including instructions in its use before discharge. Patients presenting with urticaria, angioedema, wheezing, or hypotension should be treated with aggressive supportive care including standard therapy for anaphylaxis such as intramuscular epinephrine, corticosteroids, antihistamines, intravenous fluids, oxygen, and airway management as needed (see Chapter 190). Patients suffering massive stinging episodes may also require critical care resuscitation.

Disposition

Patients with local reactions can be discharged with continued outpatient care that may include analgesia and antihistamines. More difficult disposition decisions are involved for children with systemic manifestations. Children with only diffuse urticaria who are stable after a period of observation can be discharged home to continue a short course of antihistamines and steroids and to carry an epinephrine self-administration kit. These children are at low risk for progressing to systemic anaphylaxis with future stings. Children suffering more than simple urticaria (e.g., wheezing, evidence of laryngeal edema or cardiovascular instability) should be treated aggressively and admitted for at least 24 hours of observation. They should receive a referral to allergy/immunology to test for Hymenoptera venom sensitivity and possible immunotherapy. Immunotherapy reduces the risk of systemic anaphylaxis from future stings in high-risk patients from 30–60% to <5%.

MARINE ENVENOMATION

The classes of venomous marine animals that cause the most morbidity and mortality in humans are the **Cnidaria** (including jellyfish, the Portuguese man-of-war, Pacific blue bottle, fire coral, sea nettles, anemones, and others), Mollusca (blue-ringed octopus and cone snails), Chondrichthyes (stingrays), and members of the family Scorpaenidae (lionfish, scorpionfish, and stonefish).

Venoms and Effects

All members of the Cnidaria have unique stinging cells called nematocysts. These cells contain a highly folded tubule that discharges on contact, penetrates the skin, and injects venom. The venom is antigenic and can be dermonecrotic, hemolytic, cardiotoxic, or neuropathic, depending on the species. The **Pacific box jellyfish** *(Chironex fleckeri)* of Australia, with its cardiotoxic venom, is known to cause stings that are rapidly fatal due to cardiac arrest and pulmonary edema. Although fatal anaphylaxis to jellyfish stings has been reported in coastal waters of the United States, these events are rare. For clinicians in the Americas, the primary concern with Cnidaria envenomation is localized pain that may be associated with paresthesias or pruritus. Occasionally, victims may have systemic symptoms such as nausea, vomiting, headache, and chills.

The phylum **Mollusca** includes octopi and cone snails (*Conus* sp.). The **octopus** of toxicologic significance is the *Hapalochlaena maculosa* (blue-ringed octopus), which is primarily found in Australian waters. The blue-ringed octopus secretes **tetrodotoxin** (the same toxin found in pufferfish) in its salivary gland. The beak of the octopus punctures the skin and delivers the tetrodotoxin. Tetrodotoxin blocks sodium channels in neurons, leading to paralysis. The venom also contains other toxins, including vasoactive agents and enzymes that cause local tissue injury. Cone snails have a hollow proboscis with a tooth that can be extended to inject venom into the victim. Venom of the *Conus* species contains conotoxins that target multiple receptors, including voltage, ligand, and G-mediated receptors. Conotoxins cause a variety of symptoms including severe pain, weakness, tissue ischemia, cyanosis, and numbness. Systemic symptoms are usually neurologic and include aphonia, aphasia, weakness, paralysis, respiratory failure, cardiovascular collapse, and ultimately death.

The **stingray** has a sharp, retroserrated spine and associated venom gland at the base of its tail. Envenomation often occurs when the victim steps on the animal hidden in the surf and the tail is whipped around to puncture the lower extremity. Injuries involve jagged lacerations from the spine, often with retained debris (spine fragments, glandular tissue, and sand). The venom has vasoconstrictive properties that can result in tissue necrosis and poor wound healing. Stingray envenomations are noteworthy for immediate and intense pain at the site of injury that lasts 24-48 hours. Some patients experience nausea, vomiting, and muscle cramps. Rarely, hypotension or seizures occur.

The Scorpaenidae have venomous dorsal, pelvic, and anal spines that become erect when the animal is threatened. The venom glands associated with these spines contain multiple toxins, enzymes, and vasoactive substances. Envenomation causes immediate severe pain that may persist for hours or days. Victims may experience local tissue destruction, and superinfections are common. Systemic symptoms include diaphoresis, nausea, vomiting, diarrhea, abdominal pain, muscle cramping, and headache. In severe cases, paralysis, respiratory failure, hypotension, dysrhythmias, and cardiovascular collapse have been reported.

Management

Treatment of Cnidaria stings should begin immediately after envenomation. Dousing the sting site with vinegar has been shown to inhibit nematocyst discharge. If vinegar is not immediately available, the area should be washed with seawater; freshwater should be avoided as it is thought to stimulate firing of remaining nematocysts. Visible tentacle fragments should be removed with a gloved hand or forceps, and microscopic fragments may be removed by gently shaving the affected area. Folk remedies such as rubbing the sting with sand and applying urine are not helpful and cause more irritation. Meat tenderizer is usually not effective. Antihistamines and corticosteroids are indicated for swelling and urticaria. An acute anaphylactic reaction should be treated with intramuscular epinephrine. Antibiotics are usually not necessary.

Patients who have been envenomated by Mollusca are treated supportively. There are no antivenoms available for either the blue-ringed octopus or the cone snails. Adequate pain control should be provided as needed. Cardiovascular support may be required, and severe neurologic toxicity such as respiratory failure should be managed via airway management and mechanical ventilation.

Treatment of stingray and Scorpaenidae stings is similar. These toxins are heat-labile, and immersion in hot water (approximately 42°C [107.6°F]) for 30-60 minutes denatures the protein constituents and decreases pain significantly. The wounds should be thoroughly cleansed and explored with use of local or regional anesthesia to rule out retention of spine or integument fragments. Stingray spines are radiopaque and may be seen on radiographs or identified by ultrasonography. Lacerations should be treated with delayed primary closure or allowed to heal by secondary intention. Systemic analgesia should be provided as needed. Because of the risk of secondary bacterial infection, there should be a low threshold for administering prophylactic antibiotics to cover *Staphylococcus, Streptococcus,* and *Vibrio* species, and wounds should be rechecked at 3 and 7 days postinjury. An equine Fab stonefish antivenom is available for severe stonefish envenomation with systemic toxicity or intractable pain.

Disposition

After wound care and effective analgesia, most victims can be discharged home. If there are significant systemic effects, the patient should be admitted for monitoring and further care as needed.

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Chapter 769

Laboratory Testing in Infants and Children

Stanley F. Lo and Stephen M. Roper

Normal values **(reference intervals)** are difficult to establish within the pediatric population. Differences in genetic composition, physiologic development, environmental influences, and subclinical disease are variables that need to be considered when developing reference intervals. Other considerations for further defining reference intervals include partitioning based on sex and age. The most commonly used reference range is generally given as the **mean** of the reference population ±2 standard deviations (SD). This is acceptable when the distribution of results for the tested population is essentially gaussian (normal). The serum sodium concentration in children, which is tightly controlled physiologically, has a distribution that is essentially gaussian; the mean value ±2 SD gives a range very close to that actually observed in 95% of children (Table 769.1). However, not all analytes have a gaussian distribution. The serum creatine kinase level, which is subject to diverse influences and is not actively controlled, does not show a gaussian distribution, as evidenced by the lack of agreement between the range actually observed and that predicted by the mean value ±2 SD. In these cases, a reference interval defining the 2.5-97.5 percentiles is typically used.

Reference cutoffs are typically established from large studies with a healthy reference population. Examples of these cutoffs are illustrated by reference cutoffs established for cholesterol, lipoproteins, and neonatal bilirubin. Patient results exceeding these cutoffs have a future risk of acquiring disease. A final modification needed for reporting reference intervals is referencing the Tanner stage of sexual maturation (sexual maturity rating scale), which is most useful in assessing pituitary and gonadal function.

The establishment of common reference intervals remains an elusive target. Although some patient results are directly comparable between laboratories and methods, most are not. Careful interpretation of patient results must consider when testing was performed and what method was used. **Higher-order methods**, methods that are more accurate and precise, continue to be slowly developed. These will be critical to the standardization of tests and the establishment of common reference intervals.

COMMON CHALLENGES IN PEDIATRIC LABORATORY MEDICINE

There are several challenges in pediatric lab medicine that are encountered infrequently, are less consequential, or do not apply to adult populations. For example, the rate of in-vitro hemolysis is increased in children because of the use of inappropriate needle or tubes sizes, applying too much pressure to the site of a finger or heel-stick collection, or simply drawing a specimen rapidly to minimize the discomfort of the child. Hemolyzed specimens can lead to inaccurate results for several analytes because of spectrophotometric interference caused by hemoglobin, dilution effects, or because of the release of other red blood cell components (e.g., lactate dehydrogenase [LDH]). A related issue is the frequent occurrence of physiologic jaundice. Like hemoglobin, bilirubin can absorb light and influence with spectrophotometric analyses. Although many chemistry analyzers can detect these interferences and suppress affected results, specimens frequently must be recollected. Likewise, the increased hematocrit common in the first month of life can lead to decreased amount of plasma/serum from a given blood volume. This phenomenon can result in the need for repeat phlebotomy or larger starting volumes of whole blood. In addition to blood, urine is another difficult fluid to work with in children. Noninvasive urine collections from infants often require special collection techniques (bags, cotton balls) that may only capture small volumes. Coupled with the relatively dilute urine typically produced by newborns, urine specimens may require concentration, or analyzer measurement ranges may need to be adjusted to provide useful information. Other challenges in pediatric lab medicine include, but are not limited to, the use of small ("bullet") blood collection tubes that are incompatible with automated sample handlers, the need for specialized testing (e.g., sweat test, newborn screening), and working with specimens drawn from indwelling catheters that may be contaminated with IV or total parenteral nutrition (TPN) fluid.

ACCURACY AND PRECISION OF LABORATORY TESTS

Technical accuracy, or trueness, is an important consideration in interpreting the results of a laboratory test. Because of improvements in methods of analysis and elimination of analytic interference, the accuracy of most tests is limited primarily by their precision. **Accuracy** is a measure of the nearness of a test result to the actual value, whereas **precision** is a measure of the reproducibility of a result. No test can be more accurate than it is precise. Analysis of precision by repetitive measurements of a single sample gives rise to a gaussian distribution with a mean and an SD. The estimate of precision is the coefficient of variation (CV):

$$CV = \frac{SD}{Mean} \times 100$$

The CV is not likely to be constant over the full range of values obtained in clinical testing, but it is approximately 5% in the normal range. The CV is generally not reported but is always known by the laboratory. It is particularly important in assessing the significance of changes in laboratory results. For example, a common situation is the need to assess hepatotoxicity incurred because of the administration of a therapeutic drug and reflected in the serum alanine transaminase (aminotransferase) (ALT) value. If serum ALT increases from 25 units/L to 40 units/L, is the change significant? The CV for ALT is 7%. Using the value obtained ±2 × CV to express the extremes of imprecision, a value of 25 units/L is unlikely to reflect an actual concentration of >29 units/L, and a value of 40 units/L is unlikely to reflect an actual concentration of <34 units/L. Therefore the change in the value as obtained by testing is likely to reflect a real change in circulating ALT levels. Continued monitoring of serum ALT is indicated, even though both values for ALT are within normal limits. *Likely* in this case is only a probability. Inherent biologic variability is such that the results of two successive tests may suggest a trend that will disappear on further testing.

Table 769.1 Gaussian and Nongaussian Laboratory Values in 458 Normal Schoolchildren 7-14 Years Old

	SERUM SODIUM (MMOL/L)	SERUM CREATINE KINASE (UNITS/L)
Mean	141	68
Standard deviation (SD)	1.7	34
Mean ±2 SD	138-144	0-136
Actual 95% range	137-144	24-162

The precision of a test may also be indicated by providing *confidence limits* for a given result. Usually, 95% confidence limits are used, indicating that it is 95% certain that the value obtained lies between the two limits reported. Confidence limits are calculated using the mean and SD of replicate determinations:

$$95\%\ \text{confidence limits} = \text{Mean} \pm t \times \text{SD}$$

where t is a constant derived from the number of replications. In most cases, $t = 2$.

Accuracy is expressed by determining the difference, or **bias**, between results from a comparative method and a definitive or reference method. A **definitive** or **reference** method provides results with increased precision and accuracy compared with the clinical laboratory. When these methods are used, along with highly purified materials (i.e., Standard Reference Materials from the National Institute of Standards and Technology) to establish values for assay calibrators used in the clinical laboratory, the accuracy of patient results is improved. Creatinine, hemoglobin A_{1c}, and neonatal bilirubin are examples in which the accuracy of these tests has been improved.

SENSITIVITY, ACCURACY, AND ANALYTIC TESTING

In some circumstances, the sensitivity and accuracy of an analysis are reduced or increased as functions of clinical purpose. For example, ion exchange chromatography of plasma amino acids for the diagnosis of inborn errors of metabolism is usually performed at an analytic sensitivity that allows measurement of all the amino acids with a single set of standards. The range of values is approximately 20-800 µmol/L, and accuracy is poor at values ≤20 µmol/L. The detection of homocysteine in this type of analysis suggests an inborn error of methionine metabolism. If the analysis is adjusted to achieve greater analytic sensitivity, it is possible to measure homocysteine accurately in normal plasma (3-12 µmol/L). This more sensitive test is used to assess cobalamin and folate status.

PREDICTIVE VALUE OF LABORATORY TESTS

Predictive value (PV) theory deals with the usefulness of tests as defined by their clinical **sensitivity** (ability to detect a disease) and **specificity** (ability to define the absence of a disease).

$$\text{Sensitivity} = \frac{\text{Number positive by test}}{\text{Total number positive}} \times 100$$

$$\text{Specificity} = \frac{\text{Number negative by test}}{\text{Total number without disease}} \times 100$$

$$\text{PV of positive test result} = \frac{\text{True-positive results}}{\text{Total positive results}} \times 100$$

$$\text{PV of negative test result} = \frac{\text{True-negative results}}{\text{Total negative results}} \times 100$$

The problems addressed by PV theory are *false-negative* and *false-positive* test results. Both are major considerations in interpreting the results of screening tests in general and neonatal screening tests in particular.

Testing for human immunodeficiency virus (HIV) seroreactivity illustrates some of these considerations. If it is assumed that approximately 1,100,000 of 284,000,000 residents of the United States are infected with HIV (prevalence = 0.39%) and that 90% of those infected demonstrate antibodies to HIV, then we can consider the usefulness of a simple test with 99% sensitivity and 99.5% specificity (see Chapter 322). If the entire population of the United States were screened, it would be possible to identify most of those infected with HIV:

$$1{,}100{,}000 \times 0.9 \times 0.99 = 980{,}100\ \ (89.1\%)$$

However, there will be 119,900 false-negative test results. And even with 99.5% specificity, the number of false-positive test results would be larger than the number of true-positive results:

$$284{,}000{,}000 \times 0.005 = 1{,}420{,}000$$

In addition, there will be 281,480,000 true-negative results:

$$\text{PV of positive test result} = \frac{980{,}100}{(980{,}100 + 1{,}420{,}000)} \times 100 = 41\%$$

$$\text{PV of negative test result} = \frac{281{,}480{,}000}{(281{,}480{,}000 + 119{,}900)} \times 100 = 99.96\%$$

Given the high cost associated with follow-up and the anguish produced by a false-positive result, it is easy to see why universal screening for HIV seropositivity received a low priority immediately after the introduction of testing for HIV infection.

By contrast, we can consider the screening of 100,000 individuals from groups at increased risk for HIV in whom the overall prevalence of disease is 10%, with all other considerations being unchanged.

$$\text{True-positive results} = 0.9 \times 0.99 \times 10{,}000 = 8{,}910$$

$$\text{False-positive results} = 0.005 \times 90{,}000 = 450$$

$$\text{False-negative results} = 10{,}000 - 8{,}910 = 1{,}090$$

$$\text{PV of positive test result} = \frac{8{,}910}{8{,}910 + 450} \times 100 = 95\%$$

$$\text{PV of negative test result} = \frac{89{,}500}{89{,}550 + 1{,}090} \times 100 = 99\%$$

These two hypothetical testing strategies show that the diagnostic efficiency of testing depends heavily on the prevalence of the disease being tested for, even with a superior test, such as the test for HIV antibodies. Because the treatment of pregnant women infected with HIV is effective in preventing vertical transmission, screening has now been expanded to all pregnant women. The proven effectiveness of current therapy in preventing neonatal infection has intensified screening for HIV early in pregnancy.

However, because of the long time needed to test for HIV antibodies, it was difficult to screen women during labor and provide the necessary therapy. Rapid HIV antibody testing procedures using a fingerstick or venipuncture to obtain whole blood, plasma, or serum, and tests using oral fluid were approved (Table 769.2). The HIV test results are usually obtained in <20 minutes. The collection of oral fluid samples provides an alternative for individuals who avoid HIV testing because of their dislike of needlesticks. HIV testing using whole blood or oral fluid is classified as a waived test under the **Clinical Laboratory Improvement Amendments of**

Table 769.2 Rapid HIV Antibody Tests and Status Under CLIA

RAPID HIV TEST	SPECIMEN TYPE	CLIA CATEGORY	TIME FOR PERFORMING ASSAY	WAIT TIME TO READ RESULTS	MANUFACTURER
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test	Oral fluid Whole blood (fingerstick or venipuncture)	Waived Waived	<5 min	20-40 min	OraSure Technologies www.orasure.com
	Plasma	Moderate complexity			
Uni-Gold Recombigen HIV-1	Whole blood (fingerstick or venipuncture)	Waived	<5 min	10-12 min	Trinity Biotech www.trinitybiotech.com
	Serum and plasma	Moderate complexity			
Reveal G4 Rapid HIV-1 Antibody Test	Serum and plasma	Moderate complexity	<5 min	Read result immediately	MedMira www.medmira.com
MultiSpot HIV-1/HIV-2 Rapid Test	Serum and plasma	Moderate complexity	10-15 min	Result can be read immediately or up to 4 hr later	BioRad Laboratories www.bio-rad.com
Clearview HIV 1/2 STAT-PAK and Clearview COMPLETE HIV 1/2	Whole blood (fingerstick or venipuncture)	Waived	5 min	15-20 min	Alere www.alere.com
	Serum and plasma	Waived	5 min	15-20 min	Alere
Clearview Determine HIV1/2 Ag/Ab Combo	Whole blood (fingerstick or venipuncture)	Waived	5 min	20 min	Alere
	Serum and plasma	Waived	5 min	20 min	Chembio Diagnostic Systems; distributed by Alere

Ag/Ab, Antigen/antibody; CLIA, Clinical Laboratory Improvement Amendments of 1988; HIV, human immunodeficiency virus.

1988 (CLIA), and these tests are allowed in a point-of-care setting. *Waived tests* are laboratory procedures that use methodologies that are so simple and accurate as to render the likelihood of an erroneous result by the user negligible. A positive rapid HIV test result is then confirmed by nucleic acid amplification testing or immunofluorescence assay.

According to the U.S. Centers for Disease Control and Prevention (CDC), 174 infants were born with HIV in 2014 in the United States. Rapid HIV testing during labor allows for implementation of antiretroviral therapy for HIV-infected women who have not been tested or are unaware of their HIV status. The initiation of therapy at the time of labor or within the first 12 hours of an infant's birth significantly reduces the risk of mother-to-child transmission. In the mother–infant rapid intervention at delivery study, it was shown that the sensitivity and specificity of a rapid whole blood test for HIV during labor were 100% and 99.9%, respectively, with a positive PV of 90%. The median turnaround time for obtaining results from blood collection to patient notification was only 66 minutes. The performance of the rapid blood test was better than that of the standard HIV enzyme immunoassay, which had a sensitivity and specificity of 100% and 99.8%, respectively, with a positive PV of 76%. In addition, the median turnaround time from blood collection to patient notification was 28 hours. As a result, rapid whole blood HIV testing is now the standard of care for women in labor with undocumented HIV status.

Rapid HIV testing can also be used in developing countries. In resource-poor settings, because of the lack of properly equipped laboratories, skilled technologists, and basic resources, such as electricity and water, these self-contained, point-of-care HIV tests are very attractive. In areas of Asia and Africa where HIV is epidemic, screening pregnant women with rapid HIV tests and offering antiretroviral therapy can significantly reduce the transmission of HIV to hundreds of thousands of infants.

NEONATAL SCREENING TESTS

Almost all the diseases detected in neonatal screening programs have a very low prevalence, and for the most part, the tests are *quantitative* rather than qualitative. In general, the strategy is to use the initial screening test to separate a highly suspect group of patients from normal infants (i.e., to increase the prevalence) and then to follow this suspect group aggressively. Two common strategies are used to detect congenital hypothyroidism (see Chapter 603): one uses thyroid-stimulating hormone for the initial screen, and the other uses thyroxine. In the **thyroxine** strategy for congenital hypothyroidism, which has a prevalence of 25 in 100,000 liveborn infants, the initial test performed is for thyroxine in whole blood. Infants with the lowest 10% of test results are considered suspect. If all infants with hypothyroidism were included in the suspect group, the prevalence of disease in this group would be 250 in 100,000 infants. The original samples obtained from the suspect group are retested for thyroxine and are tested for thyroid-stimulating hormone. This second round of testing results in an even more highly suspect group composed of 0.1% of the infants screened and having a prevalence of hypothyroidism of 25,000 in 100,000 individuals. This final group is aggressively pursued for further testing and treatment. Even with a 1,000-fold increase in prevalence, 75% of the aggressively tested population is euthyroid. The justifications advanced for the program are that treatment is easy and effective and that the alternative if congenital hypothyroidism is undetected and untreated—long-term custodial care—is both unsatisfactory and expensive.

At its inception, newborn screening was driven by the selection of genetic diseases whose clinical manifestations developed postnatally, such as phenylketonuria, galactosemia, and hypothyroidism. Diseases selected for screening typically had to meet certain criteria. The prevalence of disease had to meet a minimum, typically 1 in 100,000. Disease selection required demonstrated reduction in morbidity and mortality in the neonatal period. Effective therapies needed to be available, and the cost of screening and the feasibility of laboratory testing were also considerations in this selection process.

More common diseases have also become targets for neonatal screening programs. **Sickle cell disease** (see Chapter 511.1), easily detected using liquid chromatography or isoelectric focusing, can be treated more effectively if it is diagnosed before clinical signs appear. In addition, the results of neonatal screening for **cystic fibrosis** (CF; see Chapter 454) show clear benefits associated with preclinical diagnosis but also some inherent difficulties associated with genetic screening for complex autosomal recessive diseases that are common and are caused by a rather large number of pathogenic variants (>1,500) of a single gene. The definitive diagnostic test for CF is the measurement of concentrations of chloride in sweat, a test that is not practical during the first week of life. Neonates with CF generally have elevations in whole blood trypsinogen. This test allows the identification of a group of neonates at risk for CF. Unfortunately, trypsinogen as an initial screening test has a high false-positive rate, an unfavorable characteristic that creates unnecessary anxiety among newborn parents and families and is costly because of the time and expense for medical follow-up. Performing DNA analysis for common variants that cause CF reduces the size of the suspect group and identifies neonates with a higher likelihood of disease. This two-tiered strategy identifies a manageable number of infants for whom to perform sweat tests. Problems include the following: (1) uncommon variants are not included in the screening panel, and cases of CF caused by these variants can be missed; (2) common variants that cause clinically innocent elevations of whole blood trypsinogen in heterozygous neonates cause potentially alarming false-positive findings; and (3) CF in patients with normal sweat test results is rare but is likely to be missed.

Tandem mass spectrometry (MS/MS) is a technically advanced method in which many compounds are initially ionized and separated by molecular weight. Each compound is then fragmented, and the identification of compounds is based on characteristic fragments. The process requires approximately 2 minutes per sample and can detect 20 or more inborn errors of metabolism. The effects of prematurity, neonatal illness, and intensive neonatal management on metabolites in blood complicate the interpretation of results. The PV of a positive screening result is likely to be <10%; that is, 90% of positive results are not indicative of a genetic disorder of metabolism. Nonetheless, MS/MS permits a diagnosis to be made before clinical illness develops and has revolutionized the purpose and ability of newborn screening. MS/MS is not directed toward diseases defined as treatable, but it is directed toward all the diseases, each of which is rare, that the technique can identify.

MS/MS permits the detection of rare inborn errors of metabolism and has been introduced as a newborn screening tool worldwide. Since 1998, when mass spectrometry was implemented in Australia, the rate of detection per 100,000 births has been 15.7, significantly higher than the rate of 8.6-9.5 in the six preceding 4-year periods. Disorders of fatty acid oxidation, particularly medium-chain acyl coenzyme A dehydrogenase deficiency (see Chapter 106.1), accounted for the majority of increased diagnoses. Expanded newborn screening programs using MS/MS increase the detection of inherited metabolic disorders. All states in the United States use MS/MS in their neonatal screening programs; the metabolic conditions screened range from 31 to >50.

In an attempt to standardize newborn screening programs, the American College of Medical Genetics (ACMG) recommended that every baby born in the United States be screened for a core panel of 29 disorders (Table 769.3). An additional 25 conditions were recommended as secondary targets because they may be identified while screening for the core panel disorders. The March of Dimes and the American Academy of Pediatrics also endorse the ACMG recommendations. However, expansion of the screening test menu raises several issues. The cost of implementation can be significant because many states will need multiple MS/MS systems. Staffing the laboratory with qualified technical personnel to run the MS/MS system and qualified clinical scientists to interpret the profiles can be a challenge. A number of false-positive results will also be obtained with these newborn screening programs. Many of these findings are the result of parenteral nutrition, biologic variation, or treatment and are *not* the result of an inborn error of metabolism. Consequently, qualified staff will be needed to ensure that patients with abnormal results are contacted and receive follow-up testing and counseling, if needed. Even with these concerns, the ACMG report is a step in the right direction toward standardizing guidelines for state newborn screening programs.

TESTING IN REFINING A DIFFERENTIAL DIAGNOSIS

The use of laboratory tests in refining a differential diagnosis satisfies PV theory because a correct differential diagnosis should result in a relatively high prevalence of the disease under consideration. An example of testing in refining a differential diagnosis is the measurement of urinary vanillylmandelic acid (VMA) for the diagnosis of **neuroblastoma** (see Chapter 547). A simple spot test for VMA is not useful in general screening programs because of the low prevalence of neuroblastoma (3 cases/100,000) and the low sensitivity of the test (69%). Even though the specificity of urinary VMA is 99.6%, testing of 100,000 children would produce 2 true-positive test results, 400 false-positive results, and 1 false-negative result. The PV of a positive result in this setting is 0.5%, and the PV of a negative result is 99.99%, not much different from the assumption

Table 769.3 American College of Medical Genetics Core Panel of Neonatal Screening Tests

Isovalericacidemia
Glutaric aciduria type 1
3-Hydroxy-3-methylglutaricaciduria
Multiple coenzyme A (CoA) carboxylase deficiency
Methylmalonic acidemia (mutase deficiency)
3-Methylcrotonyl CoA carboxylase deficiency
Methylmalonic acidemia (cobalamin [Cbl] A, B)
Propionic acidemia
β-Ketothiolase deficiency
Medium-chain acyl-CoA dehydrogenase deficiency
Very-long-chain acyl-CoA dehydrogenase deficiency
Long-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Carnitine uptake deficiency
Phenylketonuria
Maple syrup urine disease
Homocystinuria (because of cystathionine β-synthase deficiency)
Citrullinemia
Argininosuccinic acidemia
Tyrosinemia type 1
Sickle cell anemia (Hb SS disease)
Hemoglobin (Hb) S/β-thalassemia
Hb S/C disease
Congenital hypothyroidism
Biotinidase deficiency
Congenital adrenal hyperplasia (21-hydroxylase deficiency)
Classic galactosemia
Hearing loss
Cystic fibrosis

that neuroblastoma is not present. Testing for urinary VMA in a 3-year-old child with an abdominal mass, however, gives a useful result because the prevalence of neuroblastoma is at least 50% in 3-year-old children with abdominal masses. If 100 such children are tested and the prevalence of neuroblastoma in the group is assumed to be 50%, a satisfactory PV is obtained.

$$\text{PV of positive test result} = \frac{0.69 \times 50}{0.69 \times 50 + (0.004 \times 50)} \times 100 = 99\,\%$$

$$\text{PV of negative test result} = \frac{0.996 \times 50}{0.996 \times 50 + (0.31 \times 50)} \times 100 = 76\,\%$$

Thus, in this situation, a test with low sensitivity is powerful in refining the differential diagnosis because the PV of a positive result is almost 100% in the setting of high prevalence.

Serologic Testing

Using laboratory testing to refine a differential diagnosis poses problems, as exemplified by serologic testing for **Lyme disease**, which is a tick-borne infection by *Borrelia burgdorferi* that has various manifestations in both early and late stages of infection (see Chapter 268). Direct demonstration of the organism is difficult, and serologic test results for Lyme disease are not reliably positive in young patients presenting early with erythema chronicum migrans. These results become positive after a few weeks of infection and remain positive for a number of years. In an older population being evaluated for late-stage Lyme disease, some individuals will have recovered from either clinical or subclinical Lyme disease, and some will have active Lyme disease, with both groups having true-positive serologic test results. Of individuals without Lyme disease, some will have true-negative serologic test results, but a significant percentage will have antibodies to other organisms that cross-react with *B. burgdorferi* antigens.

This set of circumstances gives rise to a number of problems. First, the protean nature of Lyme disease makes it difficult to ensure a high prevalence of disease in persons to be tested. Second, the most appropriate antibodies to be detected are imperfectly defined, leading to a wide variety of tests with varying false-positive and false-negative rates. Third, the natural history of the antibody response to infection and the difficulty of showing the causative organism directly combine to make laboratory diagnosis of early Lyme disease difficult. Fourth, in the diagnosis of late-stage Lyme disease in older individuals, the laboratory diagnosis is plagued by misleading positive (either false-positive or true-positive, but not clinically relevant) results, typically an enzyme-linked immunosorbent assay (ELISA) that uses whole *B. burgdorferi* organisms. In a review of 788 patients referred to a specialty clinic with the diagnosis of Lyme disease, the diagnosis was correct in 180 patients, 156 patients had true seropositivity without active Lyme disease, and 452 had never had Lyme disease, even though 45% of them were found to be seropositive by at least one test before referral.

A two-step approach, similar to that used in HIV testing, is often used: a screening test that has high sensitivity (e.g., ELISA) and excellent negative PV, followed by a very specific confirmatory test for verification of positive screening test results (e.g., Western blot to detect antibodies to selected bacterial antigens). Negative screening test results and negative verification test results are reported as negative. Positive verification test results are reported as positive. However, standardization of the testing procedures is difficult in North America, where only one pathogenic strain of *B. burgdorferi* is found, and is more difficult elsewhere in the Northern hemisphere, where as many as three pathogenic strains are present. Identification of microbial DNA in body fluids by polymerase chain reaction is definitive but invasive.

Table 769.4 Laboratory Profile as a Review of Systems

LABORATORY TEST	ASSESSMENT FACILITATED BY TESTS
Complete blood cell count and platelets	Nutrition, status of formed elements
Complete urinalysis	Renal function/genitourinary tract inflammation
Albumin and cholesterol	Nutrition
ALT, bilirubin, GGT	Liver function
BUN, creatinine	Renal function, nutrition
Sodium, potassium, chloride, bicarbonate	Electrolyte homeostasis
Calcium and phosphorus	Calcium homeostasis

ALT, Alanine transaminase; BUN, blood urea nitrogen; GGT, γ-glutamyltransferase.

Laboratory Screening

Screening profiles are used as part of a complete review of systems, to establish a baseline value, or to facilitate patient care in specific circumstances, such as (1) when a patient clearly has an illness, but a specific diagnosis remains elusive; (2) when a patient requires intensive care; (3) for postmarketing surveillance and evaluation of a new drug; and (4) when a drug is used that is known to have systemic adverse effects. Laboratory screening tests should be used in a targeted manner to supplement, not supplant, a complete history and physical examination (Table 769.4).

Bibliography

American Academy of Pediatrics. American Thyroid Association: newborn screening for congenital hypothyroidism. *Pediatrics*. 1987;80:745–749.

Bulterys M, Jamieson DJ, O'Sullivan MJ, et al. Rapid HIV-1 testing during labor: a multicenter study. *JAMA*. 2004;292:219–223.

Clayton EW. Issues in state newborn screening programs. *Pediatrics*. 1992;90:641–646.

Farrell PM, Kosrok MR, Rock MJ, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics*. 2001;107:1–13.

Galen RS, Gambino SR. *Beyond Normality*. New York: Academic Press; 1975.

Hu LT, Klempner MS. Update on the prevention, diagnosis, and treatment of Lyme disease. *Adv Intern Med*. 2001;46:247–275.

Minamitani K, Inomata H. Neonatal screening for congenital hypothyroidism in Japan. *Pediatr Endocrinol Rev*. 2012;10(suppl 1):79–88.

National Newborn Screening and Genetic Resource Center. Newborn screening information. http://genes-r-us.uthscsa.edu.

Rinaldo P, Tortorelli S, Matern D. Recent developments and new applications of tandem mass spectrometry in newborn screening. *Curr Opin Pediatr*. 2004;16:427–433.

Steere AC, Taylor E, McHugh GL, et al. The overdiagnosis of Lyme disease. *JAMA*. 1993;269:1812–1826.

Sun A, Lam C, Wong DA. Expanded newborn screening for inborn errors of metabolism: overview and outcomes. *Adv Pediatr*. 2012;59(1):209–245.

Watson MS, Mann MJ, Lloyd-Puryear MA, et al. Newborn screening: towards a uniform screening panel and system. *Genet Med*. 2006;8(Suppl):S12–S252.

Wilcken B, Wiley V, Hammond J, et al. Screening newborns for inborn errors of metabolism by tandem mass spectrometry. *N Engl J Med*. 2003;348:2304–2312.

Zytkovicz TH, Fitzgerald EF, Marsden D, et al. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots: a two-year summary from the New England Newborn Screening Program. *Clin Chem*. 2001;47:1945–1955.

Chapter 770

Reference Intervals for Laboratory Tests and Procedures

Stanley F. Lo and Stephen M. Roper

In Tables 770.1-770.5, the reference intervals apply to infants, children, and adolescents when possible. For many analyses, separate reference intervals for children and adolescents are not well delineated. When interpreting a test result, the reference interval supplied by the laboratory performing the test should always be used because these intervals are instrument and/or method dependent. Figures 770.1 and 770.2 provide estimations related to dosages. Figure 770.3 is a nomogram for risk assessment of hyperbilirubinemia.

Table 770.1 Prefixes Denoting Decimal Factors in Table 770.5

PREFIX	SYMBOL	FACTOR
mega-	M	10^6
kilo-	k	10^3
hecto-	h	10^2
deka-	da	10^1
deci-	d	10^{-1}
centi-	c	10^{-2}
milli-	m	10^{-3}
micro-	μ	10^{-6}
nano-	n	10^{-9}
pico-	p	10^{-12}
femto-	f	10^{-15}

Table 770.2 Abbreviations Used in Table 770.5

Ab	Absorbance	mm^3	Cubic millimeter, microliter (μL)
AU	Arbitrary unit	mm Hg	Millimeters of mercury
BB	Brain isoenzyme of creatine kinase	mmol	Millimole
cap	Capillary	mo	Month, months
CH_{50}	Dilution required to lyse 50% of indicator red blood cells; indicates complement activity	mol	Mole
		mOsm	Milliosmole
		MW	Relative molecular weight
Cr	Creatinine	ND	Not detected
CSF	Cerebrospinal fluid	nm	Nanometer (wavelength)
F	Female	Pa	Pascal(s)
g	Gram, grams	pc	Postprandial
G6PD	Glucose-6-phosphate dehydrogenase	RBC	Red blood cell(s), erythrocyte(s)
Hb	Hemoglobin	RT	Room temperature
HbCO	Carboxyhemoglobin	SD	Standard deviation
hpf	High-power field	sec	Second, seconds
hr	Hour, hours	Tr	Trace
IU	International unit(s) of hormone activity	U	International unit(s) of enzyme activity
L	Liter	V	Volume
M	Male	WBC	White blood cell(s)
MB	Heart isoenzyme of creatine kinase	WHO	World Health Organization
mEq/L	Milliequivalents per liter	wk	Week, weeks
min	Minute, minutes	yr	Year, years

Table 770.3 Abbreviations for Specimens in Table 770.5

S	Serum
P	Plasma
(H)	Heparin
(LiH)	Lithium heparin
(E)	Ethylenediaminetetraacetic acid (EDTA)
(C)	Citrate
(O)	Oxalate
W	Whole blood
(NH_4H)	Ammonium heparinate

Table 770.4 Key to Comments Section of Table 770.5

30°C, 37°C	Temperature of enzymatic analysis (Celsius)	l	Fluorometric method
a	Values obtained are significantly method dependent	m	Fluorescence-activated cell sorting (FACS)
b	Values in older males are higher than those in older females	n	Fluorescence polarization
c	Values in older females are higher than those in older males	o	Gas chromatography
d	Atomic absorption	p	High-performance liquid chromatography (HPLC)
e	Borate affinity chromatography	q	Indirect fluorescence antibody (IFA) assay
f	Cation-exchange chromatography	r	Ion-selective electrode
g	Vitros, a proprietary analytic system of Ortho Clinical Diagnostics	s	Nephelometry
i	Electrophoresis	t	Optical density
j	Enzymatic assay	u	Radial immunodiffusion (RID)
k	Enzyme-amplified immunoassay	v	Radioimmunoassay (RIA)
		w	Spectrophotometry

Table 770.5 Reference Intervals*

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
COMPLETE BLOOD COUNT						
Hematocrit (HCT, Hct)	*W(E)*		*% of packed red cells (V red cells/V whole blood cells × 100)*		*Volume fraction (V red cells/V whole blood)*	
Calculated from mean corpuscular volume (MCV) and RBC count (electronic displacement or laser)		0-30 days	44-70%	×0.01	0.44-0.70	
		1-23 mo	32-42%		0.32-0.42	
		2-9 yr	33-43%		0.33-0.43	
		10-17 yr M	36-47%		0.36-0.47	
		F	35-45%		0.35-0.45	
		>18-99 yr M	42-52%		0.42-0.52	
		F	37-47%		0.37-0.47	
Hemoglobin (Hb)	*W(E)*		*g/dL*		*mmol/L*	
		0-30 days	15.0-24.0	×0.155	2.32-3.72	MW Hb = 64,500
		1-23 mo	10.5-14.0		1.63-2.17	
		2-9 yr	11.5-14.5		1.78-2.25	
		10-17 yr M	12.5-16.1		1.93-2.50	
		F	12.0-15.0		1.86-2.32	
		>18-99 yr M	13.5-18.0		2.09-2.79	
		F	12.5-16.0		1.93-2.48	
	P(H)	*See Chemical Elements*				
Erythrocyte indices (RBC indices)						

Continued

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Mean corpuscular hemoglobin (MCH)	*W(E)*		*pg/cell*		*fmol/cell*	
		0-30 days	33-39	×0.0155	0.51-0.60	
		1-23 mo	24-30		0.37-0.46	
		2-9 yr	25-31		0.39-0.48	
		10-17 yr M	26-32		0.26-0.32	
		F	26-32		0.26-0.32	
		>18-99 yr M	27-31		0.27-0.31	
		F	27-31		0.27-0.31	
Mean corpuscular hemoglobin concentration (MCHC)	*W(E)*		*% Hb/cell or g Hb/dL RBC*		*mmol Hb/L RBC*	
			32-36	×0.155	4.96-5.58	
Mean corpuscular volume (MCV)	*W(E)*		*μm³*		*fL*	
		0-30 days	99-115	×1	99-115	
		1-23 mo	72-88		72-88	
		2-9 yr	76-90		76-90	
		10-17 yr	78-95		78-95	
		>18-99 yr	78-100		78-100	
Leukocyte count (WBC count)	*W(E)*	*×1,000 cells/mm³ (μL)*			*×10⁹ cells/L*	
		0-30 days	9.1-34.0	×1	9.1-34.0	
		1-23 mo	6.0-14.0		6.0-14.0	
		2-9 yr	4.0-12.0		45.0-12.0	
		10-17 yr	4.0-10.5		4.0-10.5	
		18-99 yr	4.0-10.5		4.0-10.5	
Leukocyte differential	*W(E)*	*%*			*Number fraction*	
Myelocytes		0%		×0.01	0	
Neutrophils ("bands")		3-5%			0.03-0.05	
Neutrophils ("segs")		54-62%			0.54-0.62	
Lymphocytes		25-33%			0.25-0.33	
Monocytes		3-7%			0.03-0.07	
Eosinophils		1-3%			0.01-0.03	
Basophils		0-0.75%			0-0.0075	
		Cells/mm³ (μL)			*×10⁶ cells/L*	
Myelocytes		0		×1	0	
Neutrophils ("bands")		150-400			150-400	
Neutrophils ("segs")		3,000-5,800			3,000-5,800	
Lymphocytes		1,500-3,000			1,500-3,000	
Monocytes		285-500			285-500	
Eosinophils		50-250			50-250	
Basophils		15-50			15-50	
Platelet count (thrombocyte count)	*W(E)*	*×10³/mm³ (μL)*			*×10⁹/L*	
		Newborn 84-478 (after 1 wk, same as adult)		×10⁶	84-478	(Buck, 1996)
		Adult 150-400			150-400	

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Reticulocyte count	*W(E,H,O)*	*Adults 0.5-1.5% of erythrocytes or 25,000-75,000/mm³ (μL)*		*×0.01 ×10⁶*	*0.005-0.015 (number fraction) or 25,000-75,000 × 10⁶/L*	
			%		*Number fraction*	
	W(cap)	1 day	0.4-6.0	×0.01	0.004-0.060	
		7 days	<0.1-1.3		<0.001-0.013	
		1-4 wk	<1.0-1.2		<0.001-0.012	
		5-6 wk	<0.1-2.4		<0.001-0.024	
		7-8 wk	0.1-2.9		0.001-0.029	
		9-10 wk	<0.1-2.6		<0.001-0.026	
		11-12 wk	0.1-1.3		0.001-0.013	
Alanine transaminase (aminotransferase) (ALT, SGPT)	*S*	*0-7 days*	*6-40 U/L*	*×1*	*6-40 U/L*	37°C,[bgw] (Soldin, Savwoir, Guo, 1997; Lockitch Halstead, Albersheim, 1988)[g] (Meites, 1989; Soldin and Morse, 1998; Lockitch Halstead, Albersheim, 1988)
		8-30 days M	10-40		10-40	
		F	8-32		8-32	
		1-12 mo	12-45		12-45	
		1-19 yr	5-45		5-45	
Albumin (BCG)	P	Premature 1 day	1.8-3.0 g/dL	×10	18-30 g/dL	
		Full term <6 days	2.5-3.4		25-34	
		8 days-1 yr	1.9-4.9		19-49	
		1-3 yr	3.4-4.2		34-42	
		4-19 yr	3.5-5.6		35-56	
Ammonia	P		11-35 μmol/L	×1	11-35 μmol/L	[g]
Amylase	S,P	1-19 yr	30-100 U/L	×1	30-100 U/L	(Lockitch Halstead, Albersheim, 1988; Gillard et al, 1983)
			% pancreatic fraction		*% pancreatic fraction*	
Amylase isoenzymes	S,P(H)	Cord-8 mo	0-34%	×0.01	0-0.34%	
		9 mo-4 yr	5-56%		0.05-0.56%	
		5-19 yr	23-59%		0.23-0.59%	
Anion gap (sodium – [chloride + bicarbonate])	P(H)	7-16 mEq/L		×1	7-16 mEq/L	
Antideoxyribonuclease B titer (anti-DNase B titer)	*S*	*Age*	*Upper limit of normal*		*Upper limit of normal*	
		4-6 yr	240-480 U	×1	240-480 U	(Kaplan et al, 1998)
		7-12 yr	480-800 U		480-800 U	
Antidiuretic hormone (hADH, vasopressin)	*P(E)*	*Plasma osmolarity (mOsm/kg)*	*Plasma ADH (pg/mL)*		*Plasma ADH ng/L*	
		270-280	<1.5	×1	<1.5	
		280-285	<2.5		<2.5	
		285-290	1-5		1-5	
		290-295	2-7		2-7	
		295-300	4-12		4-12	

Continued

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†		COMMENTS
Antistreptolysin-O titer (ASO titer)	*S*	*Age*	*Upper limit of normal*		*Upper limit of normal*		
		2-5 yr	120-160 Todd units	×1	120-160 Todd units		(Kaplan et al, 1998)
		6-9 yr	240 Todd units		240 Todd units		
		10-12 yr	320 Todd units		320 Todd units		
Aspartate transaminase (aminotransferase) (AST, SGOT)	*S*		*U/L*		*U/L*		
		0-7 days M	30-100	×1	35-100		37°C,[9] (Soldin, Savwoir, Guo, 1997; Lockitch Halstead, Albersheim, 1988)
		F	24-95		24-95		
		8-30 days	22-71		22-71		
		1-12 mo	22-63		22-63		
		1-3 yr	20-60		20-60		
		3-9 yr	15-50		15-50		
		10-15 yr	10-40		10-40		
		16-19 yr M	15-45		15-45		
		F	5-30		5-30		
Base excess	*W(H)*		*mmol/L*		*mmol/L*		
		Newborn	(−10)-(−2)	×1	(−10)-(−2)		
		Infant	(−7)-(−1)		(−7)-(−1)		
		Child	(−4)-(+2)		(−4)-(+2)		
		Thereafter	(−3)-(+3)		(−3)-(−3)		
Bicarbonate	*S,P*		*mmol/L*		*mmol/L*		
		Arterial	21-28	×1	21-28		
		Venous	22-29		22-29		
Bilirubin, total	*S*		*mg/dL*		*μmol/L*		
		Newborn	See Bhutani nomogram (Fig. 770.3)	×17.1			(Bhutani et al, 1999)
		1 mo-adult	<1.0		<17		
C-reactive protein (high sensitivity)	*S*						*(Soldin et al, 2004)*
			M (mg/dL)	*F (mg/dL)*		*M (mg/L)*	*F (mg/L)*
		0-90 days	0.08-1.58	0.09-1.58	×10	0.8-15.8	0.9-15.8
		91 days-12 mo	0.08-1.12	0.05-0.79		0.8-11.2	0.5-7.9
		13 mo-3 yr	0.08-1.12	0.08-0.79		0.8-11.2	0.8-7.9
		4-10 yr	0.06-0.79	0.5-1.0		0.6-7.9	0.5-10.0
		11-14 yr	0.08-0.76	0.06-0.81		0.8-7.6	0.6-8.1
		15-18 yr	0.04-0.79	0.06-0.79		0.4-7.9	0.6-7.9
Calcium, ionized (Ca)	*S,P(H),W(H)*		*mg/dL*		*mmol/L*		
		Cord blood	5.0-6.0	×0.25	1.25-1.50		
		Newborn, 3-24 hr	4.3-5.1		1.07-1.27		
		24-48 hr	4.0-4.7		1.00-1.17		
		Thereafter	4.8-4.92		1.12-1.23		
		or	2.24-2.46 Eq/L	×0.5	1.12-1.23		

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Calcium, total	*S*		*mg/dL*		*mmol/L*	
		Cord blood	9.0-11.5	×0.25	2.25-2.88	
		Newborn, 3-24 hr	9.0-10.6		2.3-2.65	
		24-48 hr	7.0-12.0		1.75-3.00	
		4-7 days	9.0-10.9		2.25-2.73	
		Child	8.8-10.8		2.20-2.70	
		Thereafter	8.4-10.2		2.10-2.55	
Carbon dioxide, partial pressure (Pco_2)	*W(H)*		*mm Hg*		*kPa*	
		Newborn	27-40	×0.1333	3.6-5.3	
		Infant	27-41		3.6-5.5	
		Thereafter M	35-48		4.7-6.4	
		F	32-45		4.3-6.0	
Carbon monoxide (carboxyhemoglobin)	W(E)	Nonsmoker	<2% HbCO	×0.01	HbCO fraction <0.02	
		Smoker	<10%		<0.10	
		Lethal	>50%		>0.5	
Chloride	S,P(H)	Cord blood	96-104 mmol/L	×1	96-104 mmol/L	
		Newborn	97-110		97-110	
		Thereafter	98-106		98-106	
Chloride, sweat	*Sweat*		*mmol/L*			(Farrell et al, 2008)
			≤29	CF unlikely		
			30-59	Intermediate		
			≥60	Indicative of CF		
Cortisol	*S,P(H)*		*μg/dL*		*nmol/L*	
		Newborn	1-24	×27.59	28-662	
		Adults, 8 AM	5-23		138-635	
		4 PM	3-15		82-413	
		8 PM	<50% of 8 AM	×0.01	Fraction of 8 AM	
					≤0.50	
Creatine kinase	S	Cord blood	70-380 U/L	×1	70-380 U/L	30°C,[b] (Jedeikin et al, 1982)
		5-8 hr	214-1,175		214-1,175	
		24-33 hr	130-1,200		130-1,200	
		72-100 hr	87-725		87-725	
		Adult	5-130		5-130	
Creatine kinase isoenzymes	*S*		*% MB*	*% BB*		
		Cord blood	0.3-3.1	0.3-10.5		
		5-8 hr	1.7-7.9	3.6-13.4		
		24-33 hr	1.8-5	2.3-8.6		
		72-100 hr	1.4-5.4	5.1-13.3		
		Adult	0-2	0		

Continued

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†		COMMENTS
Creatinine (IDMS)							
Enzymatic	*S,P*		*mg/dL*		*μmol/L*		[9]
		0-4 yr	0.03-0.50	×88.4	2.65-44.2		
		4-7 yr	0.03-0.59		2.65-52.2		
		7-10 yr	0.22-0.59		19.4-52.2		
		10-14 yr	0.31-0.88		27.4-77.8		
		>14 yr	0.50-1.06		44.2-93.7		
Creatinine clearance (endogenous)	S,P,U	Newborn 40-65 mL/min/1.73 m^2					
		<40 yr, M 97-137					
		F 88-128					
		Decreases <6.5 mL/min/decade					
Ferritin	*S*		*ng/mL*		*μg/L*		
		0-6 wk	0-400	×1	0-400		
		7 wk-365 days	10-95		10-95		
		1-9 yr	10-60		10-60		
		10-18 yr M	10-300		10-300		
		F	10-70		10-70		
Folate	S	Newborn 7.0-32 ng/mL		×2.265	15.9-72.4 nmol/L		
		Thereafter 1.8-9.0			4.1-20.4		
	W(E)	150-450 ng/mL RBCs			340-1,020 nmol/L cells		
Glucose	*S*		*mg/dL*		*mmol/L*		
		Cord blood	45-96	×0.0555	2.5-5.3		
		Premature	20-60		1.1-3.3		
		Neonate	30-60		1.7-3.3		
		Newborn					
		1 day	40-60		2.2-3.3		
		>1 day	50-90		2.8-5.0		
		Child	60-100		3.3-5.5		
		Adult	70-105		3.9-5.8		
	W(H)	Adult	65-95		3.6-5.3		
Glucose tolerance test (GTT) (see Chapter 629)	*S*		*mg/dL*			*mmol/L*	
Oral dose							
Adult: 75 g			*Normal* *Diabetic*			*Normal* *Diabetic*	
Child: 1.75 g/kg of ideal weight, up to a maximum of 75 g		Fasting	70-105 ≥126	×0.0555		3.9-5.8 ≥7.0	(Diabetes Care, 2019)
		120 min	70-120 ≥200			3.9-6.7 ≥11	
G6PD in erythrocytes		W(E,H,C)					
Bishop, modified		Adult			Adult		
		3.4-8.0 U/g Hb		×0.0645	0.22-0.52 mU/mol Hb		
		98.6-232 $U/10^{12}$ RBCs		$\times 10^{-3}$	0.10-0.23 $nU/10^{6}$ RBCs		
		1.16-2.72 U/mL RBC		×1	1.16-2.72 kU/L RBC		
		Newborn: 50% higher			Newborn: 50% higher		

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
γ-Glutamyl transpeptidase (GGT, GGTP)	*S*		*U/L*		*U/L*	
		Cord blood	37-193	×1	37-193	37°C,[b] (Knight and Haymond, 1981)
		0-1 mo	13-147		13-147	
		1-2 mo	12-123		12-123	
		2-4 mo	8-90		8-90	
		4 mo-10 yr	5-32		5-32	
		10-15 yr	5-24		5-24	
Immunoglobulin A (IgA)	*S*		*mg/dL*		*mg/L*	
		Cord blood	1.4-3.6	×10	14-36	[s] (Meites, 1989)
		1-3 mo	1.3-53		13-530	
		4-6 mo	4.4-84		44-840	
		7 mo-1 yr	11-106		110-1,060	
		2-5 yr	14-159		140-1,590	
		6-10 yr	33-236		330-2,360	
		Adult	70-312		700-3,120	
Immunoglobulin D (IgD)	S	Newborn: none detected			None detected	
		Thereafter: 0-8 mg/dL		×10	0-80 mg/L	
Immunoglobulin E (IgE)	S	M 0-230 IU/mL		×1	0-230 kIU/L	
		F 0-170			0-170	
Immunoglobulin G (IgG)	S		mg/dL		g/L	
		Cord blood	636-1,606	×0.01	6.36-16.06	[s] (Meites, 1989)
		1 mo	251-906		2.51-9.06	
		2-4 mo	176-601		1.76-6.01	
		5-12 mo	172-1,069		1.72-10.69	
		1-5 yr	345-1,236		3.45-12.36	
		6-10 yr	608-1,572		6.08-15.72	
		Adult	639-1,349		6.39-13.49	
Immunoglobulin M (IgM)	*S*		*mg/dL*		*mg/L*	
		Cord blood	6.3-25	×10	63-250	[s](Meites, 1989)
		1-4 mo	17-105		170-1,050	
		5-9 mo	33-126		330-1,260	
		10 mo-1 yr	41-173		410-1,730	
		2-8 yr	43-207		430-2,070	
		9-10 yr	52-242		520-2,420	
		Adult	56-352		560-3,520	
Iron	P	All ages	22-184 μg/dL	×0.1791	4-33 μmol/L	(Lockitch Halstead, Wadsworth, 1988)
Iron-binding capacity, total (TIBC)	S	Infant 100-400 μg/dL		×0.179	17.90-71.60 μmol/L	
		Thereafter 250-400			44.75-71.60	
L-lactate (perchloric acid)	*W*		*mg/dL*		*mmol/L*	
		1-12 mo	10-21	×1	1.1-2.3	(Bonnefont et al, 1990)
		1-7 yr	7-14		0.8-1.5	
		7-15 yr	5-8		0.6-0.9	
D-lactate	P(H)					[j](Rosenthal and Pesce, 1985)
		6 mo-3 yr	0.0-0.3	×1	0.0-0.3	

Continued

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†			CONVERSION FACTOR	REFERENCE VALUES (SI)†			COMMENTS
Lactate dehydrogenase (LDH)	*S*		*U/L*			*U/L*			
		<1 yr	170-580		×1	170-580			37°C,[a] (Meites, 1989)
		1-9 yr	150-500			150-500			
		10-19 yr	120-330			120-330			
Isoenzymes	*S*		*% of total activity*						
			1-6 yr	7-19 yr					
		LD1	20-38	20-35					
		LD2	27-38	31-38					
		LD3	16-26	19-28					
		LD4	5-16	7-13					
		LD5	3-13	5-12					
Lead	*W(H)*		*μg/dL*			*mmol/L*			
		Child	<3.5*		×0.0483	<0.0024			
		Initiate chelation therapy	≥70			≥3.38			
Lipase	P,S	1-18 yr	145-216 U/L		×1	145-216 U/L			(Ghoshal and Soldin, 2003)
Magnesium	P(H)		mg/dL			mmol/L			
		0-6 days	1.2-2.6		×0.411	0.48-1.05			[gw](Meites, 1989)
		7 days-2 yr	1.6-2.6			0.65-1.05			
		2-14 yr	1.5-2.3			0.60-0.95			
		0.78 ± 0.37% of total Hb			×0.01	0.0078 ± 0.0037 (mass fraction)			
Osmolality	S	Child, adult							
		275-295 mOsm/kg H_2O							
Phosphatase, alkaline	*S*		*U/L*			*U/L*			
		1-9 yr	145-420		×1	145-420			37°C,[aw]
		10-11 yr	140-560			140-560			
			M	F			M	F	
		12-13 yr	200-495	105-420			200-495	105-420	
		14-15 yr	130-525	70-230			130-525	70-230	
		16-19 yr	65-260	50-130			65-260	50-130	
Phosphorus, inorganic	S,P(H)		mg/dL			mmol/L			
		0-5 days	4.8-8.2		×0.3229	1.55-2.65			[w](Meites, 1989)
		1-3 yr	3.8-6.5			1.25-2.10			
		4-11 yr	3.7-5.6			1.20-1.80			
		12-15 yr	2.9-5.4			0.95-1.75			
		16-19 yr	2.7-4.7			0.90-1.50			
Potassium	*S*		*mmol/L*			*mmol/L*			
		0-1 wk	3.2-5.5		×1	3.3-5.5			(Greeley et al, 1993) Increased by hemolysis; serum values systematically higher than plasma values
		1 wk-1 mo	3.4-6.0			3.4-6.0			
		1-6 mo	3.5-5.6			3.5-5.6			
		6 mo-1 yr	3.5-6.1			3.5-6.1			
		>1 yr	3.3-4.6			3.3-4.6			
	P(H)	3.5-4.5 mmol/L				3.5-4.5 mmol/L			

*https://www.cdc.gov/nceh/lead/prevention/blood-lead-levels.htm

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Prealbumin (transthyretin)	*S*		*mg/dL*		*mg/L*	
		0-5 days	6.0-21.0	×10	60-210	[s](Lockitch, Halstead, Quigley, 1988)
		1-5 yr	14.0-30.0		140-300	
		6-9 yr	15.0-30.0		150-300	
		10-13 yr	20.0-36.0		200-360	
		14-19	22.0-45.0		220-450	
Protein, total	*S*		*g/dL*		*g/L*	
		Premature	4.3-7.6	×10	43-76	(Meites, 1989)
		Newborn	4.6-7.4		46-74	
		1-7 yr	6.1-7.9		61-79	
		8-12 yr	6.4-8.1		64-81	
		13-19 yr	6.6-8.2		66-82	
Pyruvate (perchloric acid)	W	7-17 yr	0.076 ± 0.026 mmol/L	×1	0.076 ± 0.026 mmol/L	(Pianosi et al, 1995)
Sodium	*S,P (LiH, NH_4H)*		*mmol/L*		*mmol/L*	
		Newborn	133-146	×1	133-146	[g](Greeley et al, 1993)
		Infant	134-144		134-144	
		Child	134-143		134-143	
		Thereafter	135-145		135-145	
Thyroid-stimulating hormone (TSH)	*S*		*mIU/L*		*mIU/L*	
		0-3 days	1.00-20.00	×1	1.0-20.00	[g](Dugaw et al, 2001)
		4-30 days	0.5-6.5		0.50-6.50	
		1-5 mo	0.5-6.0		0.5-6.0	
		6 mo-18 yr	0.5-4.5		0.5-4.5	
Thyrotropin-releasing hormone (TRH)	P	5-60 pg/mL		×2.759	14-165 pmol/L	
Thyroxine-binding globulin (TBG)	*S*		*mg/dL*		*mg/L*	
		Cord blood	1.4-9.4	×10	14-94	
		1-4 wk	1.0-9.0		10-90	
		1-12 mo	2.0-7.6		20-76	
		1-5 yr	2.9-5.4		29-54	
		5-10 yr	2.5-5.0		25-50	
		10-15 yr	2.1-4.6		21-46	
		Adult	1.5-3.4		15-34	
Thyroxine (T_4), total	*S*		*μg/dL*		*nmol/L*	
		0-3 days	8.0-20.0	×12.9	103-258	[g](Dugaw et al, 2001)
		3-30 days	5.0-15.0		64-193	
		31-365 days	6.0-14.0		77-180	
		1-5 yr	4.5-11.0		58-142	
		6-18 yr	4.5-10.0		58-129	

Continued

Table 770.5 Reference Intervals*—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Thyroxine (T_4), free	*S*		*ng/dL*		*pmol/L*	
		0-3 days	2.00-5.00	×12.9	25.7-64.3	[9](Dugaw et al, 2001)
		3-30 days	0.90-2.20		11.6-28.3	
		31 days-18 yr	0.7-2.00		9.0-25.7	
Thyroxine (T_4), total	W	Newborn screen (filter paper) 6.2-22.0 µg/dL		×12.9	80-283 nmol/L	
Triiodothyronine (T_3), free	*S*		*pg/dL*		*pmol/L*	
		Cord blood	20-240	×0.01536	0.3-3.7	
		1-3 days	200-610		3.1-9.4	
		6 wk	240-560		3.7-8.6	
		Adult (20-50 yr)	230-660		3.5-10.0	
Triiodothyronine (T_3), total	*S*		*ng/dL*		*nmol/L*	
		0-3 days	60-300	×0.0154	0.9-4.7	
		4-365 days		90-260		1.4-4.0
		1-6 yr	90-240		1.4-3.7	
		7-11 yr	90-230		1.4-3.6	
		12-18 yr	100-210		1.5-3.3	[9](Dugaw et al, 2001)
Urea nitrogen	S,P		mg/dL		mmol/L	
		Cord blood	21-40	×0.357	7.5-14.3	
		Premature (1 wk)	3-25		1.1-9.0	
		Newborn	3-12		1.1-4.3	
		infant or child	5-18		1.8-6.4	
		Thereafter	7-18		2.5-6.4	
Uric acid	*S*		*mg/dL*		*µmol/L*	
		1-3 yr	1.8-5.0	×59.48	100-300	
		4-6 yr	2.2-4.7		130-280	
		7-9 yr	2.0-5.0		120-295	
		10-11 yr M	2.3-5.4		135-320	(Lockitch Halstead, Albersheim, 1988)
		10-11 yr F	3.0-4.7		180-280	
		12-13 yr M	2.7-6.7		160-400	
		14-15 yr M	2.4-7.8		140-465	
		12-15 yr F	3.0-5.8		180-345	
		16-19 yr M	4.0-8.6		235-510	
		16-19 yr F	3.0-5.9		180-350	

*In preparing the reference range listings, a number of abbreviations, symbols, and codes were used (see Table 770.2).
†Reference values are shown in SI units (International System of Units) and U.S. units (Traditional Units).

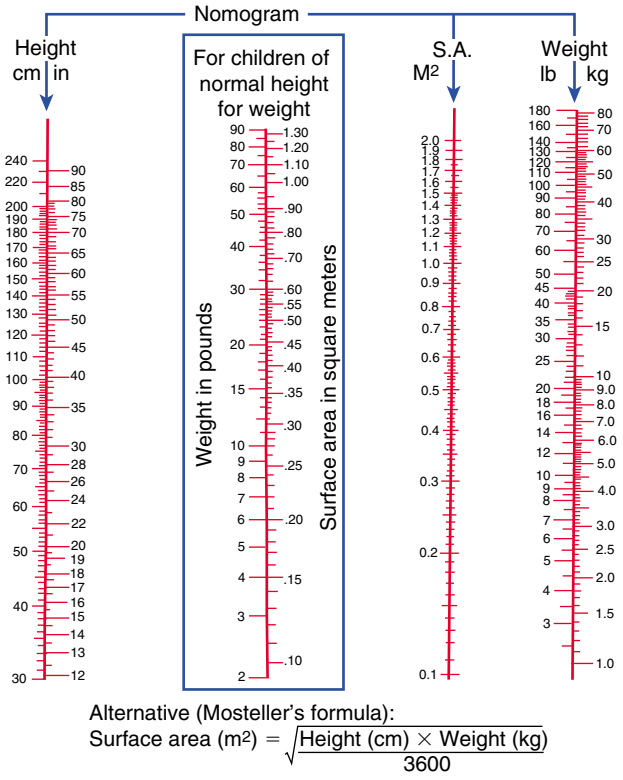

Fig. 770.1 Nomogram for the estimation of surface area. The surface area is indicated where a straight line that connects the height and weight levels intersects the surface area column, or if the patient is roughly of average size, from the weight alone *(enclosed area)*. *(Nomogram modified from the data of E. Boyd by CD West. See also Briars GL, Bailey BJ. Surface area estimation: pocket calculator v nomogram. Arch Dis Child. 1994;70:246–247.)*

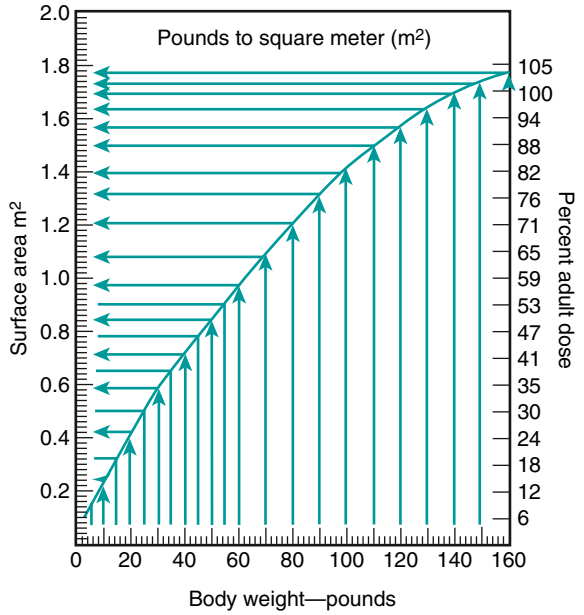

Fig. 770.2 Relationships between body weight (lb), body surface area, and adult dosage. The surface area values correspond with those set forth by Crawford JD, Terry ME, Rourke GM. Simplification of drug dosage calculation by application of the surface area principle. *Pediatrics*. 1950;5:783–790. Note that the 100% adult dose is for a patient weighing approximately 140 lb and having a surface area of approximately 1.7 m². *(From Talbot NB, Richie RH, Crawford JH. Metabolic homeostasis: a syllabus for those concerned with the care of patients. Cambridge, MA: Harvard University Press, 1959.)*

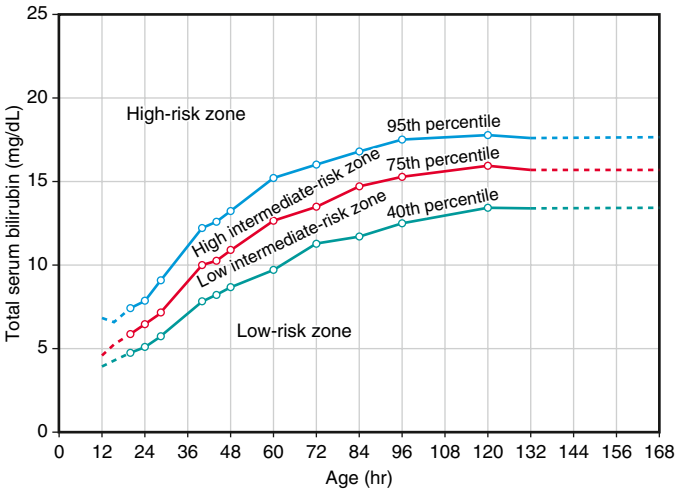

Fig. 770.3 Nomogram for risk assessment of hyperbilirubinemia. *(From Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics. 1999;103:6–14. Fig 2.)*

Bibliography (for Table 770.5)

American Diabetes Association. Classification and diagnosis of Diabetes: Standards of Medical care in Diabetes - 2019. *Diabetes Care*. 2019;42:S13–S28.

Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103:6–14.

Bonnefont JP, Specola NB, Vassault A, et al. The fasting test in children: application to the diagnosis of pathological hypo- and hyperketotic state. *Eur J Pediatr*. 1990;150:80–85.

Buck ML. Anticoagulation with warfarin in infants and children. *Ann Pharmacother*. 1996;30:1316–1322.

Diaz J, Tornel PL, Martinez P. Reference intervals for blood ammonia in healthy subjects, determined by microdiffusion. *Clin Chem*. 1995;41:1048.

Dugaw KA, Jack RM, Rutledge J. Pediatric reference ranges for TSH, free T_4, total T_4, total T_3 and T_3 uptake on the VitrosECi analyzer. *Clin Chem*. 2001;47:A108.

E. Endocrinology, C. Hills, CA 91301.

Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation Consensus Report. *J Pediatr*. 2008;153:S4–S14.

Ghoshal A, Soldin S. Evaluation of the Dade Behring dimension R × L: integrated chemistry system, pediatric reference ranges. *Clin Chim Acta*. 2003;331:135–146.

Gillard BK, Simbala JA, Goodglick L. Reference intervals for amylase isoenzymes in serum and plasma of infants and children. *Clin Chem*. 1983;29:1119–1123.

Greeley C, Snell J, Colaco A, et al. Pediatric reference ranges for electrolytes and creatinine. *Clin Chem*. 1993;39:1172.

Jedeikin R, Makela SK, Shennan AT, et al. Creatine kinase isoenzymes in serum from cord blood and the blood of healthy full-term infants during the first three postnatal days. *Clin Chem*. 1982;28:317–322.

Kaplan EL, Rothermel CD, Johnson DR. Antistreptolysin O and antideoxyribonuclease B titers: normal values for children ages 2 to 12 in the United States. *Pediatrics*. 1998;101:86–88.

Knight JA, Haymond RE. γ-Glutamyltransferase and alkaline phosphatase activities compared in serum of normal children and children with liver disease. *Clin Chem*. 1981;27:48–51.

Lockitch G, Halstead AC, Albersheim S, et al. Age- and sex-specific pediatric reference intervals for biochemistry analytes as measured with the Ektachem-700 analyzer. *Clin Chem*. 1988;34:1622–1625.

Lockitch G, Halstead AC, Quigley G, et al. Age- and sex-specific pediatric reference intervals: study design and methods illustrated by measurement of serum proteins with the Behring LN nephelometer. *Clin Chem*. 1988;34:1618–1621.

Lockitch G, Halstead AC, Wadsworth L, et al. Age- and sex-specific pediatric reference intervals and correlations for zinc, copper, selenium, iron, vitamins A and E, and related proteins. *Clin Chem*. 1988;34:1625–1628.

Meites S, ed. *Pediatric Clinical Chemistry, Reference (normal) Values*. 3rd ed. Washington, DC: American Association for Clinical Chemistry; 1989.

Muntau A, Streiter M, Kappler M, et al. Age-related reference values for serum selenium concentrations in infants and children. *Clin Chem*. 2002;48:555–560.

Nichols I. Diagnostics. San Juan Capistrano, CA 92675.

Nir A, Bar-Oz B, Perles Z, et al. N-terminal pro-B-type natriuretic peptide: reference plasma levels from birth to adolescence: elevated levels at birth and in infants and children with heart diseases. *Acta Paediatr*. 2004;93:603–607.

Pianosi P, Seargeant L, Haworth JC. Blood lactate and pyruvate concentrations, and their ratio during exercise in healthy children: developmental perspective. *Eur J Appl Physiol Occup Physiol*. 1995;71:518–522.

Rosenthal P, Pesce MA. Long-term monitoring of d-lactic acidosis in a child. *J Pediatr Gastroenterol Nutr*. 1985;4:674–676. 1985.

Sherry B, Jack RM, Weber A, et al. Reference interval for prealbumin for children 2 to 36 months old. *Clin Chem*. 1988;34:1878–1880.

Soldin SJ, Morse AS. Pediatric reference ranges for albumin and total protein in children <1 year old using the Vitros 500 analyzer. *Clin Chem*. 1998;44:A15.

Soldin SJ, Savwoir TV, Guo Y. Pediatric reference ranges for alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase in children less than 1 year old on the Vitros 500. *Clin Chem*. 1997;43:S199.

Soldin SJ, Brugnara C, Wong ED, eds. *Pediatric Reference Intervals*. 5th ed. Washington, DC: American Association for Clinical Chemistry; 2005.

Soldin O, Bierbower L, Choi J, et al. Serum iron, ferritin, transferrin, total iron binding capacity, hs-CRP, LDL cholesterol and magnesium in children: new reference intervals using the Dade Dimension Clinical Chemistry System. *Clin Chim Acta*. 2004;342:211–217.

Soldin SJ, Hicks JM, Bailey J, et al. Pediatric reference ranges for 25-hydroxy vitamin D during the summer and winter. *Clin Chem*. 1997;43:S200.