Chapter 21

MEDICAL MANAGEMENT OF CHEMICAL TOXICITY IN PEDIATRICS

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INTRODUCTION

Historically, chemical attacks were limited to the battlefield, and casualties were predominantly military personnel. Thus, the majority of knowledge concerning the medical management of chemical casualties has come from treating a military population. However, the modern global political climate has increased the likelihood of a chemical attack off the battlefield.[1–29] It is therefore prudent to understand the impact of chemical agents upon the pediatric population so children can be protected and treated efficiently in the event of an attack. Although pediatric recommendations are often extrapolated from adult data, pediatric patients should not be regarded as miniature adults; they present unique vulnerabilities and special considerations should be taken to care for them.

In response to the growing possibility of a chemical agent attack affecting children, several pediatric advocacy groups and physicians have commented on the urgent need for pediatric chemical casualty research. According to some, "we must learn to manage the consequences and limit the impact on the physical and mental health of our population, particularly our children."[30(p80)] The American Academy of Pediatrics has identified five forms of terrorism that require immediate attention: thermomechanical, biological, chemical, radiological, and psychological.[31] The committees on environmental health and infectious diseases have provided the following consensus statement regarding children and chemical and biological threats:

> Because children would be disproportionately affected by a chemical or biological weapons release, pediatricians must assist in planning for a domestic chemical-biological incident. Government agencies should seek input from pediatricians and pediatric subspecialists to ensure that the situations created by multiple pediatric casualties after a chemical-biological incident are considered.[32(p662)]

Emergency planners face numerous challenges when preparing for pediatric chemical casualties. Investigating the proper treatment of children during a chemical attack can be frustrating because of the limited primary literature on the subject.[33] This chapter will guide clinicians, nurses, pharmacists, and hospital administrators in preparing for and managing pediatric chemical casualties. It will briefly review the general principles of chemical agent exposure, vulnerabilities in children exposed to chemical agents, and the unique challenges encountered while managing pediatric casualties. Specific chemical agents, their effects on children, and management of their toxicities will be discussed, along with special considerations for the decontamination of children and specific strategies that hospitals and healthcare providers can follow to prepare for pediatric chemical casualties.

HISTORY OF CHEMICAL ATTACKS INVOLVING CHILDREN

As the September 11, 2001, attacks made clear, the terrorist threat has moved away from the traditional battlefield, making civilians, including children, prime targets for terrorists attempting to destabilize governments. Although this is a relatively new concern for the US population, other countries have dealt with similar threats for decades. In World War I, German shelling of French and Belgian communities with chemicals often resulted in civilian casualties, and participants saw how ill-prepared the general population was against such weapons. School-age children in the United States were taught protective measures against chemical attacks through drills in which they donned gas masks and evacuated simulated contaminated areas.

Although cyanide was used on concentration camp inmates in World War II, chemical weapons were not used in combat on civilian populations until the Iran-Iraq War. In the spring of 1987 Saddam Hussein bombed Sardasht, a city in Northwestern Iran, with mustard munitions, resulting in thousands of civilian casualties.[12,18] Unlike nerve agents, vesicants like mustard take hours to produce visible signs of toxicity (blisters), and the number of Sardasht victims (many of whom were children) increased in local hospitals over time. Dr Syed Abbas Foroutan, an Iranian physician, provided the first descriptions of chemical agent exposure in children in his published medical notes from the Iran-Iraq War: "children of various ages with swollen eyes moaned as they clinged [*sic*] to their mothers . . . some of the children were comatose."[18(p6)] Thousands of Sardasht residents became chemical casualties and many died, including several pediatric victims who suffered chronic pulmonary sequelae or died in intensive care unit wards days later.[18]

Following the attack on Sardasht, Iraq attacked Kurd settlements in early 1988, leading to the infamous attack on Kurdish residents of Halabja in March.[3,5–8,12,18,19] Thousands of civilian ethnic Kurds perished during the attacks, 75% of whom were women and children. Mustard and nerve agents were dropped on civilians from helicopters and planes, and eyewitnesses reported that large smoke clouds caused morbidity and

mortality among children.[6]

In the 1990s the Japanese Aum Shinrikyo cult manufactured and used nerve agents to target civilians of Matsumoto and Tokyo (see Chapter 4).[24,26–28,32,34] In 1995 the Aum deployed the nerve agent sarin in a Tokyo subway attack, and approximately 5,000 people, ranging from 3 to 86 years old, sought medical attention.[32] Around the same time, the Federal Bureau of Investigation uncovered a terrorist plot to release a chlorine gas bomb at Disneyland.[32] These events confirm that chemical weapons pose a threat to the US pediatric population.

GENERAL PRINCIPLES OF CHEMICAL EXPOSURE

Chemical weapons include nerve agents, vesicating or blistering agents, choking or pulmonary irritants, cyanides, vomiting agents, incapacitating agents, and riot control agents.[35] The most important agents used for terrorism are nerve agents (tabun, sarin, soman, VX), vesicants (mustards, lewisite), pulmonary agents (phosgene, chlorine), and cyanide. Injury from each agent is related to its chemical properties (eg, volatility, persistence), route of entry, and dose.[36] Volatility, or an agent's tendency to vaporize, is affected by temperature, wind, and delivery method. Persistence, or the tendency of a liquid agent to remain in the environment, is affected by temperature and surface texture. The major routes of agent entry are inhalation, cutaneous absorption, ingestion, and injection. Exposure through inhalation, which often occurs with toxic agents like sarin and chlorine, may result in asphyxia, lung damage, and upper airway obstruction. Their higher metabolic and respiratory rates put children at increased risk for toxicity after chemical agent exposure, and their diminutive stature exposes children to toxic agents that concentrate closer to the ground.

The extent of an agent's toxicity is determined by the concentration of the agent in the air and the amount of time a person is exposed. Low doses of agent can cause symptoms such as airway irritation, bronchospasm, and increased secretions, exacerbating underlying lung diseases. High doses can result in airway edema, obstruction, and copious secretions. Direct alveolar damage from pulmonary toxicants, such as chlorine or phosgene, can result in pulmonary edema. When managing affected patients, it is necessary to anticipate the need for emergency intubation; children's smaller airway calibers put them at greater risk for airway obstruction and lead to more rapid progression of narrowing and impending airway obstruction.

Cutaneous exposure affects the eyes and skin, and corrosive chemicals can cause ischemic necrosis that results in small vessel thrombosis, especially in the eyes. Acidic or alkali chemical burns can result in coagulation necrosis or liquefaction. Skin absorption can lead to systemic toxicity, and when skin is damaged, transepidermal water loss is inevitable. This is especially concerning because hypovolemic shock can occur when water loss is excessive. Extensive skin loss, prolonged exposure, and the temperature of the water used for decontamination can rapidly lead to hypothermia in children, whose surface-to-volume ratio is greater than that of adults.

Negative pressure, full-face gas mask use by untrained civilians is not a recommended method of preventing chemical toxicity.[37] Gas masks and respirators increase the work of breathing and physiologic dead space, factors that tend to reduce alveolar ventilation. Also, respirators require a proper fit and filter canister maintenance to adequately protect users, and canister integrity can be altered by handling, water damage, and excessive breathing pressure. In Israel, improper use of gas masks led to 13 suffocation deaths in adults when the filter caps were not removed, and 114 adult deaths from cardiorespiratory arrest when the masks were used in sealed rooms.[37]

In general, managing children exposed to chemical agents may be challenging. For example, it may be difficult to obtain vascular access in children because they have smaller caliber blood vessels than adults. Urinary catherization may also be challenging. Healthcare practitioners should be aware of and appropriately prepare for these issues by maintaining trained staff and a supply inventory that includes a range of equipment sizes; because there is no single pediatric size, a range of appropriate pediatric-sized equipment must be available.

CHALLENGES TO MANAGING PEDIATRIC CHEMICAL CASUALTIES

Managing pediatric victims of chemical terrorism is especially difficult. In addition to the obvious physiological and anatomical differences between children and adults (Table 21-1), there are important psychological and behavioral differences that put children at risk.[33] Anecdotal reports have claimed that children are likely to be the first to manifest symptoms, to develop more severe manifestations, and to be hospitalized for other related illnesses after chemical agent exposure. Children's smaller mass reduces the dose of toxic agent needed

TABLE 21-1

PEDIATRIC VULNERABILITIES AND IMPLICATIONS FOR CLINICAL MANAGEMENT

	Unique Vulnerability in Children	Implications and Impact From Chemical Toxicity
Body composition	• Larger BSA compared to body mass • Lower total lipid/fat content	• Greater dermal absorption • Less partitioning of lipid-soluble components
Volume status	• More prone to dehydration • Chemical agents lead to diarrhea and vomiting	• Can be more symptomatic and show signs of severe dehydration
Respiratory	• Increased basal metabolic rate compared to greater minute volume	• Enhanced toxicity via inhalational route
Blood	• Limited serum protein binding capacity • Greater cutaneous blood flow	• Potential for greater amount of free toxicant and greater distribution • Greater percutaneous absorption
Skin	• Thinner epidermis in preterm infants • Greater cutaneous blood flow	• Increased toxicity from percutaneous absorption of chemical agents
Organ size and enzymatic function	• Larger brain mass • Immature renal function • Immature hepatic enzymes	• Greater CNS exposure • Slower elimination of renally cleared toxins, chemicals, and metabolites • Decreased metabolic clearance by hepatic phase I and II reactions
Anatomical considerations	• Short stature means breathing occurs closer to ground where aerosolized chemical agents settle • Smaller airway • Greater deposition of fine particles in the upper airway • Higher proportion of rapidly growing tissues	• Exposure to chemicals can have significant impact on bone marrow and developing CNS • Increased airway narrowing from chemical-agent–induced secretions • Mustard significantly affects rapidly growing tissues
Central nervous system	• Higher BBB permeability • Rapidly growing CNS	• Increased risk of CNS damage
Miscellaneous	• Immature cognitive function • Unable to flee emergency • Immature coping mechanisms	• Inability to discern threat, follow directions, and protect self • High risk for developing PTSD

BBB: blood-brain barrier
BSA: body surface area
CNS: central nervous system
PTSD: posttraumatic stress disorder

to cause observable or lethal effects. Studies involving organophosphates (OPs), compounds related to nerve agents, have shown greater vulnerability in immature animals than in adults. Some OPs produce the same degree of lethality in juveniles at a fraction of the dose that produces lethality in adults.[33] The increased toxicity seen in children compared to adults from various routes of exposure can be attributed to a wide variety of factors:

- differences in anatomy,
- allometric scaling factors (eg, increased surface area-to-volume ratio),
- cardiovascular status,
- permeability of the pediatric blood-brain barrier,
- dermatologic factors (eg, increased cutaneous blood flow),
- increased skin pH,
- plasma protein binding,
- volume of distribution,
- organ size and maturity, and
- pharmacokinetic maturity (eg, metabolic differences).[38–42]

These unique anatomical and physiological features cause pediatric rates of absorption, distribution, metabolism, and excretion to differ from those of adults.

Respiratory Vulnerability

Children may inhale greater doses of toxic agents than adults, as seen in some studies that demonstrate a 2-fold increase in children's respiratory tract exposure (per unit of surface area) as compared to adults. Children ages 7 to 14 have also been observed to have a higher deposition of fine particles than adults when the data are normalized by lung surface area[43] (younger children show an even greater deposition[44]). Children's higher respiratory rates and minute volumes (per respiratory surface area) means that they will inhale a greater dose of a toxic chemical vapor,[33] and children can easily become intoxicated by breathing air that is closer to the ground because many toxic chemicals display a high vapor density.[45] Additionally, children's respiratory accessory muscles can endure less than adults', putting them at greater risk for respiratory failure.

Children's respiratory systems are especially susceptible to chemical intoxication when compared to adults. Their unique anatomical differences include a greater degree of subglottic narrowing, diminished airway diameter, tendency for nose-breathing, and large tongue size relative to the mouth.[33] OP nerve agents induce bronchospasm and copious glandular secretions during a cholinergic crisis, which would further restrict airflow.

Volume Status Vulnerability

Children's circulatory systems can be severely affected by chemical attacks[33] because they have lower fluid reserves than adults, and small fluid volume losses can cause significant effects. For example, a 5-kg child experiencing severe dehydration (15% body weight loss), loses 750 mL of fluid. The significant loss of fluid from the gastrointestinal tract that results from chemical-induced glandular secretions can affect intravascular volume. Also, children are more prone to vomiting and diarrhea than adults. Overall, children may dehydrate faster during a chemical event.[45]

Neurological Vulnerability

Children's immature central nervous systems (CNSs) can also make them more susceptible to chemical toxicity than adults.[33] Toxic agents can traverse children's immature blood-brain barriers. Infants and children are already at greater risk of seizures than adults, which is concerning because seizures are common in cases of moderate to severe nerve agent intoxication. Infants are at the highest risk from chemical toxicity because of their susceptibility to neurotransmitter system imbalances. Prolonged seizures, or status epilepticus, can cause neuronal injury and deficits in the normal brain development of children.

Dermatologic Vulnerabilities

Barrier thickness, cutaneous blood flow, surface-to-volume ratio, temperature, hydration, and skin pH are important factors to consider when assessing pediatric dermatologic vulnerabilities. Newborns' skin, while appearing vulnerable, has the same histologic features of adult skin, with some differences, including immaturity of collagen, hair follicles, and sebaceous glands. Although newborns and young children are often described as having thinner skin than adults, and even though the stratum corneum, the most superficial layer of the skin, is thinner in premature infants compared to full-term infants, children, or adults,[46–50] children's skin does not differ significantly compared to that of adults when measuring its physiological parameters (eg, transepidermal water loss, skin pH, and stratum corneum capacitance and conductance).[38] Three-month-old children have the same abdominal skin stratum corneum thickness as older children and adults.[42]

However, children have larger surface-area-to-volume (mass) ratios, resulting in greater potential for chemical absorption, and the skin surface area of infants and toddlers is especially large compared to their body weight. A typical infant weighs about one twentieth of a 70-kg adult male, and has a surface area about one eighth as great; therefore the total skin surface area exposed per kilogram of body weight in infants is 2.5 times that of adults.[36] Burns that result in extensive skin loss, as seen with certain chemical exposures, can cause significant water loss and toxicity in children.[36]

Plasma Protein Binding, Volume of Distribution, and Organ Maturity

Children may experience increased effects from chemical toxicity because they have lower levels of plasma proteins. Neonates have a low protein binding capacity for albumin and alpha-1-glycoprotein[51–53] and a decreased ability to conjugate and excrete bilirubin, which binds to plasma proteins. This can lead to a smaller pool of available protein binding sites in plasma.[54] A lower serum protein binding capacity equates to a greater fraction of free chemical available in the circulation and increased toxicity.

The volume of distribution (liters per kilogram of body weight) of chemicals and drugs is also an important factor to consider in pediatric patients. Water-soluble

chemicals may tend to have a larger volume of distribution in newborns and infants because of their relatively large water content. On the other hand, toxic lipophilic agents, such as nerve agents, are decreased in their partitioning to fat because of the lower body lipid content in young children compared to older children and adults.[52,53,55] Lower fat stores may cause lipophilic agents to reach higher concentrations in children's plasma than they would in adults'.

Organ size relative to body weight is another factor affecting the tissue distribution of chemicals in children. Young children's brains are disproportionately large and their blood-brain barriers are relatively permeable, which leads to higher concentrations of some chemicals in the brain.[56] Liver mass relative to body weight is greatest in the early postnatal period, and other tissues (eg, liver, kidney, lung, and brain) undergo rapid growth during the first 2 years of life;[57] these organs are all at increased risk from toxicity because of children's disproportionately larger size relative to body weight.

Renal clearance is particularly diminished in children compared to adults. Glomerular filtration rate and transporter (secretory) systems in the proximal convoluted tubule are decreased at birth.[52,55] In addition, although cardiac output is higher in children than in adults, a lower percentage of the output reaches the kidneys,[54] decreasing renal clearance even further and leading to greater plasma levels of toxic agent. The parental forms of nerve agents and their metabolites undergo hydrolysis with predominantly renal elimination; however, renal clearance is faster in children compared to adults because of allometric scaling differences. According to the rules of allometric scaling, smaller organisms have greater respiratory rates, cardiac output, nutrient and oxygen demands, and basal metabolic rates compared to larger organisms. This appears to be true for children, although faster metabolic rates are not seen in neonates because of hepatic enzyme immaturity and reduced hepatic clearance (which lead to a prolonged toxic agent half-life and duration of action).

Metabolic Vulnerability

Children are unable to detoxify as efficiently as adults because they have less mature metabolic systems.[33] In particular, phase I oxidative systems, phase II conjugating systems, and other systems (eg, serum esterases, hydrolases, dehydrogenases) are all immature in children compared to adults. Neonates and children up to 1 year old are most affected in their maturing enzymatic function, with the greatest effect seen in the first 2 months of life. This leads to slower metabolic clearance of many drugs, toxic chemicals, and activated metabolites.[54] In addition, several authors have reported a reduced activity of acetylcholinesterases (AChEs), pseudocholinesterases, and arylesterases (eg, paraoxonase, the enzyme that detoxifies OP pesticides) in premature and full–term newborns.[55–61] These levels do not reach adult levels until a child is about 1 year old.[62] Newborns possess half the paraoxonase found in an average adult.[33] Other studies suggest that newborns have paraoxonase levels 4-fold lower and activities 3-fold lower than their mothers.[63]

Traumatic Injury Vulnerability

Because chemical agents are often dispersed through explosive devices, trauma and injury frequently accompany chemical attacks.[64] Traumatic injury patterns differ in children compared to adults; because of their smaller size, multiple trauma occurs more frequently in children than in adults after a chemical attack. Children often sustain more head trauma because of their relatively larger head size and weaker supportive musculature, and their more compliant skeletal systems provide less protection to internal organs, leading to greater internal injuries without overlying fractures.

Neurobehavioral Vulnerability

Immature cognitive function can also put children at risk during a chemical attack.[33] Children often lack the ability to discern threat and to protect themselves, and infants, toddlers, and young children do not have the motor skills to flee from incident sites.[32] This can adversely impact their avoidance of a contaminated area and can interrupt decontamination in the event of exposure. During decontamination, healthcare workers and emergency personnel must have a plan for dealing with children who have been separated from their caregivers. Children may need to be guided through the decontamination process.[65]

Psychological Vulnerability

Children have fewer coping skills when sustaining or witnessing injury that can produce short- or long-term psychological trauma, such as parental or sibling death.[66] Children involved in attacks often suffer from posttraumatic stress disorder (PTSD).[32] Adult reactions to a chemical event can also make managing children difficult. Children are often influenced by the emotional states of their caregivers, so providers must try to remain calm. Also, fear or discomfort may cause children to disobey or act out against care providers (Table 21-2).[31]

TABLE 21-2

MARK I* KIT DOSING FOR CHILDREN WITH SEVERE, LIFE-THREATENING NERVE AGENT TOXICITY†

Approximate Age (in years)	Approximate Weight	Number of Kits to Use	Atropine Dosage Range (mg/kg)	Pralidoxime Dosage Range (mg/kg)
3–7	13–25 kg	1	0.08–0.13	24–46
8–14	26–50 kg	2	0.08–0.13	24–46
> 14	> 51 kg	3	0.11 or less	35 or less

*Meridian Medical Technologies Inc, Bristol, Tenn.
†If an adult Mark I kit is the only available source of atropine and pralidoxime, it should not be withheld even from children under 3 years old.
Data source: Columbia University Mailman School of Public Health. Atropine use in children after nerve gas exposure. *Info Brief*. 2004;1(1):1–8.

Decontamination Equipment and Treatment Supplies

Decontamination equipment is another barrier to emergency management because it is not necessarily designed for use on children. High-pressure hoses and cold water used to decontaminate victims can expose children to significant risk,[45] resulting in hypothermia and skin damage. Also, emergency care providers often need to wear bulky, full-protective suits when treating victims, and these suits make it difficult to manage small children requiring intricate procedures, such as blood draws.

In addition to inappropriate decontamination equipment, antidotes for chemical agents are not often available in ready-to-administer pediatric dosages. In the event of a chemical attack, pediatric healthcare centers may be overwhelmed, and the ability to expand the number of pediatric hospital beds may be limited.[32] Additionally, most healthcare workers are not fully aware of the signs and symptoms of chemical agent exposure. This problem is exacerbated because children typically present differently than adults.

For certain toxic agents, such as nerve agents, children present a clinical picture that can be very different than that observed in adults. For example, children in cholinergic crisis may not necessarily manifest with miosis (constriction of pupils).[33] One case series demonstrated the absence of miosis in 43% of pediatric victims. Studies involving pediatric exposure to OPs have suggested the appearance of isolated CNS effects (such as stupor and coma) in the absence of peripheral muscarinic effects. Pediatric victims of OP intoxication display significant muscular weakness and hypotonia in the absence of glandular secretions in 70% to 100% of cases involving moderate to severe levels of exposure.[33] The presentation of central intoxication (weakness and hypotonia) from OPs without peripheral muscarinic signs and symptoms is atypical in adults.

EFFECTS OF SPECIFIC AGENTS ON A PEDIATRIC POPULATION

Nerve Agents

Nerve agent exposure can quickly incapacitate victims and can lead to mortality if not recognized and treated promptly (Exhibit 21-1). Nerve agent toxicity can be enhanced in children because of their unique pediatric vulnerabilities, and it is important to recognize the different ways children may present with toxicity compared to adults.

Nerve agents include tabun, sarin, cyclosarin, soman, and VX. These agents are clear, colorless, tasteless, and in most cases, odorless. They have been demonstrated to penetrate clothing and skin and are highly toxic (as little as 10 mg of VX on the skin is considered to be the median lethal dose in adults).[33] In addition, nerve agents produce toxicity rapidly compared to biological agents. Most G-series nerve agents (sarin, designated "GB" by the North Atlantic Treaty Organization [NATO]; cyclosarin, NATO designation "GF"; tabun, NATO designation "GA"; and soman, NATO designation "GD") are highly volatile and can be dispersed into aerosols and inhaled by victims. Nerve agents may also be disseminated in liquid form. Treatment for dermal exposure begins with rapid topical decontamination.

Although military experience managing nerve agent toxicity is limited, exposures to related chemicals, such as the OP class, occur commonly each year in the United States (in 2000 there were approximately 10,000 OP exposures across the country).[67] OPs, such as malathion, are commonly used as pesticides, and toxicity manifests similarly to nerve agent toxicity,

EXHIBIT 21-1

CASE HISTORY: NERVE AGENT EXPOSURE IN NAZHMAR, IRAN

One victim of the March 22, 1988, attack on the village of Nazhmar was a young child of unreported age and weight. He presented immediately with marked miosis and was comatose. His breathing was irregular and foamy secretions were protruding from his mouth and nose. The patient was working very hard to breathe and was noted to be using his accessory muscles of respiration. Wheezing was obvious on auscultation, and he showed obvious difficulty on exhalation. Upon suction removal of oral and nasal secretions, the patient was noted to have progressively rigid extremities; finding venous access became difficult. His secretions became bloody. Over a 15-minute period, a total of 7.5 mg atropine was administered in three treatments. The patient was noted to improve, opening his eyes, moaning, and using two-word phrases. As his muscle tone decreased, his breathing improved, but wheezing was still evident. The child was decontaminated after treatment and subsequently discharged after an hour. At the time of discharge, his secretions were not completely dried up, but his pupils were fully dilated and reactive to light.

Data source: Foroutan SA. Medical notes concerning chemical warfare, Part IX. *Kowsar Med J*. 1996;3(3):1–16.

though OPs are considerably less toxic. One case series of 16 children who experienced OP poisonings confirmed that pediatric patients present with toxicity differently than adults; they often do not manifest the classic muscarinic effects, such as salivary secretions and diarrhea, seen in adults.[68]

Mechanism of Toxicity

Nerve agents inhibit esterase enzymes, especially AChE,[33] preventing the hydrolysis of acetylcholine. When acetylcholine accumulates in the synaptic space of neurons, muscarinic and nicotinic receptors are over stimulated, resulting in cholinergic crisis. The nerve-agent–AChE bond also undergoes a reaction called "aging,"[69] irreversibly inactivating the enzyme. Prompt therapy is needed to prevent irreversible toxicity.

Clinical Presentation

The signs and symptoms of cholinergic crisis range from lacrimation and urination to seizure activity (Exhibit 21-2).[33] Cholinergic crisis manifests individually depending on the dose, route of exposure, and the duration of exposure. Death from nerve agent exposure is primarily attributed to respiratory failure; nerve agents cause central apnea, flaccid neuromuscular paralysis, bronchoconstriction, and profound glandular secretions.

Children in cholinergic crisis may not exhibit constricted pupils, salivation, diarrhea, or miosis, but may present with isolated CNS effects. Because there is no literature detailing the long-term effects of nerve agent poisoning in children, speculations must be extrapolated from what has been observed in the adult population.[33] Surveillance of victims of the sarin attacks in Japan revealed a wide range of sequelae, such as continued respiratory problems, vision disturbances, headache, and fatigue. Neuropsychiatric problems have also been reported as a delayed effect.

Laboratory Findings

Use of cholinesterase levels to confirm and treat nerve agent toxicity is limited,[33] so casualty treatment should not be delayed for the results of these studies or until cholinesterase levels return to normal. Levels should be used after exposure only to confirm diagnosis (after treatment has begun), to monitor recovery, or for forensic investigation.

EXHIBIT 21-2

MNEMONIC FOR CHOLINERGIC CRISIS

BAG the PUDDLES

- **B**: bronchoconstriction
- **A**: apnea
- **G**: graying/dimming of vision
- **P**: pupillary constriction (miosis)
- **U**: urination
- **D**: diaphoresis
- **D**: defecation
- **L**: lacrimation
- **E**: emesis
- **S**: seizures

Data source: Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics*. 2003;112:648–658.

Pediatric Vulnerability

A child's smaller mass alone reduces the dose of nerve agent needed to cause symptoms or lethality. For volatile nerve agents, children are especially at risk for respiratory effects from toxicity. Their smaller airways can become compromised by copious secretions and by bronchospasm after nerve agent exposure. Also, a greater dose of nerve agent is inhaled by children than adults because of their higher respiratory rates and minute volumes.

Treatment

The overall approach to treating nerve agent exposure focuses on airway and ventilatory support, aggressive use of antidotes (atropine and pralidoxime), prompt control of seizures, and decontamination, as necessary.[70] Atropine is used for its antimuscarinic effects, and oxime is used to reactivate AChE. The combination of atropine and pralidoxime chloride (2-PAM Cl) is recommended for the prompt treatment of all serious cases, and timing atropine and 2-PAM Cl administration is critical; the faster these antidotes are given, the better the outcome. Oxime therapy is rendered ineffective if given after the enzyme aging process has been completed,[69] so autoinjectors have been developed to rapidly administer intramuscular (IM) doses of these medications. However, the US Food and Drug Administration (FDA) has yet to approve a pediatric 2-PAM Cl autoinjector. Other administration routes and methods include intravenous (IV) or intraosseous administration for atropine, and slow IV or continuous infusion for 2-PAM Cl. Data show that plasma concentrations of autoinjector medications peak in less than 5 minutes, as opposed to 25 minutes for IM administration using a needle and syringe.[33] Adult nerve intoxication therapy typically includes the use of an autoinjector set that provides both antidotes, called the Mark I kit (Meridian Medical Technologies Inc, Bristol, Tenn; see Chapter 5, Nerve Agents). The Mark I kit delivers 600 mg of 2-PAM Cl and 2 mg of atropine (via an autoinjector called the AtroPen [Meridian Medical Technologies Inc, Bristol, Tenn]) in seconds. It was originally developed for administration to soldiers. The autoinjector uses a spring-loaded needle to disperse medication in an "all-or-nothing" fashion, so it is impossible to give partial doses of an autoinjector for children, but Mark I kits can be given in their entirety to children beginning at age 3 (see Table 21-2). Drug dosing of atropine and 2-PAM Cl in pediatrics is primarily weight based, so a standard dose cannot be used. Pediatric versions of the Mark I kit are available overseas but are not currently available in the United States.[71] In June 2003 the FDA approved pediatric doses of the AtroPen to respond to the lack of pediatric-specific therapy.[72] The AtroPen is now available in four dosages, 0.25 mg, 0.5 mg, 1 mg, and 2 mg (Figure 21-1). The autoinjector needle length is 0.8 inches, with a gauge of 22. Because the AtroPen delivers only atropine and not 2-PAM Cl, the prompt treatment of pediatric nerve agent casualties remains limited. This has caused groups such as the pediatric expert advisory panel from the National Center for Disaster Preparedness to recommend the adult Mark I kit (which contains atropine and 2-PAM Cl) before use of the pediatric AtroPen alone.[71] Meridian Medical Technologies has recently received FDA approval for a dual-chambered autoinjector called the "ATNAA" (antidote treatment nerve agent autoinjector) for the military, and Duodote (Figure 21-2) for civilian emergency medical technicians and first responders. Each autoinjector contains 2 mg of atropine sulfate and 600 mg of 2-PAM Cl, which are injected sequentially.

In 1992 Amitai et al reviewed 240 instances of accidental pediatric atropine injections using adult-dose–based autoinjectors.[73] The study authors found a low incidence of toxicity and no seizures, arrhythmias,

Fig. 21-1. The AtroPen pediatric autoinjector, manufactured by Meridian Medical Technologies Inc, Bristol, Tenn. Dose sizes range from 0.25 mg for infants to 0.5 mg for children 7–18 kg, 1 mg for children 18–41 kg, and 2 mg for adolescents and adults.
Reproduced with permission from: Meridian Medical Technologies Inc, Bristol, Tenn.

Fig. 21-2. Antidote treatment nerve agent autoinjector (ATNAA) and Duodote.
Reproduced with permission from: Meridian Medical Technologies Inc, Bristol, Tenn.

or death. Subsequently, several pediatric guidelines have suggested that adult-dose atropine and 2-PAM Cl autoinjectors can be safely used in children larger than 13 kg and inserted to 0.8 inches.

Atropine and 2-PAM Cl must be administered cautiously.[33] Atropine can cause increased heart rate and dry mouth and skin, and near vision can be affected for up to 1 day. It can also prevent sweating, so elevated temperatures and heat stress may be observed. 2-PAM Cl can cause double or blurred vision and dizziness, and doses must be reduced with renal insufficiency. Laryngospasm and rigidity can occur if the medication is given too quickly via IV. Higher doses can cause hypertension, while lower doses can cause minor electrocardiogram changes.

Benzodiazepines are not considered antidotes to nerve agent poisoning; however, because status epilepticus often occurs as nerve agent crosses the blood-brain barrier and causes irritation, they are the only agents that have been proven to treat nerve-agent–induced seizures and should be used for both prevention and treatment.[33] Benzodiazepines should be quickly administered if consciousness or more than one organ is impaired or if there is muscle twitching. The US military uses the benzodiazepine diazepam, administered via an autoinjector, to prevent and treat status epilepticus (Figure 21-3). Israel is moving toward using midazolam for its population. Some physicians recommend using lorazepam in the pediatric population. Regardless of which medication is administered, repeated dosing may be needed. Benzodiazepines should be considered for the pediatric population if seizure activity is suspected. However, nonconvulsive status epilepticus and subtle seizures are common in infants and children, making it difficult for healthcare providers to recognize these as signs of nerve agent toxicity.

Each of the medications used to treat nerve agent toxicity recommend weight-based dosing for pediatric patients (Tables 21-3 and 21-4). The exact dosing for a specific patient depends on two factors: the severity of the exposure and the weight or age of the patient.

Fig. 21-3. The diazepam autoinjector.
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TABLE 21-3

MANAGEMENT OF MILD TO MODERATE NERVE AGENT EXPOSURES

		Management			
		Antidotes*		Benzodiazepines (if neurological signs)	
Nerve Agents	Symptoms	Age	Dose	Age	Dose
• Tabun • Sarin • Cyclosarin • Soman • VX	• Localized sweating • Muscle fasciculations • Nausea • Vomiting • Weakness/floppiness • Dyspnea • Constricted pupils and blurred vision • Rhinorrhea • Excessive tears • Excessive salivation • Chest tightness • Stomach cramps • Tachycardia or bradycardia	Neonates and infants up to 6 months old	**Atropine** 0.05 mg/kg IM/IV/IO to max 4 mg or 0.25 mg AtroPen† and **2-PAM** 15 mg/kg IM or IV slowly to max 2 g/hr	Neonates	**Diazepam** 0.1–0.3 mg/kg/dose IV to a max dose of 2 mg, or **Lorazepam** 0.05 mg/kg slow IV
		Young children (6 months old–4 yrs old)	**Atropine** 0.05 mg/kg IM/IV/IO to max 4 mg or 0.5 mg AtroPen and **2-PAM** 25 mg/kg IM or IV slowly to max 2 g/hr	Young children (30 days old–5 yrs old)	**Diazepam** 0.05–0.3 mg/kg IV to a max of 5 mg/dose or **Lorazepam** 0.1 mg/kg slow IV not to exceed 4 mg
		Older children (4–10 yrs old)	**Atropine** 0.05 mg/kg IV/IM/IO to max 4 mg or 1 mg AtroPen and **2-PAM** 25–50 mg/kg IM or IV slowly to max 2 g/hr	Children (≥ 5 yrs old)	**Diazepam** 0.05–0.3 mg/kg IV to a max of 10 mg/dose or **Lorazepam** 0.1 mg/kg slow IV not to exceed 4 mg
		Adolescents (≥ 10 yrs old) and adults	**Atropine** 0.05 mg/kg IV/IM/IO to max 4 mg or 2 mg AtroPen and **2-PAM** 25–50 mg/kg IM or IV slowly to max 2 g/hr	Adolescents and adults	**Diazepam** 5–10 mg up to 30 mg in 8 hr period or **Lorazepam** 0.07 mg/kg slow IV not to exceed 4 mg

2-PAM: 2-pralidoxime
IM: intramuscular
IO: intraosseous
IV: intraveneous
PDH: Pediatrics Dosage Handbook
*In general, pralidoxime should be administered as soon as possible, no longer than 36 hours after the termination of exposure. Pralidoxime can be diluted to 300 mg/mL for ease of intramuscular administration. Maintenance infusion of 2-PAM at 10–20 mg/kg/hr (max 2 g/hr) has been described. Repeat atropine as needed every 5–10 minutes until pulmonary resistance improves, secretions resolve, or dyspnea decreases in a conscious patient. Hypoxia must be corrected as soon as possible.
†Meridian Medical Technologies Inc, Bristol, Tenn.
Data sources: (1) Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics*. 2003;112:648–658. (2) Pralidoxime [package insert]. Bristol, Tenn: Meridian Medical Technologies, Inc; 2002. (3) AtropPen (atropine autoinjector) [package insert]. Bristol, Tenn: Meridian Medical Technologies, Inc; 2004. (4) Henretig FM, Cieslak TJ, Eitzen Jr EM. Medical progress: biological and chemical terrorism. *J Pediatr*. 2002;141(3):311–326. (5) Taketomo CK, Hodding JH, Kraus DM. *American Pharmacists Association: Pediatric Dosage Handbook*. 13th ed. Hudson, Ohio; Lexi-Comp Inc: 2006.

Perioperative Care of Children with Nerve Agent Intoxication

Chemical exposures and trauma often occur simultaneously, and surgical intervention is sometimes required. However, many drugs used for perioperative management can exacerbate the side effects of nerve agent exposure. For example, nerve agents can interact with medications typically used for resuscitative efforts.[74] Anesthetics, such as sodium pentothal and propofol, cause cardiac depression, which is intensified by the excessive muscarinic activity induced by nerve agents. Doses of these drugs may need to be reduced. Volatile anesthetics may be preferable because they

TABLE 21-4

MANAGEMENT OF SEVERE NERVE AGENT EXPOSURE

		Management			
		Antidotes*		Benzodiazepines (if neurological signs)	
Nerve Agents	**Severe Symptoms**	**Age**	**Dose**	**Age**	**Dose**
• Tabun • Sarin • Cyclosarin • Soman • VX	• Convulsions • Loss of consciousness • Apnea • Flaccid paralysis • Cardio-pulmonary arrest • Strange and confused behavior • Severe difficulty breathing • Involuntary urination and defecation	Neonates and infants up to 6 months old	**Atropine** 0.1 mg/kg IM/IV/IO or 3 doses of 0.25mg AtroPen† (administer in rapid succession) and **2-PAM** 25 mg/kg IM or IV slowly, or 1 Mark I† kit (atropine and 2-PAM) if no other options exist	Neonates	**Diazepam** 0.1–0.3 mg/kg/dose IV to a max dose of 2 mg, or **Lorazepam** 0.05 mg/kg slow IV
				Young children (30 days old–5 yrs and adults	**Diazepam** 0.05–0.3 mg/kg IV to a max of 5 mg/dose, or **Lorazepam** 0.1 mg/kg slow IV not to exceed 4 mg
		Young children (6 months old–4 yrs old)	**Atropine** 0.1 mg/kg IV/IM/IO or 3 doses of 0.5mg AtroPen (administer in rapid succession) and **2-PAM** 25–50 mg/kg IM or IV slowly, or 1 Mark I kit (atropine and 2-PAM) if no other options exist	Children (≥ 5 yrs old)	**Diazepam** 0.05-0.3 mg/kg IV to a max of 10 mg/dose, or **Lorazepam** 0.1 mg/kg slow IV not to exceed 4 mg
				Adolescents and adults	**Diazepam** 5–10 mg up to 30 mg in 8-hr period, or **Lorazepam** 0.07 mg/kg slow IV not to exceed 4 mg
		Older children (4–10 yrs old)	**Atropine** 0.1 mg/kg IV/IM/IO or 3 doses of 1mg AtroPen (administer in rapid succession) and **2-PAM** 25–50 mg/kg IM or IV slowly, 1 Mark I kit (atropine and 2-PAM) up to age 7, 2 Mark I kits for ages > 7–10 yrs		
		Adolescents (≥ 10 yrs old) and adults	**Atropine** 6 mg IM or 3 doses of 2 mg AtroPen (administer in rapid succession) and **2-PAM** 1800 mg IV/IM/IO, or 2 Mark I kits (atropine and 2-PAM) up to age 14, 3 Mark I kits for ages ≥ 14 yrs		

IM: intramuscular
IO: intraosseous
IV: intravenous

*In general, pralidoxime should be administered as soon as possible, no longer than 36 hours after the termination of exposure. Pralidoxime can be diluted to 300 mg/mL for ease of intramuscular administration. Maintenance infusion of 2-PAM at 10–20 mg/kg/hr (max 2 g/hr) has been described. Repeat atropine as needed every 5–10 min until pulmonary resistance improves, secretions resolve, or dyspnea decreases in a conscious patient. Hypoxia must be corrected as soon as possible. †Meridian Medical Technologies Inc, Bristol, Tenn.

Data sources: (1) Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics*. 2003;112:648–658. (2) Pralidoxime [package insert]. Bristol, Tenn: Meridian Medical Technologies, Inc; 2002. (3) AtroPen (atropine autoinjector) [package insert]. Bristol, Tenn: Meridian Medical Technologies, Inc; 2004. (4) Henretig FM, Cieslak TJ, Eitzen Jr EM. Medical progress: biological and chemical terrorism. *J Pediatr*. 2002;141(3):311–326. (5) Taketomo CK, Hodding JH, Kraus DM. *American Pharmacists Association: Pediatric Dosage Handbook*. 13th ed. Hudson, Ohio: Lexi-Comp Inc; 2006.

bronchodilate and reduce the need for nondepolarizing drugs, which are often reversed by the use of neostigmine. Halothane should be avoided in infants because the cardiac side effects can be accentuated in the presence of nerve agents. Depression of the cardiovascular system by halothane may cause further bradycardia, hypotension, and reduction in cardiac output. In general, the use of muscle relaxants is not recommended in patients exposed to nerve agents. Nerve agents provide a depolarizing block, and in the presence of inhibited AChE activity, drugs such as succinylcholine can have longer effects than expected.[75]

Analgesia must be used carefully when caring for victims of nerve agent exposure.[74] In general, opioids are considered safe to use because they do not act on the cholinergic system directly. However, some side effects of the drugs, such as histamine release and rare muscle rigidity, can cause difficulty in patient management, making careful dose titration and side-effect monitoring critical. The potent opiod remifentanyl contains an ester linkage susceptible to hydrolysis because it is partially metabolized by plasma cholinesterase. This is the same enzyme that is inactivated by nerve agents, resulting in a prolonged duration of action for remifentanyl. Therefore, using remifentanyl in the postoperative care of nerve-agent–exposed victims is not recommended.[75]

Vesicants

Vesicants, or blister agents, are chemicals that cause blister or vesicle formation upon dermal contact (Exhibits 21-3 and 21-4). Agents such as mustards or lewisite have been used in chemical warfare in the past,[76] and although vesicants are less toxic than nerve agents, they cause prolonged morbidity. There are two types of mustard: sulfur mustard (also known as "HD") and nitrogen mustard (also known as "HN"). Sulfur mustard caused more casualties in World War I than any other chemical weapon. It also caused a significant number of casualties, both civilian and military, during the Iran-Iraq War in the 1980s. Sulfur mustard vapor is the vesicant most likely to be used by terror groups.[76] It affects multiple organ systems including skin, eyes, respiratory and gastrointestinal tracts, and bone marrow.[76] Nitrogen mustards, on the other hand, have never been used on the battlefield, probably because they are harder to make than sulfur mustards; thus, their potential use in a terrorist attack is unlikely.

Lewisite, a vesicant with sulfur-mustard–like properties, causes similar signs and symptoms involving the skin, eyes, and airways, as well as systemic effects (eg, increased capillary permeability) after absorption. However, lewisite does not suppress the immune system like mustard. Lewisite exposure can be treated with an antidote, British Anti-Lewisite. The mechanism of action, clinical effects, and treatment of lewisite injury are not discussed further in this chapter because they are reviewed elsewhere in this textbook (see Chapter 8: Vesicants).

Mechanism of Toxicity

Sulfur mustard rapidly penetrates cells and generates a highly toxic reaction that disrupts cell function and eventually causes cell death.[77] It is classified as an alkylating agent and targets poorly differentiated and rapidly reproducing cells.[76] Death results from massive pulmonary damage complicated by infection (see Chapter 8: Vesicants).

Clinical Presentation

Mustard can cause local effects on skin, airways, and eyes; however, large doses can cause fatal systemic effects.[76] In a study of clinical findings among children exposed to vesicants, the most prevalent signs of toxicity were ocular, cutaneous, and respiratory (Table 21-5).[78] Erythema occurs 4 to 8 hours after exposure, and pruritus can occur with or prior to erythema.[76,78] Over the 24 hours following exposure, large yellowish blisters form in areas of thin skin, such as the groin and underarms.[76] Eye damage can occur, ranging in spectrum from pain and irritation to blindness.[76,77] Mustard also causes clinical effects that can be delayed

EXHIBIT 21-3

CASE HISTORY: MUSTARD GAS EXPOSURE IN 14 CHILDREN AND TEENAGERS FROM HALABJA, IRAQ

Mustard gas was used on the civilian population during the Iraq-Iran War (1980–1988). A case series of 14 children and teenagers affected by mustard gas was reported by Momeni et al. They found that facial involvement was the most frequent disorder (78%), followed by genital (42%), trunkal and axillar lesions (both 14%). The most prominent laboratory abnormality was eosinophilia (12% of patients). Skin lesions appeared 4–18 hours after exposure and erythema developed within 20–30 hours. Blisters appeared after the erythema. The authors concluded that the time of toxicity onset was shorter and more severe in children and teenagers than in adults.

Data source: Momeni A, Aminjavaheri M. Skin manifestations of mustard gas in a group of 14 children and teenagers: a clinical study. *Inter J Dermatol*. 1994:33(3):184–187.

EXHIBIT 21-4

CLINICAL CASES OF MUSTARD EXPOSURE FROM MOFID MEDICAL CENTER FOLLOWING THE HALABJA, IRAQ, ATTACK ON MARCH 17, 1988

A 3-year-old male presented to Mofid Medical Center 8 days after the Halabja chemical attack with fever (39.5°C), tachycardia (HR 140 bpm), and tachypnea (RR 60). Cutaneous skin lesions were mild, but erythema and edema covered 45% of his skin surface area. Laboratory findings were unremarkable except for a mild anemia. Chest roentograms revealed hilar congestion and consolidation bilaterally. The fever continued despite antibiotic therapy. On day 10 of admission (18 days after exposure), the patient developed leukocytosis with 82% PMNs and worsening respiratory distress. The patient died 21 days after exposure.

An 8-year-old Iranian male presented at 5:30 PM with fever (40°C), severe agitation, delirium, and somnolence 24 hours after exposure to chemical agents. His blood pressure was 110/70 mmHg and the patient was notably tachycardic (HR 120 bpm) and tachypneic (RR 42). The patient was noted to have serious dermatologic, ocular, and respiratory impairment. Erythema, vesicles, erosions, bullae, ulcerations, and edema were present on 35% of his body. Ocular manifestations included conjunctivitis and palpebral edema. At that point, the patient was working hard to breathe, as evidenced from accessory muscles of respiration (sternocleidomastoid). On physical examination of the lungs, wheezing and crepitation were noted throughout all lung fields. Laboratory findings were the following:

- Na+: 139,
- K+: 4.1 mEq/L,
- BUN: 25 mg/dL,
- calcium: 7.3 mg/dL, and
- white blood cell count: 9900/mm^3 with 90% neutrophils.

Arterial blood gases were as follows:

- pH: 7.30,
- pCO_2: 31,
- pO_2: 65, and
- HCO_3: 15.1.

Chest roentograms showed bilateral infiltrates. The patient died 24 hours after admission and 48 hours after exposure, despite receiving supportive care.

A 12-year-old female presented 1 day after exposure with fever (40°C), agitation, somnolence and the following vitals:

- BP: 90/40,
- HR: 106 bpm, and
- RR: 36.

Skin erythema, edema, and lesions covered 45% of her body. Upon admission, labs revealed the following:

- Na+: 133,
- K+ 5.8: mEq/L,
- Calcium: 8.3 mg/dL,
- BUN: 51 mg/dL,
- Hematocrit: 50%, and
- white blood cell count: 20,000/mm^3 with 93% neutrophils.

(**Exhibit 21-4** *continues*)

Exhibit 21-4 *continued*

Arterial blood gases were as follows:

- pH: 7.27,
- pCO_2: 14,
- pO_2: 83, and
- HCO_3: 6.3.

Chest X-ray showed bilateral, diffuse infiltrates. Bone marrow hypoplasia developed within a few days. On day 5 of admission, hematocrit dropped to 23%, white blood cell count fell to 2100 mm^3 with 82% neutrophils and 18% lymphocytes, and blood cultures grew coagulase-positive staphylococci. The patient died 7 days after exposure despite antibiotic therapy and supportive treatment.

BP: blood pressure
bpm: beats per minute
BUN: blood urea nitrogen
HR: heart rate
K+: potassium ion
Na+: sodium ion
PMN: polymorphonucleocytes
RR: respiratory rate
Data source: Azizi MD, Amid MH. Clinical presentation of chemical warfare injuries in children and teenagers. *Med J Islamic Rep Iran*. 1990; 4(2):103–108.

for hours,[76–78] so victims may not recognize toxicity until well after exposure. During this time, sulfur works subclinically to damage the skin. Mustard exposure can affect the CNS and bone marrow, as displayed by symptoms of fatigue, headache, and depression.[77] It can also lead to pneumonia, which was the cause of death for many mustard casualties during World War I in the absence of antibiotics.[77] A leukopenic pneumonia can develop between 6 and 10 days after mustard exposure. The manifestation of leukopenia (specifically lymphopenia) results from the myelosuppressive effects of mustard agents.[77]

Laboratory Findings

Although there is no confirmatory diagnostic test for mustard exposure, some laboratory tests can prove useful. Erythrocyte sedimentation rate has been shown to be elevated in pediatric patients after mustard exposure.[79] CBCs (complete blood cell counts) may show abnormalities, depending on the severity of the vapor inhalation or exposure,[76,78] and may show low hematocrit and leukopenia if the exposure was severe. White blood cell count may show only a transient decrease and subsequent recovery.[76,78] In pediatric cases of mustard vapor exposure, decreases in hematocrit or white blood cell count were likely to occur in the first 2 weeks, with the lowest levels of hemoglobin, hematocrit, white blood cells, and neutrophils observed in the samples taken 6 to 10 days after exposure.[78] These pediatric patients also suffered from hypoxemia and renal failure,[78] but serum creatinine and renal function tests were not found in this particular study's charts. Arterial blood gases may provide useful information, but they may show a varied picture. In one pediatric study of mustard casualties, most cases (43%) showed a simple metabolic acidosis.[78] The other groups showed the following:

- mixed metabolic acidosis and respiratory alkalosis (29%),
- simple respiratory alkalosis (14%),
- mixed metabolic and respiratory acidosis (7%), and
- mixed metabolic alkalosis and respiratory acidosis (7%).[78]

Blood urea nitrogen can be elevated in pediatric casualties from severe mustard exposure cases; however, it does not predict mortality. Rather, it is a marker of mustard exposure in children. Increased blood urea nitrogen will normalize in pediatric patients that survive severe mustard exposure. In one case report, elevated blood urea nitrogen levels returned to normal in three, while the other three died.[78]

Pediatric Vulnerability

Sulfur mustard exposure affects children more severely than adults.[76] Because premature infants have thinner skin, and because their dermal-epidermal

TABLE 21-5

PEDIATRIC SIGNS OF MUSTARD EXPOSURE

Ocular	Cutaneous	Respiratory	Other
Conjunctivitis (94%)	Erythema (94%)	Dry cough (81%)	Sore throat
Eye burning	Hyperpigmentation (75%)	Dyspnea (63%)	Sneezing
Palpebral edema (81%)	Ulceration (69%)	Crepitation (50%)	Nasal secretions
Apraxia of eyelid opening (63%)	Erosion (63%)	Wheezing (25%)	Dysphonia
Keratitis (38%)	Blister (56%)	Burning sensation of the upper respiratory tract	
Blepharospasm (25%)	Edema (50%)		
Corneal ulceration (19%)	Vesicles (31%)		
Chemosis (6%)	Hypopigmentation (13%)		
Photophobia	Dermal pain and burning		
Lacrimation			
Ophthalmodynia			
Diplopia			
Itchy eyes			

Data source: Azizi MD, Amid MH. Clinical presentation of chemical warfare injuries in children and teenagers. *Med J Islamic Rep Iran*. 1990;4(2):103–108.

junctions are not fully developed,[46–50] the time between exposure and the onset of blisters is shortened in children, and the number and severity of blisters increases.[76] Ocular symptoms tend to be more pronounced in children because of their inability to protect themselves and their tendency to rub their eyes.[76,78] Children are also more susceptible to pulmonary injury for reasons previously discussed.[76,78] One case report looked at the long-term effects of mustard exposure in a child.[10] The child suffered a severe chemical pneumonia and chronic bronchiolitis. Finally, signs of gastrointestinal toxicity may be greater in children because of fluid loss and lower intravascular volume reserves.[76]

The decision to evacuate and hospitalize adult mustard casualties is based on the extent of exposure (total body surface area affected > 5% requires hospitalization), severity of the skin lesions, and the extent of multiple organ involvement,[80] but the threshold to hospitalize children with mustard injuries should be lower.

Treatment

Decontamination and supportive therapy are the mainstays of treatment for mustard exposure; antidotes do not exist.[76] Adult decontamination may include bleach solutions; however, this method can cause greater toxicity in children, so soap and water are the preferred agents to use for decontaminating children (Table 21-6).[76] Supportive care consists of managing pulmonary and skin manifestations with medications such as cough suppressants and topical silver sulfadiazine.[76–78]

There are currently no standardized guidelines of casualty management nor drugs available to prevent mustard's effects on skin and mucous membranes.[77,80] Treatment includes prompt decontamination, blister aspiration or deroofing (epidermal removal), physical debridement, irrigation, topical antibiotics, and sterile dressing for cutaneous mustard injuries.[77,80] Current treatment strategies rely on symptomatic management to relieve symptoms, prevent infections, and promote healing. The general recommendations for treating mustard casualties are described in Chapter 8 of this textbook, the *Medical Management of Chemical Casualties Handbook*,[81] the *Field Management of Chemical Casualties Handbook*,[82] the *NATO Handbook on the Medical Aspects of NBC Defensive Operations*,[83] and other references.[80] Iranian physicians treating pediatric casualties of mustard vapor during the Iran-Iraq War found that most pediatric casualties presented with multiple organ system involvement (skin, ocular, gastrointestinal, bone marrow, respiratory, etc).[78]

Dermatological Management. The goal of blister management is to keep the patient comfortable and the lesions clean and to prevent infection. Because children are especially anxious at the sight of bullae and erythema, in addition to the burning, pruritus, and allodynia associated with mustard blisters, anxiolytics may be appropriate to calm pediatric casualties and prevent them from picking at bullae.[77] Burning and itching associated with erythema can be relieved by calamine lotion or soothing creams, such as 0.25% camphor, menthol corticosteroids, antipruritics (ie,

diphenhydramine), and silver sulfadiazine cream.[77,78] Pain and discomfort can be relieved with systemic analgesics, such as morphine, which should be given liberally before manipulation of the burned area.[77,78]

Vapor mustard typically causes a first- or second-degree burn, while liquid mustard produces damage similar to a third-degree burn. In any case, tense bullae are the hallmark of mustard injuries. Bullae are typically dome-shaped, thin-walled, 0.5 to 5.0 cm in diameter, superficial, translucent, yellowish, multiloculated, honeycombed,[84] and surrounded by erythema.[77] Preventing children from breaking the blisters can be challenging, especially when constant friction from clothing and blankets are irritating to the skin. Effected areas should be wrapped in protective dressings. According to Graham et al, there is a reservoir of unbound mustard in human skin following a vapor[85] or liquid exposure, leading to an off-gassing period. This period can last for 24 to 36 hours, during which application of an occlusive dressing is not beneficial due to vapor build up.[80]

It is recommended that small blisters (< 1 cm) be left alone on children, but the immediately surrounding area should be cleaned, irrigated daily, and covered with topical antibiotic.[77] Petroleum gauze bandage dressings should be wrapped around unbroken blisters and changed every few days.[77] Larger blisters (> 1 cm) should be unroofed and irrigated several times a day with saline, sterile water, clean soapy water, or Dakin's solution, and covered with topical antibiotic cream or ointment. Blister fluid does not contain mustard[86] and therefore is not hazardous to healthcare workers.[77] Options for topical antibiotic creams in children include silver sulfadiazine and triple combination antibiotic (bacitracin, neomycin sulfate, and polymyxin B sulfate).[77] Topical antibiotics should be applied to the area of bullae and surrounding areas of erythema. There is no information comparing use of triple antibiotic topical ointment in children with use in other age groups.

Mafenide acetate, a sulfonamide used to prevent bacteria and fungal infections in burn victims, is

TABLE 21-6

MANAGEMENT OF VESICANT EXPOSURES

Agent	Symptoms	Antidotes and Treatment
Mustard	• Skin erythema and pruritis • Development of large yellow blisters leading to ulcers • Eye damage • Hoarseness and cough • Mucosal necrosis • Toneless voice • Nausea • Vomiting	**Decontamination:** soap, water, no bleach; copious water irrigation for eyes **Pulmonary management:** cough suppressants, throat lozenges **Skin management:** topical agents used for burns (1% silver sulfadiazine), antibiotics for secondary infections (bacitracin, neomycin, and polymyxin B), antihistamines for itching (diphenhydramine 1 mg/kg/dose orally q6–8h, max 300 mg/day, hydroxyzine 0.5 mg/kg/dose orally q6–8h) **Immune system management**: G-CSF(filgrastim) 5–10 μg/kg/day subcutaneous for neutropenia
Lewisite	• Shock • Pulmonary injury • Blisters	**Decontamination:** soap, water, no bleach **Antidote:** BAL-dimercaprol may decrease systemic effects of lewisite **Pulmonary management:** BAL 3–5 mg/kg deep IM q4h x 4 doses (dose depends on severity of exposure and symptoms) **Skin management:** BAL ointment **Eye management:** BAL ophthalmic ointment

BAL: British Anti-Lewisite
G-CSF: granulocyte-colony stimulating factor
IM: intramuscular
Data sources: (1) Momeni A, Aminjavaheri M. Skin manifestations of mustard gas in a group of 14 children and teenagers: a clinical study. *Inter J Dermatol*. 1994:33(3):184–187. (2) Yu CE, Burklow TR, Madsen JM. Vesicant agents and children. *Pediatric Annals*. 2003;32(4):254–257. (3) Taketomo CK, Hodding JH, Kraus DM. *American Pharmacists Association: Pediatric Dosage Handbook*. 13th ed. Hudson, Ohio: Lexi-Comp Inc; 2006.

recommended for adult use as a 5% mafenide cream[77,80]; however, it is not recommended in premature or newborn infants up to 2 months old because it may lead to liver problems.[87,88] Mafenide acetate caused methemoglobinemia in two 2-year-old children treated with the cream for 50% surface area burns.[87,88] One of the patients died from the exposure to mafenide. Furthermore, a burned 12-year-old patient who was treated with 5% mafenide acetate solution to eradicate pseudomonas aeruginosa growth reportedly developed methemoglobinemia.[89] The patient's methemoglobin level was 34.5% 24 hours after application of 5% mafenide acetate cream. Mafenide may also be unsuitable in pediatrics because it can cause severe pain when applied to partial-thickness wounds and burns,[80] and it is contraindicated for patients with metabolic acidosis. If mafenide is used for pediatric burns, the healthcare provider should be aware of this rare, lethal complication in the pediatric population and should monitor methemoglobin levels concurrently.

While skin healing can take months, pigment changes (hyper- or hypopigmentation) can persist.[77,80] Not all burn injuries require treatment at a burn center, but patients will require aggressive pain management and close observation for the systemic effects of mustard exposure wherever they are treated. Skin grafting, although rare, has been successfully used for deep burns.[90]

Ophthalmology. Ophthalmologic consultation for pediatric mustard injuries will contribute to prevention of ocular scarring and infection.[77] Eyes exposed to mustard should be irrigated to remove traces of vesicant. Severe ocular involvement requires topical antibiotics (tobramycin OD) applied several times a day.[77] Topical steroids may be useful in the first 48 hours after exposure. Temporary vision loss may also occur after mustard exposure[77–79] because of palpebral edema and not corneal damage.[77]

Respiratory System. Pulmonary examination is necessary because the conducting and ventilation portions of the respiratory tract are affected by mustard vapor.[10,77,78] Bronchodilators diminish hyperreactive airways and should be used if a prior history of asthma or hyperreactive airways is documented. Further support with humidified oxygen may be required. Ventilatory support may be required for severe cases of mustard vapor exposure before laryngeal spasm makes intubation difficult. Bronchoscopy is critical for diagnosis, therapeutic dilation for mustard-induced tracheobronchial stenosis, and removal of pseudomembranes that cause airway obstruction.[77]

Antibiotic therapy should not be given during the first 3 to 4 days after mustard exposure because the toxic bronchitis produced by mustard is nonbacterial.[77] Sputum must be continually monitored with Gram's stains and culture growth to identify the specific organism responsible for any late-developing superinfection.[77] Leukopenia in children, a grave sign of mustard exposure, necessitates aggressive support with combination antibiotic treatment.[77]

Gastrointestinal Tract. Atropine or common antiemetics can be given to provide relief from nausea and vomiting, which are early signs of mustard intoxication.[76] The best choices for pediatric-specific antiemetics include medications such as promethazine, metoclopramide, and ondansetron.[77] Persistent vomiting and diarrhea are a later sign of systemic toxicity and require prompt fluid replacement.[76,77]

Bone Marrow Suppression. Mustard, a radiometric, affects rapidly dividing tissues like bone marrow, in addition to the gastrointestinal tract.[77,80] It also destroys hematopoietic precursor cells; white blood cells have the shortest lifespan and decrease in number first, followed by red blood cells and thrombocytes.[77] Resultant bone marrow suppression can be treated with filgrastim injections,[77,80] which stimulate marrow to create and release white blood cells.

Other Treatment Considerations. Fluid status, electrolytes, and urine output should be monitored in mustard-intoxicated patients. Tetanus prophylaxis should also be administered because tetanus may be fatal even after a small partial-thickness burn.[91]

Pulmonary Agents

In January 2002 a Central Intelligence Agency report stated that terrorist groups may have less interest in biological weapons compared to chemicals such as cyanide, chlorine, and phosgene, which can contaminate food and water supplies.[92] Industrial chemicals, such as chlorine and phosgene, have advantages that make them likely candidates to be used by terrorists in the future. Additionally, both are fairly easy to manufacture and handle. In the United States, millions of tons of chlorine and phosgene are produced annually to manufacture various products.[92] A detailed discussion of the general mechanisms of chlorine and phosgene toxicity can be found in Chapter 10, Toxic Inhalational Injury and Toxic Industrial Chemicals.

Clinical Presentation

Pediatric signs and symptoms of chlorine gas exposure include predominantly ocular, nasal, oropharyngeal, and pulmonary membrane irritation.[92] Respiratory complaints are the hallmark of intoxication by these choking agents.[92] Minor chlorine exposure can

lead to burning of the eyes and throat, which is indicative of mucous membrane irritation. More severely exposed patients may complain of cough, choking, sore throat, shortness of breath, chest tightness, difficulty breathing, and other respiratory-related issues.[92] Clinical findings may also include lacrimation, rhinorrhea, laryngeal edema, hoarseness, aphonia, stridor, expiratory wheezing, tracheitis, and cyanosis.[93,94] Tachypnea may develop as a direct result of pulmonary irritation, and tachycardia has been demonstrated in some case reports. [93,94] Many pediatric patients with prior histories of reactive airway disease are at increased risk of chlorine-induced bronchospasm.[92]

Pulse oximetry may indicate low oxygen saturation in patients exposed to pulmonary agents.[94] While arterial blood gases usually indicate hypoxemia, carbon dioxide levels have been shown to be decreased, increased, or normal.[93,94] A hyperchloremic metabolic acidosis may be seen on blood chemistries due to systemic absorption of hydrochloric acid.[94]

Pulmonary edema, the most significant morbidity of pulmonary agents, can be seen on chest roentograms.[92] It may develop as early as 2 to 4 hours after exposure; radiographic evidence typically appears later. Pulmonary edema may produce Kerley B lines on chest X-rays.[92] These lines resemble the rungs of a ladder running perpendicular to the lateral margin of the lungs, beginning at the costophrenic angle. Chest radiographs often show opacities of acute lung injury. Pneumomediastinum has also been reported in chlorine gas exposure.[94]

Pulmonary function tests are not helpful when confirming or treating pulmonary agent exposure.[94,95] A study of school children exposed to a chlorine gas leak reported a predominantly obstructive pattern on pulmonary function tests.[95] This could be explained by the children's smaller airways or congestion and edema narrowing the central airways.

Pediatric Vulnerability

Chlorine is a pungent, green-yellow gas, twice as heavy as air, that settles near the ground.[92–94] This poses a particular problem for children, whose short stature places them closer to the ground. Children are most commonly exposed after inhaling chlorine vapors at swimming pools,[92] encountering household bleach (sodium hypochlorite) mixed with acidic cleaning agents,[94] and experiencing industrial accidents.[95] Phosgene, a dense gas that is also heavier than air, is a more lethal pulmonary agent than chlorine. While the smell of chlorine is associated with swimming pools, phosgene odor is similar to that of freshly mown hay.[92]

Initially, both chlorine and phosgene cause coughing and intense mucosal membrane irritation, typically followed by a feeling of suffocation.[92–94] Morbidity from pulmonary agents is the direct result of pulmonary edema, appearing between 2 and 4 hours after chlorine exposure. Pulmonary edema can cause rapid dehydration or even shock in children because they have a smaller fluid reserve.[92]

Treatment

The first line of treatment for children exposed to pulmonary agents is decontamination. Decontamination can be as simple as removing the victim from the source to fresh air, followed by removing contaminated clothing.[92] Supportive care includes administering humidified air and supplemental oxygen, irrigation with water, and delivering high-flow oxygen via positive pressure for pulmonary edema.[92,94] Further treatment may include surgical debridement and supportive care with medications, such as albuterol for bronchospasm, corticosteroids for inflammation, and antibiotics for secondary bacterial infections (Table 21-7).[92,94] Antidotes or specific postexposure treatments do not exist for this class of agents.

Cyanide

Cyanide is used in processing plastic, electroplating metals, tempering metals, and extracting gold and silver. It is found in fumigants, vehicle exhaust, tobacco smoke, certain fruit pits, and bitter almonds, and is used in photographic development. [96,97] Cyanide is liberated during the combustion or metabolism of natural and synthetic nitrogen-containing polymers.[98] Cyanides can be lethal through inhalation or ingestion,[99] and although cyanide exposure leads to death in minutes, it can be effectively treated with antidotes if diagnosed early.[96,97] Pediatricians, medical first responders, and firefighters need to recognize victims of cyanide poisoning in order to initiate immediate intervention.[96,97] Cyanide is one of the few chemicals for which an effective antidote exists.

Mechanism of Toxicity

The cyanide ion kills mammalian organisms by shutting down oxidative phosphorylation in the mitochondria and, therefore, the utilization of oxygen in cells.[97,98] Cyanide has a propensity to affect certain organs (eg, brain, heart, and lungs) more than others.[96,97] Significant exposure can lead to central respiratory arrest and myocardial depression.[97] Cyanide also acts as a direct neurotoxin, disrupting cell membranes and causing excitatory injury in the CNS.[96–98]

TABLE 21-7

MANAGING PULMONARY AGENT EXPOSURES

Agent	Symptoms	Treatment
Chlorine	• Lacrimation • Rhinorrhea • Conjunctival irritation • Cough • Sore throat • Hoarseness • Laryngeal edema • Dyspnea • Stridor • Acute respiratory distress syndrome • Pulmonary edema	**Decontamination**: copious water irrigation of the skin, eyes, and mucosal membranes to prevent continued irritation and injury **Symptomatic care (no antidote):** warm/moist air, supplemental oxygen, positive pressure oxygen for pulmonary edema **Bronchospasm:** beta-agonists (albuterol) **Severe bronchospasm:** corticosteroids (prednisone; also used for patients with history of asthma but use unproven) **Analgesia and cough:** nebulized lidocaine (4% topical solution) or nebulized sodium bicarbonate (use unproven)
Phosgene	• Transient irritation (eyes, nose, throat, and sinus) • Bronchospasm • Pulmonary edema • Apnea • Hypoxia	**Decontamination:** wash away all residual liquid with copious water, remove clothing **Symptomatic care:** maintain patient's airway, breathing, and circulation, hydrate, positive pressure oxygen for pulmonary edema **Bronchospasm:** beta-agonists (albuterol), corticosteroids INH/IV, Furosemide is contraindicated **Hypoxia:** oxygen

INH/IV: inhaler/intravenous solution
Data source: Burklow TR, Yu CE, Madsen JM. Industrial chemicals: terrorist weapons of opportunity. *Pediatr Ann*. 2003;32(4):230–234.

Clinical Presentation

Cyanide intoxication is an uncommon cause of childhood poisoning;[96] the pediatric population (< 19 years old) represented only 7.8% of cyanide poisonings reported in 2000.[67] Because signs of toxicity are similar to carbon monoxide poisoning (which accounts for the largest group of poisoning deaths among children), clinicians must have a high index of suspicion to make a diagnosis of cyanide poisoning.[98,99] Rotenberg describes a typical toxidrome induced by cyanide, which includes a rapid progression from hyperpnea, anxiety, restlessness, unconsciousness, seizures, apnea, and finally death.[96] Skin, blood, and fundi may be cherry red upon physical examination[96–99] because of the inability of mitochondria to extract oxygen (Exhibit 21-5).

Laboratory Findings

Arterial blood gases can provide clues to verify cyanide exposure. Classic cases present with severe metabolic acidosis, elevated anion gap, and high lactate concentrations.[96] Impaired cellular respiration leads to a high oxygen content in venous blood[96,98]; thus, a reduced arterial-venous oxygen saturation difference suggests cyanide poisoning. Blood cyanide levels are confirmatory but delay the diagnosis, which must be based on the initial clinical presentation.[96–98] An almond-like odor on the breath may indicate that a person has been exposed to cyanide, but up to 40% of the general population is unable to detect this odor.[96]

Pediatric Vulnerability

Children are especially vulnerable to cyanide attacks because of their higher respiratory rates and surface-to-volume ratios.[96] Additionally, cyanide liquid is rapidly absorbed in greater amounts when it comes in contact with children's immature skin barriers.[96] The initial symptoms described in a case report of 10 children who ingested cyanide included abdominal pain, nausea, restlessness, and giddiness.[99] Cyanosis and drowsiness were also noted, but the signature cherry-red skin color was not reported. Postmortem examination of two children that died following exposure showed bright red blood and congested tissues. These children consumed powder packets of potassium cyanide mixed in water, while the other 8 children only licked the powder. The survivors were managed with aggressive supportive care, including gastric lavage, oxygen, and IV fluids.

Treatment

In the United States, the mainstay of treatment for cyanide poisoning consists of supportive treatment and use of a multistage antidote kit that contains

EXHIBIT 21-5

MNEMONIC FOR RECOGNITION OF CYANIDE TOXICITY

FAT RED CATS

- **F**: flushing of skin
- **A**: almonds (bitter almond smell)
- **T**: tachycardia
- **R**: red (red/pink skin, bright red retinal vessels)
- **E**: excitation of nervous system
- **D**: dizziness, death, recent depression history
- **C**: confusion, coma, convulsions
- **A**: acidosis (metabolic or lactic), anion gap
- **T**: tachypnea
- **S**: soot in nose

amyl nitrite, sodium nitrite, and sodium thiosulfate (Table 21-8).[96–98] Antidotes should be provided only for significantly symptomatic patients, such as those with impaired consciousness, seizures, acidosis, hypotension, hyperkalemia, or unstable vital signs.[100] Even when patients are rendered comatose by inhaling hydrogen cyanide gas, antidotes may not be necessary if the exposure is rapidly terminated, the patient has regained consciousness on arrival at the hospital, and there is no acidosis or vital sign abnormality.[101]

Supportive Therapy. Regardless of the antidote, treatment always consists of supportive therapy,[96] which alone may reverse the effects of cyanide even in the face of apnea.[96,97,101] Supportive therapy includes decontamination, oxygen, hydration, and administration of anticonvulsants.[96–98,101] Decontamination measures should take place prior to patient transport to a medical center. First responders and healthcare professionals should take precautions not to intoxicate themselves through direct mouth-to-mouth resuscitative efforts.[98] They must also wear personal protective equipment when transporting the victims to areas with adequate ventilation.[96] Clothes are an obvious source of recontamination and must be removed from the victim. The victim's skin should be flushed with copious volumes of water,[96,97] the temperature of which becomes a consideration for children who may not tolerate extremes of cold or hot. Timely supportive care is important because antidote kits may not be available.

Antidotal Therapy. The US standard cyanide antidote kit uses a small inhaled dose of amyl nitrite followed by IV sodium nitrite and sodium thiosulfate.[96,102] This antidote converts a portion of the hemoglobin

TABLE 21-8

MULTISTAGE ANTIDOTE KIT TREATMENT FOR MANAGING UNCONSCIOUS, CYANIDE-EXPOSED PATIENTS*

Amyl Nitrite Ampules	Sodium Nitrite (for Hb = 12)	Sodium Thiosulfate (for Hb = 12)
For children ≤ 30 kg: • Crush 1 amp in gauze close to the mouth and nose of breathing victim • Inhale fore 15 secs, rest for 15 secs • Replace pearls every 30 secs until sodium nitrite can be administered	For children ≤ 30 kg: • 0.19–0.39 mL/kg not to exceed 10 mL of 3% solution to slow IV over less than 5 mins or slower if hypotension develops • For every 1 g/dL increase or decrease change in Hb, change dose by approximately 0.03 mL/kg accordingly • May repeat dose at half the original dose in 30 min if needed	For children ≤ 30 kg: • 0.95–1.95 mL/kg not to exceed 50 mL of 25% solution IV over 10–20 min • For every increase or decrease change in Hb of 1 g/dL, change sodium thiosulfate by 0.15 mL/kg accordingly • May repeat dose at half original dose in 30 min if needed
For adults: • See above	For adults: • 10 mL of 3% solution slow IV over no less than 5 min or slower if hypotension develops	For adults: • 50 mL of 25% solution IV over 10–20 min

*Other treatments include evacuation, decontamination, administration of 100% oxygen, and correction of acidosis, hypovolemia, and seizures.

Hb: hemoglobin

IV: intravenous

Data sources: (1) Cyanide antidote [package insert]. Buffalo Grove, Ill: Taylor Pharmaceuticals; 1998. (2) Berlin CM. The treatment of cyanide poisoning in children. *Pediatrics*. 1970;46:793–796. (3) Hall AH, Rumack BH. Clinical toxicology of cyanide. *Ann Emerg Med*. 1986;15:1067–1074.

TABLE 21-9

VARIATION OF SODIUM NITRITE AND SODIUM THIOSULFATE DOSE WITH HEMOGLOBIN CONCENTRATION

Hemoglobin (g/dL)	Initial Intravenous Dose of Sodium Nitrite 3% (mL/kg)*	Initial Intravenous Dose of Sodium Thiosulfate 25% (mL/kg)†
7	0.19	0.95
8	0.22	1.10
9	0.25	1.25
10	0.27	1.35
11	0.3	1.50
12	0.33	1.65
13	0.36	1.80
14	0.39	1.95

*Not to exceed 10 mL total dose
†Not to exceed 50 mL total dose
Data sources: (1) Cyanide antidote [package insert]. Buffalo Grove, Ill: Taylor Pharmaceuticals; 1998. (2) Berlin CM. The treatment of cyanide poisoning in children. *Pediatrics*. 1970;46:793–796. (3) Hall AH, Rumack BH. Clinical toxicology of cyanide. *Ann Emerg Med*. 1986;15:1067–1074.

iron from ferrous iron to ferric iron, changing the hemoglobin into methemoglobin.[96,97,102,103] Cyanide is more strongly drawn to methemoglobin than to the cytochrome oxidase of cells, effectively pulling the cyanide off the cells and onto the methemoglobin.[97,103] Once bound with the cyanide, the methemoglobin becomes cyanmethemoglobin.[102] Therapy with nitrites alone is ineffective because methemoglobin cannot transport oxygen in the blood. Adult doses can potentially cause a fatal methemoglobinemia in children[103] or may cause profound hypotension.[96] Treatment for children intoxicated by cyanide must be individualized and is based on the child's body weight and hemoglobin concentration.[96,102,104] An ampule of amyl nitrite should be broken into a handkerchief and the contents should be held in front of the patient's mouth for 15 seconds, followed by 15 seconds of rest.[102] This should be repeated only until sodium nitrite can be administered; continuous use of amyl nitrite may prevent adequate oxygenation.[102] Taylor Pharmaceuticals, the manufacturer of the kit, recommends a sodium nitrite dose of 6 to 8 mL/m^2 (approximately 0.2 mL/kg body weight) for children, not to exceed the adult dose of 10 mL of a 3% solution (approximately 300 mg).[102] While excessive sodium nitrite can cause methemoglobinemia, it should be noted that in the 70-year history of using the kit, the only reported fatality of methemoglobinemia from its use involved a child without serious cyanide poisoning who was given two adult doses of sodium nitrite.[103,104] The scientific literature recommends pediatric dosing based on monitoring hemoglobin levels.[103,104]

The next step in the cyanide antidote kit is to administer sodium thiosulfate intravenously.[96,97,102,104] The sodium thiosulfate and cyanmethemoglobin become thiocyanate and release the hemoglobin, and the thiocyanate is excreted by the kidneys. Hemoglobin levels should be continuously monitored while administering safe doses of sodium nitrite and sodium thiosulfate (Table 21-9).[102–104] If, after inquiring about a patient's medical history, a healthcare provider is concerned about anemia in a patient, doses should be decreased.[96,103,104] Methemoglobin levels must be monitored sequentially in children and should not exceed 20%.[96]

Alternative Strategies. Alternative methods of treating cyanide intoxication are used in other countries. For example, the method in France uses hydroxycobalamin (a form of vitamin B_{12}), which combines with cyanide to form the harmless vitamin B_{12a} cyanocobalamin.[96,97] On December 15, 2006, the FDA approved hydroxocobalamin for use in the United States to treat cyanide-exposed victims in a product called the "Cyanokit" (EMD Pharmaceuticals Inc, Durham, NC; see Chapter 11, Cyanide Poisoning).

DECONTAMINATING CHILDREN

Decontamination after a chemical terrorist attack needs to be well-planned, efficient, and cognizant of children's special needs. Children's unique vulnerabilities may lead to a disproportionate number of pediatric victims after a chemical attack. The potential for a high number of preventable pediatric casualties

increases when a proper decontamination plan is not in place. Pediatricians must be involved in developing hospitals' plans for decontamination. Over the last several years, many advances have been made in managing critically injured children. Studies have shown that children managed in pediatric intensive care units have better outcomes than children managed in adult intensive care units.[65] Despite the lack of a pediatric intensive care unit, hospitals should be prepared to provide initial resuscitation and stabilization for pediatric victims of a terrorist attack. Community hospitals and centers that specialize in pediatric care should create written transfer agreements to allow the rapid transport of critically injured children to the sites that can ensure the best outcomes.

The first step in the decontamination process is to appropriately triage patients.[91] If this step is done quickly and accurately, patients will be appropriately managed and outcomes will improve. The key to triage is the ability to ration care when resources are limited. Victims are usually classified into tiered categories; classic battlefield categories include minimal, delayed, immediate, and expectant. Patients in the minimal category have minor injuries that may not require medical care or that can be managed with self-care; however, self-care may be difficult for children. The delayed category includes patients that have injuries requiring medical intervention, but their injuries are not immediately life threatening. The immediate category describes patients who are critically injured and need medical intervention to save life or limb, and the expectant category includes patients who are so critically injured that they are not expected to survive. The expectant category poses a special challenge to civilian healthcare workers who are used to expending vast resources to maximize survival. In a mass casualty event, this kind of effort may not be realistic. Although the classic categories of triage are fairly well known, they are not consistently used among hospitals. Some categories have been developed to specifically address chemical attacks. For example, at the University of Maryland Medical Center, the biochemical response triage categories differentiate between "exposed" and "not exposed" individuals. Furthermore, because not all exposed individuals will necessarily be symptomatic but may still need to be isolated, the categories are subdivided into those who are asymptomatic, exposed and symptomatic, exposed and asymptomatic, and those with unrelated emergent conditions. Regardless of the categories used, appropriately identifying the causative agent is critical; however, that can be challenging because full identification is often delayed.

The decontamination process should begin after triage.[65] All workers involved in decontamination must be appropriately protected with butyl rubber aprons and gloves, double layers of latex gloves, waterproof aprons, and chemical-resistant jumpsuits. Personal protective equipment should also include an appropriately selected air-purifying or atmosphere-supplying respirator, depending on how the threat environment has been categorized.

The construction and use of the decontamination area must be carefully planned. Often, the area is split into different zones.[105] At a minimum, there must be a dirty, contaminated zone and a clean, decontaminated zone, and traffic must go one way between them. This eliminates the possibility of a clean patient becoming cross-contaminated or an exposed patient entering a healthcare facility before being decontaminated. As patients enter the clean zone, a secondary triage is needed to allow them to receive antidotes or be referred for further care. For severely ill patients, antidote administration may precede decontamination.

It is also important to select the appropriate decontamination agent; plain water is usually the most effective.[105] Other agents that have been used for decontamination include carbonaceous adsorbent powder, dilute (0.5%) hypochlorite solution, water with soap, and dry decontaminants, such as flour or talcum powder. For children, water or water with soap are the preferred decontamination agents; bleach or hypochlorite solutions can irritate or damage children's skin.[105] Water should be at a comfortable temperature because children, especially newborns and infants, are prone to hypothermia and hemodynamic instability from cold water. Blankets can be used to quickly warm pediatric patients after water decontamination. In some situations, indoor sprinkler systems have been used to decontaminate patients when outdoor conditions were unsatisfactory. Patients should also change clothing and shower, and those who have encountered chemicals in the gaseous form should be exposed to fresh air.

Triage clinicians need to understand how chemical toxicities manifest in children and should understand what normal vital signs should be for a child. Pediatric-specific triage tools consider different vital signs, such as heart rate and respiratory rate parameters and the differing ability of patients to communicate. It is important for triage to include an examination of the child's mouth and eyes because of the frequent hand-to-mouth and hand-to-eye activity common in children. If antidote administration is needed, pediatric references should be readily available and medical personnel should understand pediatric dosing. When personnel lack experience with managing children, the otherwise efficient decontamination process can get bogged down. Some hospitals have

set up pediatric-specific areas to address the specific needs of children.

Clinicians may also need to handle uncooperative or nonverbal children. This becomes especially challenging when an IV line needs to be started. Placing a line in a child while in full protective equipment can be difficult, and the unfamiliar presence of a clinician in full personal protective equipment can cause fear and distress in a child. Children undergoing decontamination will benefit from a guardian to guide them through the process and reassure them. For those children who present alone, a guardian should be appointed and a system for parental identification should be in place. Hospitals need to plan for this extra resource; a model may be based on the system developed by an Israeli hospital that employs social workers to manage disaster patient and family needs, including psychological distress.[106] Parents and children should not be separated during a crisis, so plans should be made for the decontamination and treatment of parent-child pairs.[105]

A variety of specially sized equipment, ranging from pediatric-sized emergency equipment to supplies for basic needs (eg, formula and diapers), is needed to appropriately manage children. Because decontamination often includes disrobing, pediatric-sized clothing is needed, and toys are useful to divert children when they need to be observed for long periods of time.

PREPARING FOR A CHEMICAL EVENT

The first step in preparing for a chemical event is understanding the chemical agents used for terrorism and knowing how to manage their toxicity. Preparedness assessments should identify deficits and be used to forge partnerships among community members.[31] For example, after its assessment exercise, the University of Maryland Medical Center decided to partner with the local fire department to coordinate water decontamination outside of the medical center entrance. Planning for an attack begins with developing local health resources because time to borrow resources from nearby communities after an attack is limited. Because most children spend the majority of the day at school, community preparation for a threat should include the local educational system and focus on developing a rapid evacuation plan and in-school shelters.

Healthcare facilities responsible for treating pediatric victims of a chemical or biological event may be easily strained and overwhelmed. Alternative areas, such as auditoriums and arenas, are often needed to triage patients after a large-scale chemical or biological incident, and these areas need to be staffed with personnel who know how to manage pediatric victims.[32] First responders must be able to recognize pediatric signs and symptoms from each chemical agent, correctly don protective gear in the face of persistent agents, handle pediatric patients, and manage field decontamination. Adequate supplies of protective gear must also be available. When planning decontamination procedures, pediatric vulnerabilities and challenges need to be considered.

Another key element to appropriate preparedness is the development of a pharmaceutical cache of antidotes, antibiotics, and vaccines. Although the Strategic National Stockpile is now in place throughout the United States, it may be several hours before supplies can reach hospitals from this cache and be divided among sites. Efforts have been made to include pediatric-ready medications, such as suspensions and solutions, in the Strategic National Stockpile. Local pharmaceutical caches should also try to address pediatric needs (Table 21-10).

Pediatricians are uniquely trained to manage pediatric casualties and to advocate for children so that their needs are addressed in emergency planning.[32,107] Pediatricians can assist in educating first responders so pediatric triage and management is appropriate. Patients and families are also critical advocates for children. Through grass-roots efforts, political interest can be generated to address deficits and encourage collaboration among groups to mobilize important resources. Parents can also prepare for an event by developing a family emergency plan (Exhibit 21-6).

In addition to developing a family emergency plan, parents must recognize that children will be deeply psychologically affected after an attack.[108,109] Terrorism causes strong emotional responses that can easily lead to panic; media coverage of an event is often real-time and frequently graphic, making fear inevitable. Because psychological and emotional impact is the predominant morbidity of an attack, some hospitals have included guidelines for managing serious psychological distress under special disaster preparation plans. Children can be expected to be among both the direct and the secondary psychological victims of a terrorist event. Somatic complaints, such as headaches and abdominal pain, may be common. Pediatric providers can help families address the underlying psychological origin of physical complaints. How children respond to a terrorist event depends on maturity, prior experience, preexisting mental health, and coping skills. Family support and community resources for stress management also play a strong role in helping pediatric victims cope. Children may demonstrate fear, manifesting as

TABLE 21-10

EXAMPLE OF A PEDIATRIC-SPECIFIC HOSPITAL EMERGENCY DRUG CACHE

Drug	Strength	Dosage Form	Pediatric Dosing	Therapy or Prophylaxis	Disease
Albuterol MDI	17gm	INH	2–4 puffs q4h	Respiratory distress from chemical agents	Chemical exposure
Amoxicillin oral suspension	400 mg/5 mL 100 mL	Oral suspension	27 mg/kg q8h–up to 40kg > 40kg 500 mg q8h	Chemoprophylaxis	Anthrax
Atropine	1 mg/mL	Injection	See dosing table	Chemotherapy	Nerve agent exposure
Ciprofloxacin oral suspension	250 mg/5 mL 100 mL	Oral suspension	20–30 mg/kg/ day divided q12h for 60 days	Chemoprophylaxis	Anthrax, plague
Clindamycin	600 mg/NS 50 mL	IV	30 mg/kg/day q8h (max 4.8 g/day)	Chemotherapy	Anthrax
Cyanide antidote package	1 kit	kit	See dosing table	Chemotherapy	Cyanide poisoning
Diazepam IV	5 mg/mL x 2 mL	Injection	See dosing table	Seizures post chemical exposure	Seizures post chemical exposure
Doxycycline oral suspension	25 mg/5 mL 60 mL	Oral suspension	2.5 mg/kg q12h– up to 40 kg, > 40 kg 100 mg q12h for 60 days	Chemoprophylaxis	Anthrax, cholera, brucellosis, plague
Oseltamivir suspension	12 mg/mL 25 mL	Suspension	For children ≥ 1–12 years old: ≤ 15 kg: 2 mg/kg/dose (max 30 mg) BID x 5 days > 15–23kg: 45 mg/dose BID x 5 days > 23–40 kg: 60 mg/dose BID x 5 days > 40 kg 75 mg/dose BID x 5 days	Chemotherapy	Avian influenza
Potassium iodide	65 mg	Tablet	For children 4–18 yrs: 65 mg; For children 1 m–3 yrs: 32.5 mg; For children < 1 mo: 16.25 mg	Chemotherapy	Radiation emergency
Pralidoxime	1 gm/20 mL vial	Powder for injection	See dosing table	Chemotherapy	Nerve agent exposure
Ribavirin solution	40 mg/mL 100 mL	Solution	LD 30 mg/kg followed by 15 mg/kg/day BID x 10 days	Chemotherapy	Viral hemorrhagic fever
Rifampin solution	20 mg/mL 100 mL	Compounded solution	10–20 mg/kg/day q12h (max daily dose 600 mg)	Chemotherapy	Anthrax, brucellosis
Triple antibiotic ointment	0.9 g	Tube	Apply as needed	Chemotherapy	Skin chemical exposure

BID: bis in di´e (twice a day)
INH: inhaler
IV: intravenous solution
LD: loading dose
NS: normal saline

EXHIBIT 21-6

DEVELOPING A FAMILY EMERGENCY PLAN

- Discuss, prepare, and practice for various types of disasters with those who share your residence.
- Formulate a plan to stay in contact if separated (eg, specify at least two meeting places as alternatives to your home and your neighborhood).
- Select an out-of-state contact that all the family members can call to provide location and personal situation information.
- Post emergency numbers at home and also have all the family members carry them when away from home.
- Practice turning off water, power, and gas at home.
- Install and check smoke detectors.
- Obtain battery-operated radios.
- Ready battery-operated flashlights to avoid using matches to see when electricity fails.
- Prepare supply kits with water, food, first aid supplies, tools, clothing, bedding, batteries for radios and flashlights, and other special items, such as medication, baby formula, or diapers. (It may be appropriate to have a kit at home and in automobiles.)

Data source: Bradley BJ, Gresham LS, Sidelinger DE, et al. Pediatric health professionals and public health response. *Pediatric Ann*. 2003;32(2):87–94.

nightmares, insomnia, fear of the dark, or separation anxiety. Under stress, they may regress developmentally and adopt the behaviors of a younger child or sibling. Parents and teachers should be taught that these behaviors may signify children are having difficulty coping. Older children may manifest with depression, pessimism, and substance abuse. Some children may be diagnosed with PTSD. PTSD is diagnosed when a patient demonstrates symptoms of increased arousal, relives the event, and avoids reminders of the event for at least 1 month. Those children directly involved in an attack are at higher risk of developing PTSD.

In responding to an event, it is important to talk to children to help them understand what has occurred and to allow them to express their feelings. Even young children should be kept informed because they can sense that a serious event has occurred and can become concerned when the issue is not explained. It may be helpful to limit children's television viewing and assure them of their safety after a disaster (Exhibit 21-7). Pediatricians and parents play a critical role in identifying coping mechanisms among children and providing the support they need to adjust to the aftermath of a terrorist attack.

EXHIBIT 21-7

STRATEGIES TO HELP CHILDREN COPE WITH TERRORIST EVENTS

- Inform children about a terrorist even as soon as possible.
- Help children understand the event by stating the basic facts in simple, direct, and clear terms.
- Limit television viewing to avoid exposing children to detailed information and graphic images.
- Reassure children they should feel safe in their schools, homes, and communities.
- Reassure children of their complete lack of responsibility.
- Watch for signs of guilt and anger.
- Act as a role model by sharing feelings of fear, sadness, and empathy.
- Offer to discuss terrorist events with older children and adolescents, but do not force conversations.
- Anticipate delayed and anniversary reactions (sadness or fear on the anniversary of a tragic event).
- Provide concrete advice on how to make participation in commemorative events meaningful.

Data source: Schonfeld DJ. Supporting children after terrorist events: potential roles for pediatricians. *Pediatr Ann*. 2003;32(3):182–187.

HELPFUL RESOURCES

Various groups have provided guidance and expertise on managing chemical threats to children. Important contributions have come from the Chemical Warfare Involving Kids (CWiK) Response Project, the Program for Pediatric Preparedness from the National Center for Disaster Preparedness, and the "Children, Terrorism, and Disasters" Web site of the American Academy of Pediatrics. The Duke University Health System has also provided pediatric mass casualty incident guidelines on the Web that include instructions for managing chemical exposures.[110]

The Chemical Warfare Involving Kids Response Project

Doctors Robert Luten and James Broselow developed a system for managing pediatric chemical exposures. The system is called "The Chemical Warfare Involving Kids (CWiK) Response Project" and its purpose is 3-fold:

1. to create resuscitation aids specifically designed to address pediatric medication dosing problems of chemical terrorism,
2. to provide a focused review of clinically significant pediatric issues in victim treatment, and
3. to disseminate these tools to help prepare to care for children.

The project aims to distribute information about pediatric vulnerabilities and antidote preparation and administration. In addition, an "antidote for chemical warfare" card was developed as a quick reference for providers managing pediatric chemical casualties. These cards are intended to be used during a chemical event and provide precalculated medication doses. Separate from this initiative, pediatric-specific dosing cards have been developed that provide medication dose ranges for each chemical agent.

Broselow-Luten System: a Systematic Approach with Color Coding

A major difficulty of managing disasters is that they may occur in areas that have limited pediatric resources. Even in areas with optimal resources for everyday practice, an acute presentation of multiple victims with a disproportionate number of affected children may be overwhelming. Healthcare providers trained to treat adults may suddenly be confronted with large numbers of acutely ill or injured children, as has been seen in areas like Afghanistan and Iraq. One solution that has been proposed is the Broselow-Luten system, which uses color-coded therapeutic pathways; children are entered into a color category according to weight (or length, measured by Broselow tape, when weight cannot be obtained). The color categories provide information on standardized therapeutic pathways and display doses of medications in milligrams and their volumetric equivalents. In addition to chemical weapons antidotes, this approach encompasses the entire spectrum of acute pediatric care (eg, fluid resuscitation, dehydration and electrolyte problems, pain management, antibiotics, equipment selection, burns), which may be a part of the care of pediatric disaster victims.

Meeting the Generic Needs of Children in a Disaster Situation

According to a recent review of the pediatric resuscitation process, an increase in logistical time is inherent in treating pediatric emergencies as opposed to adult emergencies.[111] One of the reasons for this increase is the age- and size-related variations unique to children, which introduce the need for more complex, nonautomatic or "knowledge-based" mental activities, such as calculating drug doses and selecting equipment. These detract from other important mental activities such as assessment, evaluation, prioritization, and synthesis of information, which can be referred to in the resuscitative process as "critical thinking activity." These logistical difficulties lead to inevitable time delays and a corresponding increase in the potential for decision-making errors in the pediatric resuscitative process. This is in sharp contrast to adult resuscitation. Medications used frequently in adults, such as epinephrine, atropine, glucose, bicarbonate, and lidocaine, are packaged in prefilled syringes containing the exact adult dose, making their ordering and administration automatic. The same concept is seen in equipment selection when the necessary equipment is laid out for immediate access and use. The adult provider does not need to recall formulas and calculations. The use of appropriate aids in pediatric resuscitation (those that contain precalculated doses, drug volumes, and other size-related variables) significantly reduces the cognitive load otherwise caused by obligatory calculations of dosage and equipment selection, and relegates these activities to a lower order of mental function referred to as automatic or "rule-based," increasing critical thinking time. The Broselow-Luten system has been commercially available for over 10 years and is

stocked in several emergency departments across the country.[112] It has become the "standard of care" in the United States and abroad. This system is recommended in textbooks such as *Emergency Medicine* and *Pediatric Emergency Medicine* and by the American Heart Association's Pediatric Advanced Life Support Course.[113] It has been validated in several studies that have proven that the weights estimated from the measuring tape correlate with the actual weight of children up to 25 kg, and the system improves the ability to estimate a pediatric patient's weight over visual inspection or age-based equations.[114,115] Being able to obtain an accurate weight is critical to appropriately calculating medication doses. The system's color-coded chart has also been shown to improve the ability to select the right size intubation supplies and nasogastric tubes and to reduce the time to make those selections.[116] It reduces error, facilitates task completion, and saves time and resources (Figure 21-4).[111] The tools of the Broselow-Luten system, based on core concepts such as color-coding, arm bands, and chart stickers, are demonstrated visually in the chemical warfare antidote drug card for pediatric dosing of atropine (Figure 21-5). The system is being implemented in Afghanistan and Iraq to evaluate its effectiveness in a forward situation.

Meeting the Specific Needs of Children in a Chemical Disaster

Depending on the level of care, a provider may be involved in the ordering phase (physicians), the preparation and administration phase (nurses), or in both (prehospital personnel). With this in mind, tools need to be developed that are appropriate for both phases.

Drug cards and posters that contain color-coded, precalculated doses of antidotes to chemical agents and summary information on the particular needs of exposed children often give doses and drug volumes for IV, intraosseous, and IM drug administration (see Figure 21-4). Although 2-PAM Cl is recommended for both IV and IM use, the package insert only gives reconstitution directions for IV use. The insert recommends dilution of the 1 gm vial with 20 mL of sterile water to obtain a concentration of 50 mg/mL for injection.[117] No mention is made of a more concentrated dilution for IM use. However, sources have recommended 2-PAM Cl doses for both the IV and IM routes[33] because it is highly water-soluble.[118] Sidell described the preparation of a 30% solution of 2-PAM Cl for IM use,[119] implying that a dilution of 1 gm in 3 mL water (300 mg/mL) is a reasonable method of preparing 2-PAM Cl for IM delivery. This is critical information for safe administration to pediatric patients in which fluid overload could lead to toxicity.

The other route for administration is via autoinjector. Two options have recently been recommended for the use of adult autoinjectors in children. They do not address the potential morbidity from the injector needle, which is unknown, so the recommendations are based on theoretical assumptions and therefore lack supporting clinical data. Option 1 is based on the milligram-per-kilogram dose of atropine and 2-PAM Cl

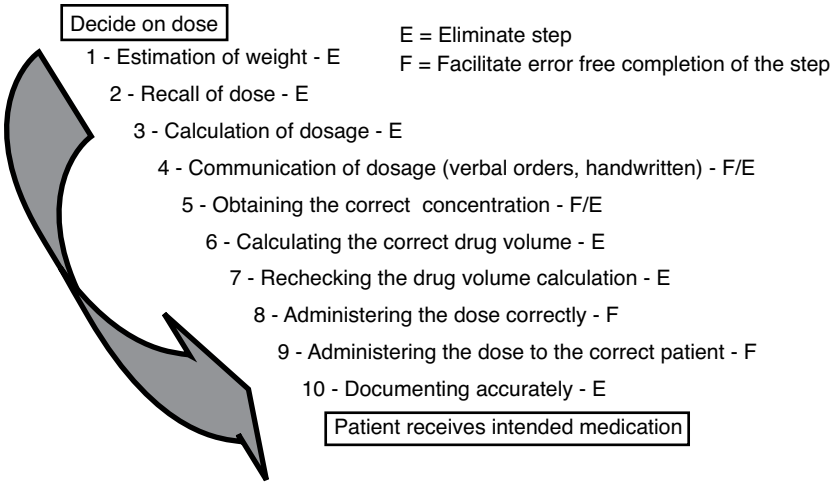
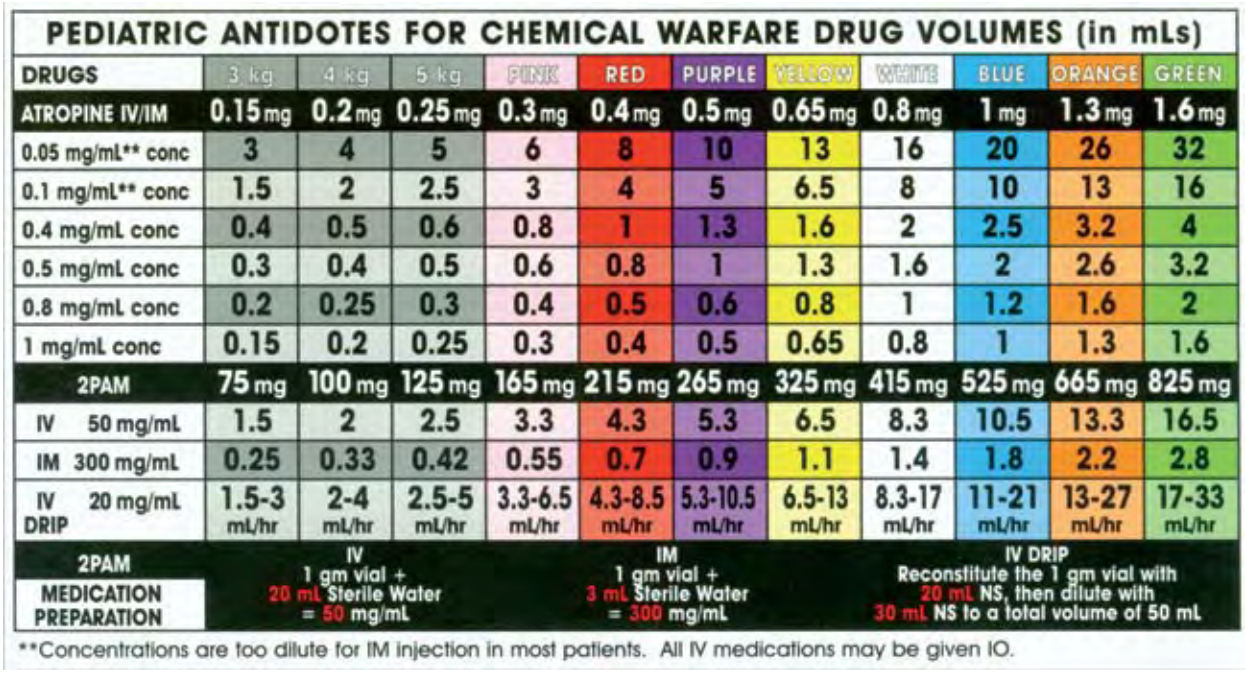


Fig. 21-4. Steps involved in administering a dose of medication. Using the Broselow-Luten color-coded standard dosing system can eliminate problematic areas such as calculations, and, if not totally eliminate, at least facilitate the error-free completion of other steps.



PEDIATRIC ANTIDOTES FOR CHEMICAL WARFARE DRUG VOLUMES (in mLs)

DRUGS	3 kg	4 kg	5 kg	PINK	RED	PURPLE	YELLOW	WHITE	BLUE	ORANGE	GREEN
ATROPINE IV/IM	0.15 mg	0.2 mg	0.25 mg	0.3 mg	0.4 mg	0.5 mg	0.65 mg	0.8 mg	1 mg	1.3 mg	1.6 mg
0.05 mg/mL** conc	3	4	5	6	8	10	13	16	20	26	32
0.1 mg/mL** conc	1.5	2	2.5	3	4	5	6.5	8	10	13	16
0.4 mg/mL conc	0.4	0.5	0.6	0.8	1	1.3	1.6	2	2.5	3.2	4
0.5 mg/mL conc	0.3	0.4	0.5	0.6	0.8	1	1.3	1.6	2	2.6	3.2
0.8 mg/mL conc	0.2	0.25	0.3	0.4	0.5	0.6	0.8	1	1.2	1.6	2
1 mg/mL conc	0.15	0.2	0.25	0.3	0.4	0.5	0.65	0.8	1	1.3	1.6
2PAM	75 mg	100 mg	125 mg	165 mg	215 mg	265 mg	325 mg	415 mg	525 mg	665 mg	825 mg
IV 50 mg/mL	1.5	2	2.5	3.3	4.3	5.3	6.5	8.3	10.5	13.3	16.5
IM 300 mg/mL	0.25	0.33	0.42	0.55	0.7	0.9	1.1	1.4	1.8	2.2	2.8
IV DRIP 20 mg/mL	1.5-3 mL/hr	2-4 mL/hr	2.5-5 mL/hr	3.3-6.5 mL/hr	4.3-8.5 mL/hr	5.3-10.5 mL/hr	6.5-13 mL/hr	8.3-17 mL/hr	11-21 mL/hr	13-27 mL/hr	17-33 mL/hr
2PAM MEDICATION PREPARATION	IV: 1 gm vial + 20 mL Sterile Water = 50 mg/mL				IM: 1 gm vial + 3 mL Sterile Water = 300 mg/mL				IV DRIP: Reconstitute the 1 gm vial with 20 mL NS, then dilute with 30 mL NS to a total volume of 50 mL		

**Concentrations are too dilute for IM injection in most patients. All IV medications may be given IO.

Fig. 21-5. Antidote drug card for pediatric dosing of atropine; close-up of drug chart component.

as a result of a single Mark I injection (2 mg atropine, and 600 mg 2-PAM Cl), which has been extrapolated to the weight zones of the color-coded system,[70] suggesting that children in the yellow zone (3 years old) or higher may receive one Mark I autoinjector.[70,71] Option 2 is based on the comparison of the total milligram-per-kilogram dose an adult would normally receive over 60 to 90 minutes versus the milligram-per-kilogram amount that would be received with a single Mark I injection, even in a smaller child.[71] This suggests that in the absence of another option, one Mark I may be given to any child in extremis, regardless of size. Baum, Henretig, and Wiley are developing a comprehensive color-coded toolkit for the management of both biological and chemical agents in children based on these philosophies.

Other Pediatric Resources

Another group instrumental in providing guidance on terrorism in children is the Program for Pediatric Preparedness of the National Center for Disaster Preparedness at Columbia University. This group was established to determine appropriate management and intervention for children in all types of disasters, including chemical emergencies. The program has five main goals:

1. to assess pediatric preparedness at the community, facility, local, regional, and national levels;
2. to conduct and foster research on pediatric disaster, terrorism, and public health emergency preparedness and response;
3. to provide resources to children, parents, communities, and governmental and nongovernmental agencies on pediatric preparedness;
4. to build collaboration among disciplines and occupations that must work together to care for children during an emergency; and
5. to advocate for children in all forums related to preparedness.

To achieve these goals, the group produces a quarterly newsletter on pediatric issues and preparedness, distributes informational bulletins on pediatric issues, has developed an expert advisory board to help guide development of preparedness tools, and has created a Web site to share its resources. The group also initiated a pediatric preparedness national consensus conference. The first conference was held in Washington, DC, in February 2003, and led to recommendations and treatment guidelines.[120]

The American Academy of Pediatrics also continually provides updated and valuable resources regarding children, terrorism, and disaster planning. It provides an updated bibliography of literature related to chemi-

cal casualty management in pediatrics.

The Regional Emergency Medical Advisory Committee of New York City, the City of New York Fire Department, and the City of New York Bureau of Emergency Medical Services, in collaboration with the Center for Pediatric Emergency Medicine of the New York University School of Medicine and the Bellevue Hospital Center, have developed and published a pediatric nerve agent antidote dosing schedule.[121] Dosing cards for the treatment of children exposed to weapons of mass destruction have been developed by US Public Health Service pharmacist officers.[122]

SUMMARY

Much progress has been made in understanding how to manage pediatric patients affected by chemical agents. Several pediatric organizations, such as the American Academy of Pediatrics, have offered guidance on handling these situations. Gathering information about pediatric chemical casualties is challenging because experience is limited; further research and resources are needed to fully understand all the physical and psychological impacts a terror attack has on children. In a chemical attack, prior preparation and planning will make a difference in whether lives are saved or lost. Efforts must be made to learn how to best manage chemical attacks and how to best prepare to protect the pediatric population.

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REFERENCES

1. United Nations Security Council. *Report of the Specialists Appointed by the Secretary-General to Investigate Allegations by the Islamic Republic of Iran Concerning the Use of Chemical Weapons*. UN Security Council: New York, NY; 1984. Report S/16433.

2. United Nations Security Council. *Report of the Mission Dispatched by the Secretary-General to Investigate Allegations of the Use of Chemical Weapons in the Conflict Between the Islamic Republic of Iran and Iraq*. UN Security Council: New York, NY; 1986. Report S/17911.

3. Hu H, Cook-Deegan R, Shukri A. The use of chemical weapons: conducting an investigation using survey epidemiology. *JAMA*. 1989;262(5):640–643.

4. Hay A, Roberts G. The use of poison gas against the Iraqi Kurds: analysis of bomb fragments, soil, and wool samples. *JAMA*. 1990;263(8):1065–1066.

5. Kelly L, Dewar D, Curry B. Experiencing chemical warfare: two physicians tell their story of Halabja in Northern Iraq. *Can J Rural Med*. 2004;9(3):178–181.

6. Goldberg J. The great terror. *New Yorker*. March 25, 2002: 52–75.

7. O'Leary CA. The Kurds of Iraq: recent history, future prospects. *Middle East Rev Int Affairs J*. 2002;6(4):17–29.

8. Mohamed-Ali H. Late lesions due to poison gas in survivors of the Iraqi poison warfare against the Kurdish people. *Wien Med Wochenschr*. 1992;142(1):8–15.

9. Gosden C, Amitay M, Gardener D, Amin B. Examining long-term severe health consequences of CBW use against civilian populations. *Bull UN Institute Disarm Res (UNIDIR)*. 1999;Disarmament Forum Three.

10. Dompeling E, Jobsis Q, Vandevijver NMA, et al. Chronic bronchiolitis in a 5-yr-old child after exposure to sulfur mustard gas. *Eur Respir J*. 2004;23:343–346.

11. Momeni A, Aminjavaheri M. Skin manifestations of mustard gas in a group of 14 children and teenagers: a clinical study. *Inter J Dermatol*. 1994:33(3):184–187.

12. Foroutan SA. Medical notes concerning chemical warfare, Part I. *Kowsar Med J*. 1996; 1(1):1–8.

13. Foroutan SA. Medical notes concerning chemical warfare, Part II. *Kowsar Med J*. 1996; (2):1–23.

14. Foroutan SA. Medical notes concerning chemical warfare, Part III. *Kowsar Med J*. 1997;2(1):1–15.

15. Foroutan SA. Medical notes concerning chemical warfare, Part IV. *Kowsar Med J*. 1997;2(2):1–15.

16. Foroutan SA. Medical notes concerning chemical warfare, Part V. *Kowsar Med J*. 1997;2(3):1–9.

17. Foroutan SA. Medical notes concerning chemical warfare, Part VI. *Kowsar Med J*. 1998;2(4):1–18.

18. Foroutan SA. Medical notes concerning chemical warfare, Part VII. *Kowsar Med J*. 1998;3(1):1–10.

19. Foroutan SA. Medical notes concerning chemical warfare, Part IX. *Kowsar Med J*. 1996;3(3):1–16.

20. Foroutan SA. Medical notes concerning chemical warfare, Part X. *Kowsar Med J*. 1999;3(4):1–12.

21. Foroutan SA. Medical notes concerning chemical warfare, Part XI. *Kowsar Med J*. 1999;4(1):1–7.

22. Vogel FJ. *The Chemical Weapons Convention: Strategic Implications for the United States*. Monograph. The Strategic Studies Institute at the US Army War College: Carlisle, Penn; 1997.

23. Sidell FR. Chemical agent terrorism. *Ann Emerg Med*. 1996;28(2):223–224.

24. Nagao M, Takatori T, Matsuda Y, Nakajima M, Iwase H, Iwadate K. Definitive evidence for the acute sarin poisoning diagnosis in the Tokyo subway. *Toxic Appl Pharm*. 1997;144:198–203.

25. Tsuchihashi H, Katagi M, Nishikawa M, Tatsuno M. Identification of metabolites of nerve agent VX in serum collected from a victim. *J Anal Toxicol*. 1998;22(5):383–388.

26. Matsuda Y, Nagao M, Takatori T, Niijima H, Nakajima M, Iwase H, et al. Detection of the sarin hydrolysis product in formalin-fixed brain tissues of victims of the Tokyo subway terrorist attack. *Toxicol Appl Pharm*. 1998;150:310–320.

27. Solberg Y, Nachtomi-Shick O, Shemer Y, Alcalay M. Terror in Japan: mass-intoxication with the nerve-agent sarin. *Harefuah*. 1998;135(7–8):268–271.

28. Okudera H. Clinical features on nerve gas terrorism in Matsumoto. *J Clin Neurosci*. 2002;9(1):17–21.

29. Yanagisawa N, Morita H, Nakajima T. Sarin experiences in Japan: acute toxicity and long-term effects. *J Neurol Sci*. 2006;249:76–85.

30. Blaschke GS, Lynch J. Terrorism: its impact on primary pediatrics, Part I. *Pediatr Ann*. 2003;32(2):80–84.

31. Blaschke GS, Palfrey JS, Lynch J. Advocating for children during uncertain times. *Pediatr Ann*. 2003;32(4):271–274.

32. Committee on Environmental Health and Committee on Infectious Diseases. Chemical-biological terrorism and its impact on children: a subject review. *Pediatrics*. 2000;105:662–670.

33. Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics*. 2003;112:648–658.

34. Brackett DW. *Holy Terror Armageddon in Tokyo*. New York, NY: Weatherhill, Inc; 1996.

35. Sidell FR, Takafuji ET, Franz DR, eds. *Medical Aspects of Chemical and Biological Warfare*. In: Zajtchuk R, Bellamy RF, eds. *Textbooks of Military Medicine*. Washington, DC: Department of the Army, Office of the Surgeon General, Borden Institute; 1997.

36. Lynch EL, Thomas TL. Pediatric considerations in chemical exposures: are we prepared? *Pediatr Emerg Care*. 2004;20(3):198–205.

37. Abramowicz M, ed. Prevention and treatment of injury from chemical warfare agents. *Med Letter*. 2002;44:1–4.

38. Fluhr JW, Pfisterer S, Gloor M. Direct comparison of skin physiology in children and adults with bioengineering methods. *Pediatr Dermatol*. 2000;17(6):436–439.

39. Simonen P, O'Brien M, Hamilton C, Ashcroft J, Denham J. Normal variation in cutaneous blood content and red blood cell velocity in humans. *Physiol Meas*. 1997;18(3):155–170.

40. Fluhr JW, Behne MJ, Brown BE, Moskowitz DG, Selden C, Mao-Wiang M, et al. Stratum corneum acidification in neonatal skin: secretory phospholipase A2 and the sodium/hydrogen antiporter-1 acidify neonatal rat stratum corneum. *J Invest Dermatol*. 2004;122(2):320–329.

41. Behrendt H, Green M. Skin pH pattern in the newborn infant. *AMA J Dis Child*. 1958;95(1):35–41.

42. Fairley JA, Rasmussen JE. Comparison of stratum corneum thickness in children and adults. *J Am Acad Dermatol*. 1983;8(5):652–654.

43. Bennett WD, Zeman KL. Deposition of fine particles in children spontaneously breathing at rest. *Inhalation Toxicol*. 1998;10:831–842.

44. Martonen TB, Musante CJ, Sega RA, et al. Lung models: strengths and weaknesses. *Respir Care*. 2000;45(6):712–736.

45. Children more vulnerable than adults in the event of a chemical spill or chemical weapons attack. *Cedars-Sinai Medical Center News*. July 14, 2003.

46. Rutter N, Hull D. Water loss from the skin of term and preterm babies. *Arch Dis Child*. 1979;54:858–868.

47. Harpin VA, Rutter N. Barrier properties of the newborn infants' skin. *J Pediatr*. 1983;102:419–425.

48. Nopper AJ, Horii KA, Sookdeo-Drost S, Wang TH, Mancini AJ, Lane AT. Topical ointment therapy benefits premature infants. *J Pediatr*. 1996;128(5):660–669.

49. Seidenari S, Giusti G, Bertoni L, Magnoni C, Pellacani G. Thickness and echogenicity of the skin in children as assessed by 20-MHz ultrasound. *Dermatology*. 2000;201(3):218–222.

50. Mancini AJ. Skin. *Pediatrics*. 2004;113(4 Suppl):114–1119.

51. Besunder JB, Reed MD, Blumer JL. Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic-pharmacodynamic interface. Part I. *Clin Pharmacokinet*. 1988;14(5):261–286.

52. Kearns GL, Reed MD. Clinical pharmacokinetics in infants and children. A reappraisal. *Clin Pharmacokinet*. 1989;17(Suppl 1):29–67.

53. Clewell HJ, Teeguarden J, McDonald T, et al. Review and evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. *Crit Rev Toxicol*. 2002;32(5):329–389.

54. Ginsberg G, Hattis D, Sonawane B. Incorporating pharmacokinetic differences between children and adults in assessing children's risks to environmental toxicants. *Toxicol Appl Pharmacol*. 2004;198(2):164–183.

55. Morselli PL. Clinical pharmacology of the perinatal period and early infancy. *Clin Pharmacokinet*. 1989;17(Suppl 1):13–28.

56. Saunders NR, Knott GW, Dziegielewska KM. Barriers in the immature brain. *Cell Mol Neurobiol*. 2000;20(1):29–40.

57. National Research Council Committee on Pesticides in the Diets of Infants and Children. *Pesticides in the diets of infants and children*. Washington, DC: National Academy Press; 1993.

58. Stead AL. The response of the newborn infant to muscle relaxant. *Br J Anaesth*. 1955;27(3):124–130.

59. Lehmann H, Cook J, Ryan E. Pseudocholinesterase in early infancy. *Proc R Soc Med*. 1957;50(3):147–150.

60. Augustinsson KB, Brody S. Plasma arylesterase activity in adults and newborn infants. *Clin Chim Acta*. 1962;7:560–565.

61. Ecobichon DJ, Stephens DS. Perinatal development of human blood esterases. *Clin Pharmacol Ther*. 1973;14(1):41–47.

62. Morselli PL. Clinical pharmacokinetics in neonates. *Clin Pharmacokinet*. 1976;1(2):81–98.

63. Holland N, Furlong C, Bastaki M, et al. Paraxonase polymorphisms, haplotypes, and enzyme activity in Latino mothers and newborns. *Environ Health Perspect*. 2006;114(7):985–991.

64. Abraham RB, Rudick V, Weinbroum AA. Practical guidelines for acute care of victims of bioterrorism: conventional injuries and concomitant nerve agent intoxication. *Anesthesiology*. 2002;97(4): 989–1004.

65. Wheeler DS, Poss WB. Mass casualty management in a changing world. *Pediatr Ann*. 2003;32(2):98–105.

66. Henretig FM, Cieslak TJ, Eitzen Jr EM. Medical progress: biological and chemical terrorism erratum. *J Pediatr*. 2002;141(5):743–746.

67. Litovitz TL, Klein-Schwartz W, White S, et al. 2000 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Amer J Emerg Med*. 2001;19(5):337–395.

68. Lifshitz M, Shahak E, Sofer S. Carbamate and organophosphate poisonings in young children. *Pediatr Emerg Care*. 1999;15(2):102–103.

69. Dunn MA, Sidell FR. Progress in medical defense against nerve agents. *JAMA*. 1989;262(5):649–652.

70. Henretig F, Cieslak TJ, Eitzen EM. Medical progress: biological and chemical terrorism. *J Pediatr*. 2002;141(3):311–326.

71. Columbia University Mailman School of Public Health. Atropine use in children after nerve gas exposure. *Info Brief*. 2004;1(1):1–8.

72. Meadows M. The FDA and the fight against terrorism. *FDA Consum*. 2004;38(1):20–27.

73. Amitai Y, Almog S, Singer R, Hammer R, Bentur Y, Danon YL. Atropine poisoning in children during the Persian Gulf crisis: a national survey in Israel. *JAMA*. 1992;268:630–632.

74. Abraham RB, Weinbroum AA, Rudick V, Paret G. Perioperative care of children with nerve agent intoxication. *Paediatr Anaesthesia*. 2001;11:643–649.

75. Rotenberg JS. Diagnosis and management of nerve agent exposure. *Pediatr Ann*. 2003;32(4):242–250.

76. Yu CE, Burklow TR, Madsen JM. Vesicant agents and children. *Pediatr Ann*. 2003;32(4):254–257.

77. Sidell FR, Urbanetti JS, Smith WJ, Hurst CG. Vesicants. In: Sidell FR, Takafuji ET, Franz DR, eds. *Medical Aspects of Chemical and Biological Warfare*. In: Zajtchuk R, Bellamy RF, eds. *Textbooks of Military Medicine*. Washington, DC: Department of the Army, Office of the Surgeon General, Borden Institute; 1997.

78. Azizi MD, Amid MH. Clinical presentation of chemical warfare injuries in children and teenagers. *Med J Islamic Rep Iran*. 1990;4(2):103–108.

79. Motakallem MH. Evaluation of 17 patients severely injured with sulfur mustard. *Med J Islamic Rep Iran*. 1988;2(2):99–104.

80. Graham JS, Chilcott RP, Rice P, Milner SM, Hurst CG, Maliner BI. Wound healing of cutaneous sulfur mustard injuries: strategies for the development of improved therapies. *J Burns Wounds*. 2005;4:e1.

81. US Army Medical Research Institute of Chemical Defense. *Medical Management of Chemical Casualties Handbook*. 3rd ed. Aberdeen Proving Ground, Md: USAMRICD; 2000.

82. US Army Medical Research Institute of Chemical Defense. *Field Management of Chemical Casualties Handbook*. 2nd ed. Aberdeen Proving Ground, Md: USAMRICD; 2000.

83. Department of the Army. Vesicants (blister agents). In: *NATO Handbook on the Medical Aspects of NBC Defensive Operations AMedP-6(B).* Part III: Chemical. Washington, DC: DA; 1996.

84. Moradi A, Sodeifi M, Abdollahi B, Pakdaman A, Vessal K. Clinical presentation of chemical warfare injuries. *Iran J Med Sci*. 1986;13:1–5.

85. Logan TP, Graham JS, Martin JL, Zallnick JE, Jakubowski EM, Braue EH. Detection and measurement of sulfur mustard (HD) offgassing from the weanling pig following exposure to saturated sulfur mustard vapor. *J Appl Toxicol*. 2000;20:S199–S204.

86. Buscher H, Conway N, trans. *Green and Yellow Cross*. Cincinnati, Ohio: Kettering Laboratory of Applied Physiology, University of Cincinnati; 1944.

87. Geffner ME, Powars DR, Choctaw WT. Acquired methemoglobinemia. *West J Med*. 1981;134:7–10.

88. Ohlgisser M, Adler M, Ben-Dov D, Taitelman U, Birkhan HJ, Bursztein S. Methaemoglobinaemia induced by mafenide acetate in children. *Br J Anaesth*. 1978;50:299–301.

89. Fullerton JK, Smith CE, Neumeister MW. Methemoglobinemia induced by 5% mafenide acetate solution and topical lidocaine spray in a pediatric burn patient: a case report. *J Burns & Surg Wound Care*. 2002;1(1):14.

90. Ruhl CM, Park DJ, Danisa O, et al. A serious skin sulfur mustard burn from an artillery shell. *J Emerg Med*. 1994;12(2):159–166.

91. Marshall JH, Bromberg BE, Adrizzo JR, Heurich AE, Samet CM. Fatal tetanus complicating a small partial-thickness burn. *J Trauma*. 1972;12(1):91–93.

92. Burklow TR, Yu CE, Madsen JM. Industrial chemicals: terrorist weapons of opportunity. *Pediatr Ann*. 2003;32(4):230–234.

93. Güloğlu C, Kara IH, Erten PG. Acute accidental exposure to chlorine gas in the southeast of Turkey: a study of 106 cases. *Environ Res*. 2002;88:89–93.

94. Traub SJ, Hoffman RS, Nelson LS. Case report and literature review of chlorine gas toxicity. *Vet Human Toxicol*. 2002;44(4):235–239.

95. Pherwani AV, Khanna SA, Patel RB. Effect of chlorine gas leak on the pulmonary functions of school children. *Indian J Pediatr*. 1989;56:125–128.

96. Rotenberg JS. Cyanide as a weapon of terror. *Pediatr Ann*. 2003;32(4):236–240.

97. Baskin SI, Brewer TG. Cyanide poisoning. In: Sidell FR, Takafuji ET, Franz DR, eds. *Medical Aspects of Chemical and Biological Warfare*. In: Zajtchuk R, Bellamy RF, eds. *Textbooks of Military Medicine*. Washington, DC: Department of the Army, Office of the Surgeon General, Borden Institute; 1997.

98. Riordan M, Rylance G, Berry K. Poisoning in children: 5 rare and dangerous poisons. *Arch Dis Child*. 2002;87:407–410.

99. Prajapati NC, Puri RK, Sarangi MP, Yadav S, Khalil A. Potassium cyanide poisoning. *Indian Pediatr*. 1992;29:903–905.

100. Goldfrank LR, Flomenbaum NE, Lewin NA. Cyanide and hydrogen sulfide. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Weisman RS, Howland MA, Hoffman RS, eds. *Goldfrank's Toxicologic Emergencies*. 6th ed. Stamford, Conn: Appleton & Lange; 1998.

101. Peden NR, Taha A, McSorley. Industrial exposure to hydrogen cyanide: implications for treatment. *Br Med J*. 1986;293:538.

102. Cyanide antidote [package insert]. Buffalo Grove, Ill: Taylor Pharmaceuticals; 1998.

103. Berlin CM. The treatment of cyanide poisoning in children. *Pediatrics*. 1970;46:793–796.

104. Hall AH, Rumack BH. Clinical toxicology of cyanide. *Ann Emerg Med*. 1986;15:1067–1074.

105. Rotenberg JS, Burklow TR, Selanikio JS. Weapons of mass destruction: the decontamination of children. *Pediatr Ann*. 2003;32(4):261–267.

106. Rosenbaum C. Chemical warfare: disaster preparation in an Israeli hospital. *Soc Work Health Care*. 1993;18:137–145.

107. Bradley BJ, Gresham LS, Sidelinger DE, Hartstein BH. Pediatric health professionals and public health response. *Pediatr Ann*. 2003;32:87–94.

108. Schonfeld DJ. Potential roles for pediatricians. *Pediatr Ann*. 2003;32:182–187.

109. *Effects of the World Trade Center Attack on NYC Public School Students: Initial Report to the New York City Board of Education*. New York, NY: New York City Department of Education; 2002.

110. Frush K, Hohenhaus S. Pediatric Mass Casualty Incident Guidelines. Durham, NC: Duke University Health System Emergency Medical Services for Children; 2004. Available at: http://www.wnysmart.org/References/MCI_Duke_Protocol_April04.pdf. Accessed February 29, 2008.

111. Luten R, Wears RL, Broselow J, Croskerry P, Joseph MM, Frush K. Managing the unique size-related issues of pediatric resuscitation: reducing cognitive load with resuscitation aids. *Acad Emerg Med*. 2002;9;840–847.

112. Frush K, Hohenhaus S, Luo X, Gerardi M, Wiebe RA. Evaluation of a Web-based education program on reducing medication dosing error: a multicenter, randomized controlled trial. *Ped Emerg Care*. 2006;22:62–70.

113. Luten R, Broselow J. Rainbow care: the Broselow-Luten system. Implications for pediatric patient safety. *Ambul Outreach*. 1999;fall:14–16.

114. Lubitz DS, Seidel JS, Chameides L, Luten RC, Zaritsky AL, Campbell FW. A rapid method for estimating weight and resuscitation drug dosages from length in the pediatric age group. *Ann Emerg Med*. 1988;17:576–581.

115. Vilke GM, Marino A, Fisher R, Chan TC. Estimation of pediatric patient weight by EMT-PS. *J Emerg Med*. 2001;21:125–128.

116. Agarwal S, Swanson S, Murphy A, Yaeger K, Sharek P, Halamek LP. Comparing the utility of a standard pediatric resuscitation cart with a pediatric resuscitation cart based on the Broselow tape: a randomized, controlled, crossover trial involving simulated resuscitation scenarios. *Pediatrics*. 2005;116:326–333.

117. Pralidoxime [package insert]. Bristol, Tenn: Meridian Medical Technologies, Inc; 2002.

118. Remington JP, Gennaro AR. *Remington: the Science and Practice of Pharmacy*. 19th ed. Easton, Pa: Mack Publishing Co; 1995.

119. Sidell FR. Clinical considerations in nerve agent intoxication. In: Somani SM, ed. *Chemical Warfare Agents*. San Francisco, Calif: Academic Press, Inc; 1992.

120. Markenson D, Redlener I. Pediatric terrorism preparedness national guidelines and recommendations: findings of an evidenced-based consensus process. *Biosecur Bioterror*. 2004;2:301–309.

121. Foltin G, Tunik M, Curran J, et al. Pediatric nerve agent poisoning: medical and operational considerations for emergency medical services in a large American city. *Pediatr Emerg Care*. 2006;22:239–244.

122. Montello MJ, Tarosky M, Pincock L, et al. Dosing cards for treatment of children exposed to weapons of mass destruction. *Am J Health Syst Pharm*. 2006;63:944–949.