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PEDIATRIC DISASTER PREPAREDNESS AND RESPONSE

TOPICAL COLLECTION

CHAPTER 9: CHEMICAL EVENTS

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CHAPTER 9:
CHEMICAL EVENTS

The American Academy of Pediatrics (AAP) published specific recommendations in its policy and technical report, "Chemical-Biological Terrorism and Its Impact on Children" in February 2020.

LESSONS LEARNED FROM PAST CHEMICAL EVENTS

- Chemical terrorism can be a real incident anywhere and anytime. Medical health systems need to be prepared.
- When many patients present with similar symptoms from the same place, suspicion for chemical exposure should be raised.
- Information about the actual chemical used will be delayed.
- Chemical attacks can easily overwhelm hospital resources, and a written disaster plan that has been exercised or tested out is necessary.
- The majority of patients will come independent of the prehospital system and can overwhelm local hospital resources. Be prepared to care for the sicker patients who will arrive later.
- Medical providers will be forced to care for patients with incomplete information and a high degree of suspicion for a chemical etiology.
- Treatment needs to be guided by clinical findings in the beginning.
- On-site decontamination and triage should be set up immediately once a chemical event is suspected.
- Medical supplies, including antidotes, will be quickly exhausted during a massive chemical attack. Hospitals should have disaster plans in place to obtain additional medication from local, regional, and national stockpiles.
- Time course of symptoms can vary depending on substance. Knowing the expected symptoms and time course about specific chemical agents will guide the triage/treatment plan. Some chemicals have delayed effects.
- Resources, such as the HHS Chemical Hazards Emergency Medical Management website, poison control centers, and the Pediatric Environmental Health Specialty Units website are available to assist medical providers.

INTRODUCTION

Chemical terrorism is the intentional use of toxic chemicals to inflict mass casualties and mayhem on an unsuspecting civilian population, including children. Such an incident could potentially overwhelm the capacity of regional emergency medical services and pose extraordinary medical management challenges to pediatricians. However, careful community planning, robust research and development (by academic, private, and governmental collaborative efforts), and rigorous medical education could mitigate such a catastrophe.

The risk of chemical terrorism is more tangible since the events of September 11, 2001, and the subsequent intentional spread of anthrax through the US mail. However, the specter of purposeful toxic exposures predates the September 11 attack. The 20th century witnessed Iraqi military attacks with nerve agents on civilian villages in Iran in the 1980s, the release of the nerve agent sarin in the Tokyo subway system in 1995, and a chlorine bomb scare at Disneyland

in 1995. Unfortunately, chemical attacks continue to occur with the finding of ricin in US Senate office buildings in 2004, the sarin attacks in Syria in 2013 and 2017, and the use of nerve agent VX at Kuala Lumpur airport in 2017.

Chemical terrorism often refers to the use of military chemical weapons that have been illicitly obtained or manufactured de novo. However, additional concerns might include the intentional explosion of an industrial chemical factory, a tanker car, or a transport truck in proximity to a civilian residential community, school, child care facility, or worksite. These events underscore the need for all pediatricians to expand their working knowledge of the approach to mass casualty incidents involving traditional military chemical weapons and other toxic chemicals that might be used as "weapons of opportunity."

The medical consequences and epidemiology of a chemical terrorist attack mimic more conventional disasters but also reflect some distinct differences. Such an incident combines elements of both a traditional mass disaster (eg, an earthquake) and a hazardous materials incident. Potential differences of a chemical terrorist attack compared with a "routine" hazardous materials incident include the following:

- Intent to cause mass casualties
- Great toxicity of substances
- Delayed initial identification of substance
- Greater risk to first responders
- Overwhelming numbers of patients
- Many anxious individuals
- Mass hysteria, panic
- Discovery of dispersal device

Casualties occur almost immediately, and the attack would likely be recognized rapidly. Decontamination and initial care of small children on scene pose enormous management issues for personnel wearing bulky personal protective equipment (PPE). In addition, many children who have been exposed but not critically injured will be taken by parents to hospitals and pediatricians' offices without prior on-scene decontamination—thus posing similar challenges for and possibly personal risk to pediatric care providers themselves.

SPECIFIC PEDIATRIC VULNERABILITIES TO CHEMICAL AGENTS

Children have inherent physiologic, developmental, and psychological differences from adults that may enhance susceptibility and worsen prognosis after a chemical agent exposure. Additional information is available in Chapter Three: How Children are Different.

Table 9.1: Pediatric Vulnerabilities to Chemical Terrorism summarizes pediatric-specific vulnerabilities to chemical agents.

Table 9.1: Pediatric Vulnerabilities to Chemical Terrorism

Realm	Potential Vulnerability	Potential Response
Physiologic	• Nerve agents may penetrate the blood-brain barrier more easily in children than adults.	Early warning, sheltering (gas masks

	Children may only exhibit central nervous system (CNS) effects. • Children younger than 4 years with status epilepticus have the highest risk of death • A child's smaller mass alone reduces the dose of nerve agent required for toxic/lethal effects. Animal studies have shown that the lethal dose of nerve agent in an immature vs adult animal is 10%. • Increased respiratory exposure (high minute ventilation, live closer to the ground).	not advised because of risk of poor fit, suffocation)
	Increased dermal exposure (larger body surface area/mass ratio).	Protective clothing, early decontamination
	Increased risk of dehydration, shock with illness-induced vomiting, diarrhea (decreased fluid reserves, larger body surface area/mass ratio).	Recognition, aggressive fluid therapy
	Increased risk of hypothermia during decontamination (larger body surface area/mass ratio).	Warm water decontamination
	More fulminant disease; (possible) physiologic detoxification immaturity; more permeable blood-brain barrier.	Pediatric-specific research for early diagnosis and treatment of chemical weapons victims
Developmental	Less ability to escape attack site, take appropriate evasive actions (developmental immaturity, normal dependence on adult caregivers who might be injured or dead).	
Psychological	Less coping skill of children who suffer injury or witness parental, sibling death (psychological immaturity).	Child psychiatry involvement, research for preventing pediatric post-traumatic stress disorder
	Greater anxiety over reported incidents, hoaxes, media coverage, etc.	Pediatric counseling of parents and children
Emergency medical services (EMS)	Less capacity to cope with influx of critical pediatric patients.	Community and regional planning with significant pediatric input
	Loss of routine hospital transfer protocols.	
	Limited ability to expand pediatric hospital bed capacity through the National Disaster Medical System	

CHEMICAL INJURIES AND APPROACH TO THE UNKNOWN CHEMICAL ATTACK

A listing of many of the most notable chemical agents of concern has been compiled by the Centers for Disease Control and Prevention (CDC) https://emergency.cdc.gov/agent/agentlistchem.asp. Toxic effects from chemical agents usually follow dermal or inhalational exposure and may develop via injury to the skin, eyes, and respiratory epithelium as well as via systemic absorption. The intensity and route of exposure to chemical agents affect both the rapidity of onset (seconds to hours) and the severity of symptoms. For example, a mild exposure to sarin vapor results in lacrimation, rhinorrhea, miosis, and slightly blurry vision; an intense exposure leads to seizures, apnea, and rapid death within minutes.

Toxidromes after exposure to various chemical agents (nerve agents, vesicants, pulmonary agents, cyanide, and riot-control agents) are summarized in **Table 9.2: Chemical Agents, Summary of Symptoms** and detailed in the following sections.

Table 9.2: Chemical Agents, Summary of Symptoms

Agent	Toxidromes	Onset
Nerve Agent (eg, tabun, sarin, soman, VX)	Cholinergic symptoms: miosis, increased secretions (bronchorrhea, salivation, lacrimation, urination, diaphoresis), vomiting, dyspnea, fasciculations, coma, seizure	Vapor: seconds Liquid: minutes-hours
Vesicants (eg, mustard, lewisite)	Skin erythema/vesicles, eye irritation, respiratory irritation in high concentration exposure	Mustard: hours Lewisite: immediate pain
Pulmonary agents (eg, chlorine, phosgene)	Respiratory irritation, dyspnea, pulmonary edema, ocular irritation	Minutes: eyes, nose, throat irritation, bronchospasm Hours: pulmonary edema
Asphyxiant (eg, cyanide)	Dyspnea, coma, seizure	Seconds
Riot control agents (eg, CS, CN, capsaicin)	Ocular pain, tearing, blepharospasm	Seconds

Understanding the epidemiology of acute mass exposure to a toxin is helpful in recognizing a covert chemical attack with unknown agents. Mass exposure to a toxin will likely manifest as an acute onset of illness (within seconds to minutes or within hours in the case of some of the vesicants and pulmonary agents). In more severe chemical incidents, numbers of people may collapse or die within minutes of exposure.

Chemical weapons can be categorized based on the predominant symptoms they cause:

- Neurologic (nerve agents or cyanide).

- Respiratory (phosgene or chlorine, high-dose riot-control agents, or sulfur mustard with a delay of several hours from time of exposure).
- Mucocutaneous syndromes (vesicants).

For additional advice on more definitive diagnosis and management strategies, contact public health authorities or the regional poison control center (800-222-1222).

Cyanide and nerve agents attacks can have similar presentations but different therapies. In both cases, large numbers of victims may collapse suddenly, have seizures, or go into a coma. Many deaths occur rapidly. Nerve agent casualties are likely to be cyanotic and have miotic pupils with altered vision, copious oral and nasal secretions, and acute bronchospasm and bronchorrhea. The differentials and treatments of cyanide and nerve agent are summarized in **Table 9.3: Differential Diagnosis and Antidotes of Nerve Agents and Cyanide**.

Table 9.3: Differential Diagnosis and Antidotes of Nerve Agents and Cyanide

	Nerve Agent	Cyanide
Odor	None to very faint	Some say they perceive a smell of bitter almond, yet others fine this sign unreliable.
Clinical symptoms	Miosis, copious secretions (bronchorrhea, salivation, lacrimation, urination, defecation), fasciculation then flaccid paralysis	Normal/dilated pupils, relatively few secretions, twitching of body but no fasciculation. With higher doses, the time of onset of symptoms typically is seconds and it may cause abrupt onset of profound CNS, cardiovascular, and respiratory effects, leading to death within minutes. Signs and symptoms may present over a much longer period of time if the poisoning is gradual with lower doses.
Lab findings	Respiratory alkalosis to hypoxemia with respiratory acidosis	High anion-gap acidosis, high venous oxygen saturation, severe lactic acidosis.

Antidotes	Atropine: 0.05 mg/kg, IV or IM (min 0.1 mg, max 5 mg), repeat every 2-5 min as needed for bronchorrhea Pralidoxime: 25 mg/kg, IV or IM (max 1 g IV, 2 g IM), may repeat within 30-60 min as needed, then again every hour for 1 or 2 doses as needed for persistent weakness Diazepam: 0.3 mg/kg, IV (max 10 mg); Lorazepam: 0.1 mg/kg IV, IM (max 4 mg); Midazolam: 0.2 mg/kg, IM (max 10 mg) as needed for seizures or severe exposure	Hydroxocobalamin: 70 mg/kg up to 5 g (adult dose) IV. Sodium thiosulfate (25%): 1.65 mL/kg IV (max 50 mL). Sodium bicarbonate as needed for metabolic acidosis.

The initial protection of everyone in a community exposed to a hazardous chemical requires safe evacuation or local sheltering. Local and federal authorities will assist in informing the public whether to shelter in place or evacuate.

Information regarding evacuation in a chemical emergency can be found at https://emergency.cdc.gov/planning/evacuationfacts.asp. Information regarding sheltering in place in a chemical emergency can be found at https://emergency.cdc.gov/planning/shelteringfacts.asp.

INITIAL APPROACH, DECONTAMINATION, AND TRIAGE

The general treatment of contaminated victims begins with extrication, triage, resuscitation as needed, and decontamination performed by rescue workers or health care providers wearing appropriate PPE. Ideally, decontamination would be performed at the scene to avoid the considerable challenges posed by the arrival of contaminated patients, including children, at health care facilities. However, in a large-scale terrorist incident, it is far more likely that some victims will arrive at hospitals or other health care facilities without having been previously decontaminated. In this context, significantly contaminated victims should be decontaminated before they are allowed into the emergency department (ED). Even if decontamination has been performed in the field, hospitals are likely to repeat decontamination procedures to protect the facility from contamination (which would result in closure or having to go “offline”); this would also address the possibility of cross-contamination moving from the scene. Decontamination to limit secondary exposures is especially important in exposures to nerve agents and vesicants.

Appropriate PPE for ED staff involved in patient decontamination is an important consideration. The amount of chemical agent believed to contaminate patients who arrive at the ED after a chemical terrorist attack would essentially consist of that on their skin and clothing (ie, far lower concentration of chemicals than rescue workers would face at the scene of exposure).

Similar to other mass casualty events, the number of victims can easily overwhelm local hospitals in a chemical terrorism attack. Health care providers will need to be trained in triage to

provide optimal medical care during such an event. There are many different triage systems with varying sensitivity and specificity such as START (**s**imple **t**riage **a**nd **r**apid **t**reatment), JumpSTART and SALT (**s**ort, **a**ssess, **l**ifesaving interventions, **t**reatment/**t**ransport).

In general, triage in a chemical event is similar to the approaches in a typical mass casualty event, but there are unique features in the triage process for chemical exposure victims:

- Clinical assessment of chemical exposure is required at the same time with triage. Often, the offending agent is not clear when the first patients arrive at a health care facility.
- Adequate antidote administration should be included in lifesaving interventions during triage based on clinical assessment in appropriate setting.
- Proper PPE should be used as described above to prevent secondary exposure. This PPE makes verbal communication and auditory and tactile examination/treatment challenging.
- Medical personnel might have difficulty in the assessment of the symptoms, because some chemicals have instant onset of symptoms (eg, nerve agent, cyanide) and immediate need for intervention, and some chemicals show no symptoms on presentation because of delayed onset symptoms (eg, sulfur mustard, phosgene).

Cardiopulmonary and airway support, including emergent intramuscular antidotal therapy, are provided as necessary and appropriate for the specific exposure. Contaminated clothing should be removed as soon as possible. The contamination hazard can be reduced by as much as 85% simply by removing clothing. More definitive decontamination follows. For vapor-exposed victims, decontamination may be accomplished primarily by clothing removal and washing of hair. In contrast, for victims with liquid dermal exposure, more thorough decontamination is required. Their skin and clothing pose considerable risk to ED personnel. Clothing should be carefully removed and disposed of in double bags. Victims with ocular exposure require eye irrigation with copious amounts of saline or water. Skin and hair should be washed thoroughly, but gently, with soap and tepid water. In the past, some authorities had recommended 0.5% sodium hypochlorite (dilute bleach) for skin decontamination of nerve agents and vesicants. However, bleach may be a skin irritant, thus increasing permeability to the agent. In addition, its use is time consuming and has not been proven superior to washing with copious soap and water or water alone. Furthermore, there is little experience with this approach in infants and young children. A difficult question that remains is whether EMS and ED staff wearing bulky PPE will be able to provide significant advanced life support to small children before decontamination.

INDUSTRIAL CHEMICALS

The potential of a terrorist attack on industrial sources of hazardous chemicals (eg, factories, railroad and vehicular tank cars, or storage depots) expands the list of potential “chemical weapons” considerably. In general, many of the relevant industrial chemicals (see **Table 9.4: Representative Classes of Industrial Chemicals**) might be expected to induce respiratory effects analogous to those of chlorine or phosgene (see the section on pulmonary agents) or dermatologic injury from irritant or caustic properties, as well as more systemic effects in severe exposures.

Table 9.4: Representative Classes of Industrial Chemicals			
Agent	Clinical Findings	Onset	Management
Strong acid/bases	Eye: caustic injury Skin: chemical burns GI: chemical burns of mouth, larynx, esophagus, stomach	Rapid	Supportive care, early endoscopy for significant ingestion
Respiratory tract irritants (eg, ammonia, hydrochloric acid, and HF gases)	Eyes, ears, nose, throat, and respiratory tract irritation with cough, chest pain, dyspnea, wheeze (possible pulmonary edema in severe cases)	Rapid	Supportive respiratory care (consider nebulized calcium gluconate solution for HF); see https://chemm.hhs.gov/
Fentanyl and other opioids	CNS and respiratory depression, miosis	Rapid	Supportive care, naloxone 0.01-0.1 mg/kg)
Cellular asphyxiants (eg, phosphine, sodium azide)	Cough, dyspnea, headache, dizziness, vomiting, tachycardia, hypotension, severe metabolic acidosis; may progress to coma, seizure, death; may have delayed onset pulmonary edema with phosphine	Rapid (except pulmonary edema with phosphine	Supportive care, 100% oxygen
Arsine	Severe hemolysis	2-4 h	Supportive care, enhance urine flow, consider alkalinization

COMMUNITY PREPAREDNESS

In the aftermath of September 11, 2001, many agencies are collaborating to ensure coordinated care of pediatric victims. All pediatricians are encouraged to participate in disaster management training. Pediatricians have a role in recognizing toxidromes and contacting appropriate agencies if suspected as well as working in their communities to optimize the overall capacity for providing disaster care to chemically exposed children.

Successful planning and response to events involving chemical terrorism require strong collaboration and integrated functioning of many agencies and facilities, both governmental and nongovernmental, including local treatment facilities, local and state health departments, and federal agencies including the Office of the Assistant Secretary for Preparedness and Response, (ASPR), the Federal Emergency Management Agency (FEMA), the Federal Bureau of Investigation (FBI), and the CDC.

ADDITIONAL RESOURCES

In large-scale mass casualty chemical exposure incidents, additional information about event management can be found at the following:

- Chemical Hazards Emergency Medical Management (CHEMM): provided by the National Library of Medicine, mainly for first responders, first receivers, and other health care providers to use during chemical events: https://chemm.hhs.gov/.
- The American Association of Poison Control Centers has 55 regional poison centers that can be reached 24/7 at 800-222-1222.
- The CDC is available 24/7 at 770-488-7100, or 800-232-4636. The CDC has the Laboratory Response Network (LRN), a network of laboratories that can respond to chemical and biological terrorism. Online resources are available at https://emergency.cdc.gov/chemical/index.asp.
- The US Coast Guard National Response Center hotline is 800-424-8802 (https://nrc.uscg.mil/) and is the federal point of contact for reporting all hazardous substances release and oil spills.
- The FBI can be reached at 202-324-3000 (headquarters).
- The FEMA can be reached at 800-621-3362.
- The US Army Medical Research Institute of Chemical Defense/Chemical Casualty Care Division (MRICD) provides consultation on medical aspects of chemical warfare agents at https://usamricd.amedd.army.mil/Pages/default.aspx.
- WISER (Wireless Information System for Emergency Responders) assists emergency responders in hazardous material incidents, and provide a quick review of the character of specific substances, symptoms, PPE recommendations, and treatment (https://wiser.nlm.nih.gov/).
- TOXNET (TOXicology Date NETwork) is a series of online databases managed by the National Institutes of Health National Library of medicine, and these databases cover chemicals, drugs, and environmental health (https://www.nlm.nih.gov/toxnet/index.html).

NERVE AGENTS

Nerve agents are organophosphorus compounds similar to the organophosphate insecticides used in agriculture or industry but far more toxic. Four compounds are currently regarded as nerve agents: tabun, sarin, soman, and VX. All of these agents are hazardous by ingestion, inhalation, or cutaneous absorption, the latter being particularly true for VX. The toxic effects of nerve agent vapors depend on the concentration of the agent inhaled and on the time exposed to the agent. The toxicity of nerve agent liquid depends on the time exposed and the bodily site of exposure. Nerve agents exist as liquids at standard temperatures and pressures. In gaseous form, they are denser than air and vary in volatility, with some (eg, VX) being more persistent than others (eg, sarin).

Background

The Iran-Iraq War of the 1980s reportedly resulted in more than 100,000 casualties from chemical weapons. Iranian sources reported that the number of casualties caused by nerve agents was far greater than the number of casualties caused by mustard agent. Many nerve agent casualties that were only mildly to moderately affected were not counted.

A chemical warfare campaign by the Iraqi military on Kurdish civilians in the late 1980s caused thousands of deaths. The exact agents are not definitively known, but Iraq was known to have stockpiled tabun, sarin, and VX.

A Japanese religious cult that manufactured sarin deployed it in 1994 in attacks on a residential neighborhood of Matsumoto and again in 1995, in the Tokyo subway. Immediate mortality was low, but thousands of individuals arrived at EDs. The lack of a decontamination process resulted in significant morbidity to health care personnel. The sarin was released by a relatively primitive method (punctured plastic bags allowing sarin vapor to escape); many experts believe a more sophisticated delivery system might have resulted in far higher mortality.

Multiple chemical attacks have been reported between 2013 and 2018 in Syria. During the August 21, 2013 sarin attack, 14,000 people were killed, and 89 deaths (including 33 children) were reported on April 4, 2017 in another sarin attack. Nerve agent exposures in the United States have been individual cases associated with industrial exposures.

Toxicology and Clinical Manifestations

Nerve agents inhibit the action of acetylcholinesterase at cholinergic neural synapses, where acetylcholine then accumulates markedly. The resulting cholinergic syndrome is classically divided into central, nicotinic (neuromuscular junction and sympathetic ganglia), and muscarinic (smooth muscle and exocrine gland) effects.

Clinical manifestations vary with the type of exposure. Symptoms after a vapor exposure appear suddenly with a full range of clinical effects, or there may be a partial expression of the syndrome. Symptoms after dermal exposure to liquid nerve agents may have delayed effects and start with local sweating.

Central Nervous System Effects

Effects on the CNS include headache, seizures, coma, respiratory arrest, confusion, slurred speech, and respiratory depression. Although the seizures probably begin because of excess cholinergic stimulation in the first 5 minutes, other effects (eg, excitatory glutamate receptor stimulation and antagonism of inhibitory gamma-aminobutyric acid [GABA] receptors) may also play a role after 5 minutes of exposure. Case series of anticholinesterase pesticide poisonings in children suggest a disproportionate degree of depressed muscle weakness, hypotonia, and CNS depression (stupor, coma) compared with peripheral muscarinic effect. Thus, children may manifest primarily central and/or neuromuscular effects after nerve agent exposure.

Autonomic Nervous System Effects

These include both nicotinic and muscarinic findings. Nicotinic effects on sympathetic activity can result in the following:

- Tachycardia
- Hypertension
- Metabolic aberrations (eg, hyperglycemia, hypokalemia, and metabolic acidosis)

Muscarinic effects involve multiple systems:

- Ocular (miosis, eye pain, visual blurring, lacrimation)

- Respiratory (watery rhinorrhea, increased bronchial secretions, and bronchospasm causing cough, wheezing, dyspnea, and cyanosis)
- Cardiovascular (bradycardia, hypotension, atrioventricular block)
- Dermal (flushing, sweating)
- Gastrointestinal (salivation, nausea, vomiting, diarrhea progressing to fecal incontinence, abdominal cramps)
- Urinary (frequency, urgency, incontinence)

Neuromuscular Effects

At the neuromuscular junction, initial stimulation of cholinergic synaptic transmission is followed by paralysis. Thus, nicotinic effects include muscle fasciculations and twitching, followed by weakness progressing to flaccid paralysis and respiratory failure.

The clinical syndrome of organophosphate toxicity is summarized by the mnemonic DUMBBELS. See **Table 9.5: DUMBBELS**.

Table 9.5: DUMBBELS	
D	Diarrhea
U	Urination
M	Miosis
B	Bronchoconstriction
B	Bronchorrhea
E	Emesis
L	Lacrimation
S	Salivation

Diagnostic Tests

The diagnosis of nerve agent toxicity is primarily based on clinical recognition and response to antidotal therapy. Measurements of acetylcholinesterase in plasma (pseudocholinesterase) or red blood cells (RBC; cholinesterase) may confirm organophosphate poisoning, but correlation between cholinesterase levels and clinical toxicity is poor in some contexts; also, these analyses are rarely available on an emergent basis. RBC cholinesterase levels may help in monitoring recovery or in forensic investigations. In symptomatic patients, treatment is indicated without waiting for cholinesterase levels, while in exposed asymptomatic patients, antidotal therapy is not needed, even if cholinesterase is depressed.

Treatment

If recognized early, this is a treatable and reversible syndrome. Triage, resuscitation, and decontamination should begin at the scene and at accepting health care facilities. Individuals directly exposed to liquid nerve agents should be observed for at least 18 hours.

Treatment focuses on airway and ventilatory support; aggressive use of antidotes, particularly atropine and pralidoxime (2-PAM); prompt control of seizures with benzodiazepines; and decontamination as necessary. Antidotal therapy is titrated according to clinical severity. See **Table 9.6: Nerve Agent Triage and Dosing**.

Table 9.6: Nerve Agent Triage and Dosing

Severity	Triage Level and Disposition	Anticholinergics	Oxime-pralidoxime Chloride (2-PAM)	Benzodiazepine
Asymptomatic	Delayed: observation	None	None	None
Mild: miosis, mild rhinorrhea	Delayed: admit or observation	None	None	None
Moderate: miosis, and any other symptoms	Immediate: admit	Atropine, 0.05 mg/kg, IV, IM, IO to max 4 mg; repeat as needed every 5-10 min until pulmonary resistance improves or secretions resolve Correct hypoxia before IV use, as it can increase risk of ventricular fibrillation Alternatives: scopolamine for nervous system and peripheral effects; glycopyrrolate for peripheral effects only	2-PAM, 25-50 mg/kg, IV, IM, to max 1800 mg; repeat every h as needed; watch for muscle rigidity, laryngospasm, tachycardia, hypertension	If neurologic symptoms or rapid progression: Midazolam 0.15-0.2 mg/kg IM, IV, repeat as necessary or start continuous IV drip; less likely to cause apnea by IM route Diazepam IV, as needed (see below) Lorazepam IV at 0.05-0.1 mg/kg (IM absorption variable)
Severe: apnea, convulsions,	Immediate: admit, intensive-care	Atropine, 0.05-0.10 mg/kg, IV, IM, IO, repeat every 5-10 min,	2-PAM, 25-50 mg/kg, IV, IS, as above	Midazolam, as above

cardiopulmonary arrest		as above, no max)		Diazepam, 30 days to 5-y-old: 0.05-0.3 mg/kg, IV, max 5 mg/dose; >5-y-old: 0.05-0.3 mg/kg, IV, max 10 mg/dose, repeat every 5-30 min as needed Lorazepam IV, IM
Autoinjector use		Atropine, 2 mg for >40 kg; 1 mg for >20 kg; 0.5 mg for >10 kg	2-PAM, 600 mg for >12 kg (50 mg/kg/dose)	Diazepam 10 mg for >30 kg (0.3 mg/kg/dose)

Atropine, in relatively large doses, is used for its antimuscarinic effects, and pralidoxime chloride serves to reactivate acetylcholinesterase and, thus, enhance neuromuscular function. Atropine counters bronchospasm and increased bronchial secretions; bradycardia; and gastrointestinal (GI) effects of nausea, vomiting, diarrhea, and cramps and may lessen seizure activity. Typical dosing for atropine after nerve agent exposure is usually between 5 and 20 mg in total. Severely affected nerve agent casualties in the military have received up to 200 mg of atropine. Atropine should be administered until respiratory status improves, because tachycardia and/or pupillary size are not an absolute end-point for atropinization. Atropine cannot reverse neuromuscular symptoms, and paralysis may persist without pralidoxime.

Pralidoxime cleaves the organophosphate away from the cholinesterase, thus regenerating the intact enzyme if aging (irreversible dealkylation of organic phosphorus compound-cholinesterase complex) has not occurred. This effect is noted most at the neuromuscular junction, with improved muscle strength. Prompt use of pralidoxime is recommended in all serious cases. Despite recommendations for the use of pralidoxime by many authorities, evidence behind this is not robust and mostly low quality. Cochrane conducted a review of oximes for acute organophosphate pesticide poisoning in 2011 and concluded, “Current evidence was insufficient to indicate whether oximes are harmful or beneficial.”

Both atropine and pralidoxime should be administered by intravenous (IV) infusion in severe cases (intraosseous [IO] access is likely equivalent to IV). Continuous IV infusion may be required for organophosphate pesticide poisoning, but usually the amount of atropine needed for nerve agent is less than that of organophosphate poisoning. The intramuscular (IM) route is acceptable if IV access is not readily available. This may be of considerable relevance in a mass casualty incident involving children. In fact, most EMS programs in the United States now stock military IM autoinjector kits of atropine and 2-PAM (Mark I kit, 2 separated autoinjector for atropine and 2-PAM). Although an autoinjector with pediatric doses for 2-PAM are currently not available in the United States, pediatric autoinjectors of atropine in 0.25-mg, 0.5-mg, and 1.0-mg sizes are available in other countries. In dire circumstances, the adult 2-PAM autoinjector (600

mg) might be used in children older than 2 to 3 years or weighing more than 13 kg. The Mark I kit is no longer manufactured in the United States, and a newer model Antidote Treatment-Nerve Agent, Autoinjector (ATNAA), which gives atropine and 2-PAM simultaneously, is now available.

Seizures are primarily controlled with benzodiazepines. Diazepam is principally used by the US military, but other benzodiazepines may be equally efficacious (eg, midazolam or lorazepam). Midazolam is believed optimal for IM administration in the treatment of status epilepticus in general, and therefore, may be especially useful in nerve agent toxicity in children. Finally, routine administration of anticonvulsant doses of benzodiazepines has been recommended in severe cases even without observed convulsive activity, because animal studies have indicated some amelioration of subsequent seizures and morphologic brain damage with such use.

Convulsive antidote nerve agent (CANA), diazepam autoinjector, is also currently in use for this purpose.

Supportive care is critical to patient outcome and includes the following:

- Protect airway/relieve bronchospasm/pulmonary toilet.
  - 100% oxygen, bronchodilators, suction, nasogastric tubes.
- Monitor for cardiac arrhythmias.
- Treat complicating injuries and infections.
  - Wounds and foreign bodies may be contaminated.
  - Treat skin lesions.
- Provide fluids, electrolytes, and nutrition.
  - Nursing mothers should discard breast milk.
- Prevent hypothermia.
- Provide eye care.
  - Consider ophthalmic analgesics for ocular pain.
  - Consider topical mydriatics for miosis (atropine given systemically may not reverse miosis).
- Consider electroencephalogram (EEG) and brain imaging for victims who do not promptly regain consciousness.

Isolation and Control Measures

Isolation is required only for potentially exposed victims before they are definitively decontaminated. Health care workers should wear PPE to treat victims before decontamination is complete.

CYANIDE

Cyanide has long been used for sinister purposes, including as an agent of murder, suicide, chemical warfare, and judicial execution. In addition, it may pose an occupational hazard, and it has been ingested (usually in a precursor form) by children. Its efficacy as an agent of chemical terrorism is considered somewhat limited by its volatility in open air and relatively low lethality compared with nerve agents. However, if cyanide were released in a crowded, closed space, the effects could be devastating. This was more than amply illustrated by its notoriety as the chemical weapon used by the Nazis in the concentration camp gas chambers. More than 900

people ingested potassium cyanide salt in the 1978 Jonestown mass suicide incident. Chemical warfare agents involving cyanide include the liquids hydrocyanic acid (HCN, the form used by the Nazis, as "Zyklon B") and cyanogen chloride (deployed during World War I), which rapidly vaporize after detonation. Cyanogen chloride may cause some initial eye, nose, throat, and airway irritation, but otherwise its effects are the same as those of hydrocyanic acid and result from systemic cyanide toxicity.

Toxicology

Cyanide has a strong affinity for the ferric iron (Fe3+) of the heme ring and, thus, inhibits many heme-containing enzymes. Its primary effect in acute toxicity is inhibition of cytochrome a3, thereby interfering with normal mitochondrial oxidative metabolism in the electron transport chain, causing cellular anoxia and lactic acidosis. It may also interfere with other important enzymes, including succinic acid dehydrogenase and superoxide dismutase, which may underlie some of its chronic toxicity. In addition, cyanide is believed to be a direct neurotoxin contributing to an excitatory injury in the brain, probably mediated by glutamate stimulation of N-methyl D-aspartate receptors. The primary human enzyme, rhodanese, detoxifies cyanide by combining it with a sulfate moiety such as thiosulfate to form the relatively nontoxic thiocyanate ion, which is then excreted by the kidneys. Therefore, exposure to a potentially lethal dose of cyanide that occurs slowly though continually over time may be tolerated, making it relatively unique among the agents of chemical terrorism.

Clinical Presentation

Clinical manifestations of cyanide toxicity vary considerably depending on dose, route of exposure, and acuteness of exposure but in general reflect the effects of cellular anoxia on organ systems. Thus, the most metabolically active tissues, the brain and heart, tend to be the most affected. With exposure to low concentrations of vapor, early findings include tachypnea and hyperpnea, tachycardia, flushing, dizziness, headache, diaphoresis, nausea, and vomiting. As exposure continues, symptoms may progress to those associated with exposures to high concentrations of vapor. The latter include rapid onset (within 15 seconds) of tachypnea and hyperpnea, followed by seizures (30 seconds), coma and apnea (2-4 minutes), and cardiac arrest (4-8 minutes). "Classical" signs of cyanide poisoning include severe dyspnea without cyanosis—or even with cherry-red skin (caused by lack of peripheral oxygen use)—and may have a bitter almond odor to breath and body fluids. However, some patients do develop cyanosis (likely secondary to shock), and only about half the population is genetically capable of detecting the cyanide-induced bitter almond odor. Laboratory abnormalities in cyanide poisoning include metabolic acidosis with a high anion gap and increased serum lactate and an abnormally high mixed venous oxygen saturation (also caused by decreased use of peripheral oxygen). Lactate levels greater than or equal to 8 mmol/L with clinical suspicion is highly sensitive for the diagnosis of cyanide poisoning. Blood cyanide levels can be determined but not usually on an emergent basis.

In an aerosol attack using recognized military chemical weapons, if people are convulsing or dying within minutes of exposure, the weapon is likely to be either cyanide or a nerve agent. Although the symptoms of exposure to cyanide and nerve agents may be hard to distinguish, when there are high concentrations of cyanide, seizures begin within seconds and death within minutes, generally with little cyanosis or other findings. The course for lethal nerve agent

toxicity is characteristically somewhat longer and accompanied by copious nasal secretions, miotic pupils, muscle fasciculation, and cyanosis before death.

Treatment

Management of cyanide poisoning begins with removing the victim from the contaminated environment to fresh air. Dermal decontamination is rarely necessary because these agents are so volatile, but in case of contact with liquid agent, wet clothing should be removed and underlying skin washed.

Basic supportive intensive care is critical, including providing 100% oxygen, mechanical ventilation as needed, and circulatory support with crystalloid and vasopressors; correcting metabolic acidosis with IV sodium bicarbonate; and controlling seizures with benzodiazepines. Symptomatic patients, especially those who have lost consciousness or have other severe manifestations, may benefit further from antidotal therapy, which include hydroxycobalamin (Cyanokit), amyl nitrite, sodium nitrite, and sodium thiosulfate. Hydroxycobalamin is a relatively new medication approved by US Food and Drug Administration in 2006 as a cyanide antidote. Although there is no randomized clinical study to show its superiority to the combination treatment of nitrite and sodium thiosulfate, it is widely accepted as the first line of cyanide poisoning because of its safety, simplicity of administration, and efficacy based on case series, clinical trial, and animal studies. The cobalt ion in hydroxycobalamin combines with cyanide and forms cyanocobalamin (vitamin B_{12}), which has low toxicity and is excreted in urine. For adults, an initial dose of 5 g of hydroxycobalamin is given over 15 minutes, and second dose of 5 g can be given depending on clinical response. In children, 70 mg/kg is the recommended dose. It can cause increased blood pressure, allergic reaction, and reddish discoloration of skin, urine, and plasma. This blood color change may affect some of common lab tests including creatinine, lactate, AST, ALT, bilirubin and magnesium for 24-48 hours, and may lead to false alarm of blood leak on hemodialysis machines. Hydroxycobalamin can be given as a solo antidote, but the combination with sodium thiosulfate may have synergistic effects. It is recommended to give hydroxocobalamin first followed by sodium thiosulfate, and avoid giving them through the same IV line or at the same time as thiosulfate can block hydroxycobalamin effect. Sodium thiosulfate will provide a sulfur donor, which is used as substrate by the thiosulfate sulfurtransferase (rhodanese enzyme) for conversion to thiocyanate. Thiocyanate can be toxic to patients with renal failure, causing abdominal pain, vomiting, rash, and CNS dysfunction, but in general it is much less toxic than cyanide. The usual dose for adults is 50 mL of a 25% solution either bolus or infusion over 10 to 30 minutes. The recommended pediatric dosage of thiosulfate is 1 mL (of the standard 25% solution)/kg, IV (with a maximal, or adult, dose of 50 mL).

Hydroxycobalamin, with or without sodium thiosulfate, is the preferred treatment in most of the cases, but when hydroxycobalamin is not available, classic cyanide antidote kit (amyl nitrite, sodium nitrite, and sodium thiosulfate) may need to be used. First, a methemoglobin-forming agent is administered, typically inhaled amyl nitrite or IV sodium nitrite, because methemoglobin has a high affinity for cyanide and dissociates it from cytochrome oxidase. However, nitrite administration can be hazardous, because it may cause hypotension, and overproduction of methemoglobin may compromise oxygen-carrying capacity. Thus, nitrite is probably not indicated for mild symptoms or if the diagnosis of cyanide poisoning is uncertain. Furthermore,

people with cyanide poisoning who may have concomitant hypoxic insult (eg, most victims of smoke inhalation) probably are not good candidates for nitrite therapy. Optimal nitrite dosing, especially when given parenterally, depends on body weight and hemoglobin concentration, which is of particular importance in pediatric patients, who have a broad range of hemoglobin concentrations. In the prehospital setting, or whenever IV access is not possible, amyl nitrite may be used to begin nitrite therapy. Amyl nitrite is provided in glass pearls, which are used by crushing the pearl and then either allowing spontaneous inhalation or introducing the vapor into a ventilation circuit, for 30 seconds of each minute. As soon as IV access is established, sodium nitrite may be given. The recommended pediatric dosage, assuming a hemoglobin concentration of 12 g/dL, is 0.33 mL (of the standard 3% solution)/kg, given slowly by IV infusion over 5 to 10 minutes (with a maximal, or adult, dose of 10 mL). Dosing may be adjusted for patients with significant anemia, although this would not likely be known in emergent treatment of a poisoned child in critical condition. Amyl and sodium nitrite have the potential to put the fetus of a pregnant woman at serious risk. In addition, there is increased vulnerability of infants and young children, those with active respiratory disease or diminished pulmonary reserve as well as those who have cardiovascular disease, particularly the elderly or frail, to increased methemoglobin levels (especially if combined with carbon monoxide exposure). If there is concern that a patient is not oxygenating well, such as in smoke exposure, consider going directly to hydroxocobalamin or sodium thiosulfate.

The second step of this classic antidote kit is sodium thiosulfate, as mentioned above. Thiosulfate treatment itself is believed efficacious and relatively benign, and thus it may be used alone empirically in cases in which the diagnosis is uncertain. This approach has also been recommended, for example, in the management of the situation described above of cyanide toxicity complicating smoke inhalation, with likely concomitant lung injury and carbon monoxide poisoning.

Both sodium nitrite and sodium thiosulfate may be given a second time at up to half the original dose as needed, or in the case of thiosulfate, even a full dose would be unlikely to pose inherent toxicity.

VESICANTS

The term “vesicant” is commonly applied to chemical agents that cause blistering of the skin. Direct contact with these agents can also result in damage to the eyes and respiratory system. Systemic absorption may affect the GI tract, hematologic system, and CNS as well.

The 4 compounds historically included in this category—sulfur mustard, the nitrogen mustards, lewisite, and phosgene oxime—were all manufactured initially as potential chemical warfare agents. Phosgene oxime is technically not a true vesicant, because the skin lesions it causes are urticarial as opposed to vesicular. The nitrogen mustards, although first synthesized in the 1930s for anticipated battlefield use, were found to be less effective for chemical warfare than the already existing sulfur mustard. Subsequent development for of nitrogen mustards for weapons use was, therefore, largely abandoned. However, one form of nitrogen mustard, HN2, became a highly used and effective chemotherapeutic agent. Lewisite was first synthesized during the latter part of World War I, but other than reports of its use by Japan against China between 1937 and 1944, it is not known to have ever been used on the battlefield. An antidote, British

antilewisite (BAL, or dimercaprol), can minimize its effects if given promptly. Because so little is known about the toxicity and mechanisms of action of phosgene oxime and lewisite, and because anticipated medical management issues of these agents are somewhat similar, the following section focuses on the clinical effects and management issues regarding sulfur mustard exposure—historically the most frequently used and available of this class of chemical agent.

Sulfur mustard has been the most widely used of all chemical warfare agents over the last century. Approximately 80% of chemical casualties in World War I were attributable to sulfur mustard, and its use has been verified in multiple military conflicts since then. In addition, Iraq used sulfur mustard on numerous occasions during its war against Iran from 1980 to 1988 and as a weapon of terror against thousands of Kurdish civilians, including children, in aerially dispersed mustard bombs in 1988. Commercial fisherman's dermal exposure to liquid sulfur mustard attributable to artillery shells dredged from the sea reported in Massachusetts in 2012 reminds us its lengthy persistence in the environment because of its poor water solubility and low volatility.

Sulfur mustard is not difficult to manufacture, making it even more favorable for use by terrorists. In addition to its accessibility and ease of production, several other factors enhance its suitability as a terrorist or warfare agent. Although mortality associated with sulfur mustard is considerably lower than that caused by other chemical weapons such as nerve agents, sulfur mustard exposure results in significant and prolonged morbidity that may potentially overwhelm health care resources. The risk of direct contamination either from patient contact or from the agent's persistence in the environment may force health care providers to wear bulky protective gear, which makes it difficult to administer care, particularly to children. Although tissue damage occurs within minutes of exposure, clinical symptoms are delayed for hours, potentially rendering the victim ignorant of exposure until the opportunity for effective decontamination has passed. Lastly, unlike the case for lewisite, there is no known antidote for sulfur mustard exposure.

Characteristics

Sulfur mustard is an alkylating agent that is highly toxic to rapidly reproducing and poorly differentiated cells. Under normal environmental conditions, it is an oily liquid that varies in color from yellow to brown, depending on amounts and types of impurities. Its odor has been described as similar to garlic or to mustard itself. In warmer climates, mustard vapor is a particular concern because of its low volatility, but at lower temperatures (<14°C or 58°F); it becomes a solid and may persist in the environment for an extended time. On contact with tissue surfaces, mustard vapor or liquid is rapidly absorbed and exerts its cellular damage within minutes.

Clinical Effects

After exposure to sulfur mustard, skin findings may not appear for 2 to 48 hours, depending on the mode of exposure, the sensitivity of the individual, and the environmental conditions (see **Table 9.7: Clinical Effects from Sulfur Mustard Exposure**). The most common early sign in exposed areas is erythema resembling sunburn, which may coincide or even be preceded by significant pruritus. If the exposure is mild, this may be the only skin manifestation. More typically, yellowish blisters begin to form over the next 24 hours. Penetration of the agent is

enhanced by thin skin, warmth, and surface moisture, rendering areas such as the groin, axillae, and neck particularly susceptible. Once they appear, the vesicles frequently coalesce to form bullae. Although largely painless, these fragile bullae commonly rupture, resulting in painful ulcers that may take weeks or months to heal. The fluid from the blisters does not contain free mustard and is, therefore, not hazardous. If skin exposure has been severe, these earlier stages of developing lesions may be bypassed altogether with the direct appearance—albeit delayed—of skin sloughing similar to that seen in a full-thickness thermal burn.

Although skin findings may be dramatic, the organ most sensitive to mustard exposure is the eye, with mild symptoms occurring at concentrations 10-fold lower than those needed to produce effects on the skin. Like the skin findings, ocular symptoms are also delayed, but the delay is shorter than dermal symptoms. The first symptoms are usually pain and irritation, followed progressively by photophobia, worsening conjunctivitis, corneal ulceration, and perforation of the globe with severe exposures. Severe lid edema caused by inflammation of soft tissue around the eyes is also common.

Although visual impairment is common, it is usually transient and simply reflects eye closure from intense pain and reflex blepharospasm; at high concentration, exposure may cause corneal damage with ulceration and occlusion of conjunctival blood vessels.

With inhalation of mustard vapor, both the proximal and distal respiratory tract may be affected. Proximal involvement usually manifests after several hours and consists of rhinorrhea, hoarseness, a dry and painful cough with expectoration. With more significant inhalational exposures, necrosis of the airway mucosa can lead to a sterile tracheobronchitis with the necrotic epithelium forming pseudomembranes that may obstruct the airway.

Bacterial superinfection may develop as well, usually days later, facilitated by a weakened immune response. Respiratory failure can be the end result of either early mechanical obstruction from laryngospasm or pseudomembrane formation, or later by overwhelming bacterial infection enhanced by the denuded respiratory mucosa and necrotic tissue.

All cellular elements of the bone marrow can be affected by sulfur mustard because of its DNA alkylating effects, which impair replication in rapidly dividing stem cells. During the first few days after exposure, there may be a reactive leukocytosis that may or may not progress to leukopenia, depending on the level of exposure. When leukopenia happens, it reaches its minimum level around the ninth day.

GI symptoms can develop from the general cholinergic activity of sulfur mustard, resulting in nausea and vomiting that occurs after several hours and is rarely severe. Direct injury to the GI mucosa from ingestion of mustard either directly or from contaminated food or water can lead to a later onset of more severe vomiting, diarrhea, abdominal pain, and prostration.

Although historically a large percentage of battlefield victims have reported CNS findings such as lethargy, headaches, malaise, and depression, the role of the mustard agent itself in development of symptoms, as opposed to that of other environmental stressors, is unclear. Clinicians should be aware that, regardless of their etiology, these symptoms are a frequent

presentation. In addition, absorption of high doses of sulfur mustard can result in CNS hyperexcitability, convulsions, abnormal muscular activity, and coma.

Table 9.7: Clinical Effects from Sulfur Mustard Exposure

	Eyes	Skin	Respiratory Tract	Bone Marrow	GI	CNS
Minimal	Tearing, burning, mild conjunctivitis, photophobia	Erythema	Rhinorrhea, hoarseness, hacking cough	Reactive leukocytosis	Nausea, vomiting	Apathy, depression, anxiety
Moderate	Severe conjunctivitis with blepharospasm, lid edema	Blisters	Severe cough, expectoration, aphoria	Leukopenia (often preceded by leukocytosis)	As above	As above
Severe	Corneal edema, severe pain, ocular perforation	Deep burning with full-thickness skin loss	Dyspnea, pulmonary edema, asphyxia, bronchopneumonia	Severe leukopenia, aplastic anemia	Later nausea, vomiting (possible bloody), diarrhea	Agitation, hyper-excitability, abnormal muscular activity, coma

Treatment

The most effective treatment is decontamination, because once sulfur mustard penetrates tissues, its effects are irreversible. Unfortunately, sulfur mustard is rapidly absorbed on contact, usually exerting damage within 3 to 10 minutes of exposure. Effectiveness of decontamination is, therefore, extremely time dependent. Self-decontamination may be the quickest method and should include removing clothing and physically eliminating any mustard residue on the skin.

Anyone providing aid to an exposed person should take proper precautions including ocular, respiratory, and skin protection, ideally with a chemical protection overgarment, rubber boots, and gloves. Exposed individuals should be washed with soap and warm water, or just rinsed with water, as soon as possible. If water supply is limited, applying adsorbent powders such as flour and talcum powder, and then wiping off with a moist towel or rinsing with limited amount of water is another option. Regardless of decontamination method, the most important aspect is speed. Although ideally, all victims should be decontaminated before entering a medical treatment facility, if exposed individual arrive via personal transportation or on foot, they may first need to be taken to a separate area for decontamination. Even if delayed, decontamination should be performed to protect others from exposure, to avoid further absorption, and to prevent spread to other areas of the body.

After decontamination and basic life-support issues and other life-threatening concomitant injuries have been addressed, it is important to remain aware of the latency of most symptoms of vesicant exposure. Even if no symptoms are seen at presentation, exposed patients should be observed for at least 8 hours before being discharged. Because of the lack of a specific antidote, the remainder of therapy is supportive.

Skin lesions are treated similarly to those of burn victims. However, fluid losses tend to be less. For this reason, traditional formulas for fluid replacement in burn victims often overestimate losses in vesicant-exposed patients. Erythema and symptoms such as pruritus should be treated with topical and systemic analgesia and antipruritics, as well as soothing lotions such as calamine. Small vesicles (<2 cm) should be left intact, but larger vesicles and bullae should be incised and treated with frequent irrigation and topical application such as silver sulfadiazine (Flamazine) or mafenide acetate (sulfamylon). Widespread and severe partial or full-thickness involvement should be managed in a burn unit if possible. Skin grafting should be considered for full-thickness burns.

Eye treatment should center on removing the agent and on preventing scarring and infection. After irrigation of the eye with copious amounts of water, cyclopegic agents should be applied for comfort and to prevent formation of synechiae. Topical antibiotics should then be applied directly along with lubricating ointments, such as petroleum jelly, to the eyelids to prevent adhesions and subsequent scarring.

Mild respiratory symptoms involving the upper airway can be treated with cough suppressants, throat lozenges, and cool mist vapor. More severe lower respiratory involvement generally requires ventilation with positive end-expiratory pressure. The patient should be intubated promptly if there are any signs of laryngeal spasm or edema. Direct bronchoscopy may be necessary for removal of obstructive pseudomembranes. The temptation to use systemic antibiotics during the first 3 to 4 days despite the not uncommon findings of fever, leukocytosis, and cough should be avoided to prevent the growth of resistant organisms. However, if these signs and symptoms persist beyond this period and there is radiographic evidence of consolidation, systemic antibiotics may then be indicated. Bronchodilators such as beta agonists (eg, albuterol) and anticholinergics (eg, ipratropium) is shown to be helpful, and humidification or mucolytics such as n-acetylcysteine may be effective.

If anemia from bone marrow involvement is severe, blood transfusions may be of benefit. Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) should be considered in severe leukopenia. Bone marrow transplantation can be considered in extreme cases.

PULMONARY AGENTS

Toxic industrial chemicals used as terrorist weapons are a potentially significant threat to civilian populations. The Chemical Weapons Convention, a disarmament and nonproliferation treaty with 192 signatory countries, identifies 57 chemical and chemical precursors that can be used as weapons. Although some of the chemicals are well-known weapons (eg, sarin, VX, sulfur mustard), others are more familiar as common industrial chemicals such as chlorine, phosgene, and others. In the United States today, millions of tons of these chemicals are manufactured yearly for the production of dyes, textiles, medicines, insecticides, solvents, paints, and plastics.

The potential terrorist threat posed by industrial chemicals is well known. Huge industrial productions of these agents and often nonsecured storage and transport make it easy target for terrorists. In fact, there are many incidental exposures to pulmonary irritants reported, and multiple insurgents with chlorine use in Iraqi were acknowledged. Although of clear interest to

terrorist groups, traditional nerve agents require a greater degree of technical sophistication to manufacture and deliver as weapons.

Chlorine and Phosgene

Pathophysiology/Clinical Effects

Pulmonary irritants include wide variety of chemicals that destroy mucosal barrier of the respiratory tract via different mechanisms that cause respiratory failure. Chlorine and phosgene are 2 major pulmonary irritants, used excessively in World War I, but there are many other pulmonary irritants such as ammonia, hydrogen chloride, hydrogen sulfide, nitrous oxide, ozone, etc. When inhaled into the lung, these agents cause damage to both type I and type II pneumocytes, followed by the release of inflammatory cytokines release, disruption of the integrity of the lung's alveolar-capillary barrier, and collection of cellular debris and plasma exudate in alveolar space. These are characteristic features of ARDS (acute respiratory distress syndrome).

Whether victims present with upper respiratory tract symptoms (naso-oropharyngeal pain, cough, hoarseness, drooling, inspiratory stridor, cough, edema) or with lower respiratory tract symptoms (tracheobronchitis, bronchiolitis, bronchospasm, ARDS) depends on water solubility, density of the gas, detection threshold, and duration of exposure. In general, water-soluble substances (eg, ammonia) cause immediate irritation and discomfort at oral, nasal, and ocular mucosa. This discomfort motivates people to escape from the exposure and results in reduced toxicity and limited upper airway symptoms. On the other hand, poorly water-soluble gas (eg, phosgene) tends to cause delayed irritation, prolonged exposure, and lower lung injury, and ARDS. The most characteristic and serious complication of pulmonary irritants is ARDS, which can be delayed and may not be apparent on presentation. Radiologic signs of ARDS often lag behind clinical symptoms. Pulmonary edema may be exceptionally profuse; in a study from the 1940s, pulmonary sequestration of plasma-derived fluid could reach volumes of up to 1 L/hour. This problem may be exceptionally profound in children, who have less fluid reserve and are at increased risk of rapid dehydration or frank shock from pulmonary edema. Additionally, because children have a faster respiratory rate, there is exposure to a relatively higher toxic dose.

Chlorine

Chlorine is a greenish-yellow gas that is denser than air and, therefore, settles closer to the ground and in low-lying areas. This may have significant consequences for small children and infants, who would be exposed to higher concentrations of the vapor and thus receive higher inhaled doses of the agent. Chlorine has a strong, pungent odor that most people associate with swimming pools. Because the odor threshold (at 0.08 ppm) is less than the toxicity threshold, the odor may warn individuals that exposure is occurring.

The initial complaints in chlorine exposure may be either intense irritation or the sensation of suffocation, or both. Low-level exposures to chlorine result in mucosal irritation of the eyes, nose, and upper airways. Higher doses lead to respiratory symptoms that progress from choking and coughing to hoarseness, aphonia, and stridor—classically upper respiratory tract symptoms. Dyspnea after chlorine exposures indicates damage to lower respiratory tract and incipient pulmonary edema.

Phosgene

Phosgene was estimated to have caused approximately 80% of the 100,000 poison gas deaths in World War I. Like chlorine, phosgene is also heavier than air, thus posing an increased risk for children who are exposed. Phosgene itself is colorless, but associated condensation of atmospheric water produces a dense white cloud that settles low to the ground. It has the characteristic odor of newly mown hay. However, the odor threshold for phosgene (at 1.5 ppm) is higher than the toxicity threshold, and unlike the case with chlorine, detection of the odor would be inadequate and too late to serve as a warning against toxic exposure. In addition, phosgene's aroma of fresh hay may not trigger immediate evacuation from the scene.

Phosgene is primarily associated with the development of pulmonary edema. Because in low to moderate doses, it does not cause the mucosal irritation in upper airway, the significance of the exposure may be underestimated. Exposure to progressively higher doses produces mild cough, sneezing, and other effects. Dyspnea is seldom present initially except when doses have been massive; instead, there is a clinically asymptomatic, or latent, period usually of several hours and inversely correlated with dose. The delay can be up to 24 hours, so prolonged observation is necessary. Dyspnea and associated clinical deterioration have in several instances been triggered by slight to moderate exertion.

Treatment

Decontamination

Decontamination consists primarily of removing the victim from the source of the pulmonary agent to fresh air. For first responders such as paramedics and fire-rescue workers, PPE with self-contained breathing apparatus is required; however, because the gases are volatile, cross-contamination is unlikely. Victims of chlorine exposure may require copious water irrigation of the skin, eyes, and mucosal membranes to prevent continued irritation and injury.

Management

Management is primarily supportive; there are no antidotes or specific postexposure treatments for inhalational agents. Victims should be observed and monitored for development of respiratory symptoms, including pulmonary edema. Most deaths are attributable to respiratory failure and usually occur within the first 24 hours. Because of the delay in onset of pulmonary edema, prolonged observation of victims of phosgene and chlorine attacks is warranted.

Treatment of upper respiratory tract symptoms involves administering warm, moist air and supplemental oxygen, and treating bronchospasm either produced de novo by the toxicant in normal airways or resulting from toxicant-induced exacerbation of airway hyperresponsiveness in individuals with underlying pathology such as asthma or reactive airways. Aggressive bronchodilator therapy with beta-agonists is appropriate. The value of corticosteroids is inconclusive because of relative lack of well-structured studies, but they may be efficacious in victims with severe bronchospasm or a history of asthma. Steroids should be used early in the course as they are associated with worse mortality with delayed use after 14 days. Nebulized sodium bicarbonate, approximately 2%, as chemical neutralization for chlorine exposure did not show mortality benefit but was associated with small improvement of forced expiration volume.

IV or nebulized N-acetylcysteine is also suggested as a treatment option with some effects on animal study, but its clinical effectiveness is still unclear.

The possibility of laryngospasm should always be anticipated, and the necessity and timing of intubation carefully assessed. Associated central damage from inhaled particles of smoke in situations involving fire should also be considered. Pseudomembrane formation may lead to airway obstruction and may require bronchoscopic identification and removal of pseudomembranous debris. Necrotic debris from central damage provides an excellent culture medium for secondary bacterial colonization and infection, and bacterial superinfections are commonly seen 3 to 5 days after exposure. Early aggressive antibiotic therapy directed against culture-identified organisms is imperative. Prophylactic antibiotics are of no value.

Treatment of lower respiratory tract from pulmonary agents includes adequate oxygenation, establishment of effective intra-alveolar pressure gradients using positive end-expiratory pressure (for example, in conscious patients, with continuous positive airway pressure, or CPAP), and careful attention to fluid balance. The length of the latent period in a dyspneic patient can provide clinically valuable information about the intensity of exposure; patients who develop breathing difficulty within the first 4 hours after exposure may face a grave prognosis, and even patients with mild dyspnea, because of the timing of the dyspnea, may be candidates for urgent or priority evacuation. All patients at risk of pulmonary edema induced by pulmonary agents should be maintained on strict bed rest to avoid cardiopulmonary decompensation associated with exertion.

RIOT CONTROL AGENTS

Modern riot control agents comprise a heterogeneous group of chemical compounds that have been used widely around the world since the 1950s (see **Table 9.8: Riot Control Agents**). These agents have the ability to incapacitate at low aerosol concentrations and have a high safety ratio (ratio of lethal dose to effective dose). However, prolonged exposure or release in enclosed areas can intensify the physical effects of these agents. CS (2-chlorobenzylidene), CN (1-chloroacetophenone, Mace), and pepper spray (*Oleoresin capsicum*) are commercially available to the public in the United States.

Table 9.8: Riot Control Agents

Chemical Name	Abbreviated/Common Designation	Uses
2-Chlorobenzylidene	CS	Military, law enforcement, personal protection
1-Chloroacetophenone	CN (Mace)	Military, law enforcement, personal protection
Dibenzoxazepine	CR	Military
Oleoresin capsicum	Pepper spray	Military, law enforcement, personal protection
Diphenylaminearsine	DM	Military (rare)
Bromobenzylcyanide	CA	Military (rare)

Transmission and Pathogenesis

Mode of transmission varies by agent. Common means include spraying a solution, release of pressurized canisters, explosive dispersion (smoke "grenades"), and burning. Explosive modes of transmission may cause traumatic injuries in addition to the incapacitating effects. CS is very flammable and poses a fire hazard. Most agents disperse soon after release, although persistent forms of CS exist. Riot control agents may contaminate clothing, buildings, and furniture and may cause ongoing symptoms in continued or repeat exposure. When dispersed, riot control agents are chemical irritants of the skin and mucous membranes of the eyes, nose, mouth, airways, and GI tract. The active agent in pepper spray, capsaicin, interact on transient receptor potential vanilloid 1 (TRPV1) in nociceptors. Activation of TRPV1 receptors causes depolarization and pain, inflammatory response through release of neuropeptides. Bradykinin release and further inflammatory change are also involved in the response to the stimulation of these receptors. This mechanism causes pain, capillary leakage, and vasodilation.

Clinical Manifestations

Riot control agents have specific effects on the eyes, nose, mouth, and airway with variation in intensity depending on mode of exposure and agent used. Symptoms occur quickly after exposure and typically resolve in 1 to 2 hours once the victim has been removed from the agent. On contact, these agents induce eye burning, eye pain, tearing, conjunctival infection, blepharospasm, periorbital edema, and photophobia. Exposures at close range, particularly to exploding CS and CN grenades or canisters, may cause serious damage to the eye including corneal edema, conjunctival laceration, hyphemia, vitreous hemorrhage, and secondary glaucoma. Permanent effects such as cataracts and traumatic optic neuropathy may also be seen.

After dispersal of riot control agents, nasal burning and pain, copious rhinorrhea, and persistent sneezing begin along with oral irritation and salivation. Pulmonary effects include chest tightness and burning, bronchorrhea, bronchospasm, and coughing. Gagging, retching, and vomiting frequently accompany mucosal and airway irritation. Exposed skin stings and may progress to erythema, vesiculation, and bullae depending on the conditions of exposure; prolonged exposure, high ambient temperature, and humidity exacerbate skin effects. These manifestations may occur hours to days after exposure to CS. Skin exposed to CR may become painful in water for up to 2 days after exposure. CN and CS can cause allergic contact dermatitis in people who are repeatedly exposed.

Severe clinical effects from riot control agents are uncommon. Intense exposure to CS, CN, and pepper spray has caused laryngospasm, pneumonitis, bronchospasm, noncardiogenic pulmonary edema, respiratory arrest and even death. Often, the agent was released in an enclosed space, or the victim was not able to leave the vicinity of the agent. Individuals with asthma are predisposed to serious pulmonary symptoms. Prolonged reactive airway disease has also been described after exposure in a previously healthy person. In general, riot control agents are incapacitating but rarely lethal, especially relative to other deployable chemical agents such as the nerve agents, vesicants, and pulmonary agents.

Diagnosis

Some physical characteristics of the compounds can assist in detection when riot control agents are used. The most common agents (CS, CN, and pepper spray) are deployed in identifiable canisters. CS and pepper spray have a pungent pepper odor. CN has a flowery apple odor.

Differentiation of clinical effects caused by riot control agents from those of other chemicals can be a challenge during early management. Tearing, salivation, bronchorrhea, bronchospasm, and vomiting suggest the cholinergic effects of nerve agent exposure. Intense exposure to riot control agents with pneumonitis and pulmonary edema mimic symptoms of exposure to pulmonary agents, such as chlorine and phosgene. The potential for delayed skin effects, including vesiculation and bullae, with riot control agents makes them similar to vesicants such as sulfur mustard. However, symptoms rapidly resolve once contact with the agent ceases. Lack of progression to more severe symptoms such as bone marrow failure, paralysis, and seizures, combined with negative results from field detection systems and the physical characteristics, mentioned above, make identification of riot control agent release ultimately possible.

Treatment and Control

Decontamination requires that all victims be moved to a well-ventilated, uncontaminated space and have their outer clothing removed. Clothing should be double bagged to prevent secondary exposure. Medical treatment of riot control agent exposure focuses on ending contact, assessing for serious pulmonary effects, and addressing ongoing eye and skin irritation.

In most instances, clinical signs and symptoms resolve over 30 to 60 minutes, and specific medical treatment is not needed. Pulmonary effects may be delayed. Victims who exhibit prolonged dyspnea or have other objective lung findings should be admitted to a medical facility for ongoing monitoring and treatment.

All first responders should wear PPE including, but not limited to, a full-face gas mask, properly rated outer clothing, gloves, and boots. Field incident command should identify a hot zone, decontamination area, and cold zone. Ideally, decontamination should begin in the field and be complete before entry into a medical facility.

BIBLIOGRAPHY

CHEMICAL EVENTS

Borron SW. Introduction: Hazardous materials and radiologic/nuclear incidents: lessons learned? *Emerg Med Clin North Am*. 2015;33(1):1-11

Chung S, Baum CR, Nyquist A; American Academy of Pediatrics, Disaster Preparedness Advisory Council, Council on Environmental Health, Committee on Infectious Diseases. Policy statement. Chemical-biological terrorism and its impact on children. *Pediatrics*. 2020;145(2):e20193749

Chung S, Baum CR, Nyquist A; American Academy of Pediatrics, Disaster Preparedness Advisory Council, Council on Environmental Health, Committee on Infectious Diseases.

Technical report. Chemical-biological terrorism and its impact on children. *Pediatrics*. 2020;145(2):e20193750

Dolgin E. Syrian gas attack reinforces need for better anti-sarin drugs. *Nat Med.* 2013;19(10):1194-1195

Gulland A. Lack of atropine in Syria hampers treatment after gas attacks. *BMJ*. 2013;347:f5413

Kirk MA, Deaton ML. Bringing order out of chaos: effective strategies for medical response to mass chemical exposure. *Emerg Med Clin North Am*. 2007;25(2):527-548

Mackie E, Svendsen E, Grant S, Michels JE, Richardson WH. Management of chlorine gas-related injuries from the Graniteville, South Carolina, train derailment. *Disaster Med Public Health Prep*. 2014;8(5):411-416

Okumura T, Suzuki K, Fukuda A, et al. The Tokyo subway sarin attack: disaster management, Part 1: Community emergency response. *Acad Emerg Med*. 1998;5(6):613-617

Okumura T, Suzuki K, Fukuda A, et al. The Tokyo subway sarin attack: disaster management, Part 2: Hospital response. *Acad Emerg Med*. 1998;5(6):618-624

Okumura T, Suzuki K, Fukuda A, et al. The Tokyo subway sarin attack: disaster management, Part 3: National and international responses. *Acad Emerg Med*. 1998;5(6):625-628

Okumura T, Takasu N, Ishimatsu S, et al. Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med*. 1996;28(2):129-135

Rosman Y, Eisenkraft A, Milk N, et al. Lessons learned from the Syrian sarin attack: evaluation of a clinical syndrome through social media. *Ann Intern Med*. 2014;160(9):644-648

SPECIFIC PEDIATRIC VULNERABILITIES TO CHEMICAL AGENTS

Berger RE. Preparedness for acts of nuclear, biological, and chemical terrorism. In: American Academy of Pediatrics (AAP), American College of Emergency Physicians (ACEP), eds. *APLS The Pediatric Emergency Medicine Resource*. 5th ed. Burlington, MA: Jones & Bartlett Learning; 2012

Centers for Disease Control and Prevention. Chemical Agents Emergency Preparedness & Response. Available at: https://emergency.cdc.gov/agent/agentlistchem.asp. Accessed February 18, 2022

Chemical Hazards Emergency Medical Management - CHEMM. Available at: https://chemm.hhs.gov/. Accessed February 18, 2022

Chung S, Baum CR, Nyquist A; American Academy of Pediatrics, Disaster Preparedness Advisory Council, Council on Environmental Health, Committee on Infectious Diseases. Policy

statement. Chemical-biological terrorism and its impact on children. *Pediatrics*. 2020;145(2):e20193749

Chung S, Baum CR, Nyquist A; American Academy of Pediatrics, Disaster Preparedness Advisory Council, Council on Environmental Health, Committee on Infectious Diseases. Technical report. Chemical-biological terrorism and its impact on children. *Pediatrics*. 2020;145(2):e20193750

Kirk MA, Deaton ML. Bringing order out of chaos: effective strategies for medical response to mass chemical exposure. *Emerg Med Clin North Am*. 2007;25(2):527-548

Kirk M, Iddins CJ. Resources for toxicologic and radiologic information and assistance. *Emerg Med Clin North Am*. 2015;33(1):69-88

Moore BL, Geller RJ, Clark C. Hospital preparedness for chemical and radiological disasters. *Emerg Med Clin North Am*. 2015;33(1):37-49

Okumura T, Takasu N, Ishimatsu S, et al. Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med*. 1996;28(2):129-135

SALT mass casualty triage: concept endorsed by the American College of Emergency Physicians, American College of Surgeons Committee on Trauma, American Trauma Society, National Association of EMS Physicians, National Disaster Life Support Education Consortium, and State and Territorial Injury Prevention Directors Association. *Disaster Med Public Health Prep*. 2008;2(4):245-246

Scafone RJ. Biological and chemical terrorism. In: Shaw KN, Bachur RG, eds. *Fleisher & Ludwig's Textbook of Pediatric Emergency Medicine*. 7th ed. Philadelphia, PA: LWW; 2015

US Army Medical Center of Excellence. Available at: https://medcoe.army.mil/. Accessed February 18, 2022

US Army Medical Research Institute of Chemical Defense. Available at: https://usamricd.amedd.army.mil/Pages/default.aspx. February 18, 2022

Vogel L. WHO releases guidelines for treating chemical warfare victims after possible Syria attacks. *CMAJ*. 2013;185(14):E665

Zarocostas J. Syria chemical attacks: preparing for the unconscionable. *Lancet*. 2017;389(10078):1501

NERVE AGENTS

Ahmed SM, Das B, Nadeem A, Samal RK. Survival pattern in patients with acute organophosphate poisoning on mechanical ventilation: a retrospective intensive care unit-based study in a tertiary care teaching hospital. *Indian J Anaesth*. 2014;58(1):11-17

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(5):630-632

Buckley NA, Eddleston M, Li Y, Bevan M, Robertson J. Oximes for acute organophosphate pesticide poisoning. *Cochrane Database Syst Rev*. 2011;(2):CD005085

Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. *Lancet*. 2008;371(9612):597-607

Holstege CP, Kirk M, Sidell FR. Chemical warfare. Nerve agent poisoning. *Crit Care Clin*. 1997;13(4):923-942

Lawrence DT, Kirk MA. Chemical terrorism attacks: update on antidotes. *Emerg Med Clin North Am*. 2007;25(2):567-595

Lee EC. Clinical manifestations of sarin nerve gas exposure. *JAMA*. 2003;290(5):659-662

Okumura T, Takasu N, Ishimatsu S, et al. Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med*. 1996;28(2):129-135

Rotenberg JS, Newmark J. Nerve agent attacks on children: diagnosis and management. *Pediatrics*. 2003;112(3 Pt 1):648-658

Sidell FR, Borak J. Chemical warfare agents: II. Nerve agents. *Ann Emerg Med*. 1992;21(7):865-871

Worek F, Wille T, Koller M, Thiermann H. Toxicology of organophosphorus compounds in view of an increasing terrorist threat. *Arch Toxicol*. 2016;90(9):2131-2145

Zarocostas J. Syria chemical attacks: preparing for the unconscionable. *Lancet*. 2017;389(10078):1501

CYANIDE

Baud FJ, Borron SW, Bavoux E, Astier A, Hoffman JR. Relation between plasma lactate and blood cyanide concentrations in acute cyanide poisoning. *BMJ*. 1996;312(7022):26-27

Baud FJ, Borron SW, Mégarbane B, et al. Value of lactic acidosis in the assessment of the severity of acute cyanide poisoning. *Crit Care Med*. 2002;30(9):2044-2050

Bebarta VS, Pitotti RL, Dixon P, Lairet JR, Bush A, Tanen DA. Hydroxocobalamin versus sodium thiosulfate for the treatment of acute cyanide toxicity in a swine (Sus scrofa) model. *Ann Emerg Med*. 2012;59(6):532-539

Berlin CM. The treatment of cyanide poisoning in children. *Pediatrics*. 1970;46(5):793-796

Borron SW, Bebarta VS. Asphyxiants. *Emerg Med Clin North Am*. 2015;33(1):89-115

Hamad E, Babu K, Bebarta VS. Case Files of the University of Massachusetts Toxicology Fellowship: Does This Smoke Inhalation Victim Require Treatment with Cyanide Antidote? *J Med Toxicol*. 2016;12(2):192-198

Holstege CP, Kirk MA. Cyanide and hydrogen sulfide. In: Hoffman RS, Howland MA, Lewin N, eds. *Goldfrank's Toxicologic Emergencies*. 10th ed. New York, NY: McGraw-Hill Education/Medical; 2014

Marziaz ML, Frazier K, Guidry PB, Ruiz RA, Petrikovics I, Haines DC. Comparison of brain mitochondrial cytochrome c oxidase activity with cyanide LD(50) yields insight into the efficacy of prophylactics. *J Appl Toxicol*. 2013;33(1):50-55

Sauer SW, Keim ME. Hydroxocobalamin: improved public health readiness for cyanide disasters. *Ann Emerg Med*. 2001;37(6):635-641

Sutter M, Tereshchenko N, Rafii R, Daubert GP. Hemodialysis complications of hydroxocobalamin: a case report. *J Med Toxicol*. 2010;6(2):165-167

Streitz MJ, Bebarta VS, Borys DJ, Morgan DL. Patterns of cyanide antidote use since regulatory approval of hydroxocobalamin in the United States. *Am J Ther*. 2014;21(4):244-249

VESICANTS

Anderson DR, Holmes WW, Lee RB, et al. Sulfur mustard-induced neutropenia: treatment with granulocyte colony-stimulating factor. *Mil Med*. 2006;171(5):448-453

Balali-Mood M, Hefazi M. The pharmacology, toxicology, and medical treatment of sulphur mustard poisoning. *Fundam Clin Pharmacol*. 2005;19(3):297-315

Barranco VP. Mustard gas and the dermatologist. *Int J Dermatol*. 1991;30(10):684-686

Borak J, Sidell FR. Agents of chemical warfare: sulfur mustard. *Ann Emerg Med*. 1992;21(3):303-308

C. Dacre J, Goldman M. Toxicology and pharmacology of the chemical warfare agent sulfur mustard - a review. *Pharmacol Rev*. 1996;48(2):289-326

Davis KG, Aspera G. Exposure to liquid sulfur mustard. *Ann Emerg Med*. 2001;37(6):653-656

Jenner J, Graham SJ. Treatment of sulphur mustard skin injury. *Chem Biol Interact*. 2013;206(3):491-495

Kehe K, Szinicz L. Medical aspects of sulphur mustard poisoning. *Toxicology*. 2005;214(3):198-209

McManus J, Huebner K. Vesicants. *Crit Care Clin*. 2005;21(4):707-718

Momeni AZ, Aminjavaheri M. Skin manifestations of mustard gas in a group of 14 children and teenagers: a clinical study. *Int J Dermatol*. 1994;33(3):184-187

US Army Medical Center of Excellence. Available at: https://medcoe.army.mil/. Accessed February 18, 2022

Weibrecht K, Rhyee S, Manuell ME, et al. Sulfur mustard exposure presenting to a community emergency department. *Ann Emerg Med*. 2012;59(1):70-74

PULMONARY AGENTS

Borak J, Diller WF. Phosgene exposure: mechanisms of injury and treatment strategies. *J Occup Environ Med*. 2001;43(2):110-119

Clark KA, Chanda D, Balte P, et al. Respiratory symptoms and lung function 8-10 months after community exposure to chlorine gas: a public health intervention and cross-sectional analysis. *BMC Public Health*. 2013;13:945

de Lange DW, Meulenbelt J. Do corticosteroids have a role in preventing or reducing acute toxic lung injury caused by inhalation of chemical agents? *Clin Toxicol (Phila)*. 2011;49(2):61-71

Grainge C, Rice P. Management of phosgene-induced acute lung injury. *Clin Toxicol (Phila)*. 2010;48(6):497-508

Gutch M, Jain N, Agrawal A, Consul S. Acute accidental phosgene poisoning. *BMJ Case Rep*. 2012;2012

Hardison LS, Wright E, Pizon AF. Phosgene exposure: a case of accidental industrial exposure. *J Med Toxicol*. 2014;10(1):51-56

Jones R, Wills B, Kang C. Chlorine gas: an evolving hazardous material threat and unconventional weapon. *West J Emerg Med*. 2010;11(2):151-156

Lehavi O, Leiba A, Dahan Y, et al. Lessons learned from chlorine intoxications in swimming pools: the challenge of pediatric mass toxicological events. *Prehosp Disaster Med*. 2008;23(1):90-95

Nelson LS, Odujebe OA. Simple asphyxiants and pulmonary irritants. In: Hoffman RS, Howland MA, Lewin N, eds. *Goldfrank's Toxicologic Emergencies*. 10th ed. New York, NY: McGraw-Hill Education/Medical; 2014

US Army Medical Center of Excellence. Available at: https://medcoe.army.mil/. Accessed February 18, 2022

Van Sickle D, Wenck MA, Belflower A, et al. Acute health effects after exposure to chlorine gas released after a train derailment. *Am J Emerg Med*. 2009;27(1):1-7

RIOT CONTROL AGENTS

Billmire DF, Vinocur C, Ginda M, et al. Pepper-spray-induced respiratory failure treated with extracorporeal membrane oxygenation. *Pediatrics*. 1996;98(5):961-963

Blain PG. Tear gases and irritant incapacitants. 1-chloroacetophenone, 2-chlorobenzylidene malononitrile and dibenz[b,f]-1,4-oxazepine. *Toxicol Rev*. 2003;22(2):103-110

Rothenberg C, Achanta S, Svendsen ER, Jordt S-E. Tear gas: an epidemiological and mechanistic reassessment. *Ann N Y Acad Sci*. 2016;1378(1):96-107

Schep LJ, Slaughter RJ, McBride DI. Riot control agents: the tear gases CN, CS and OC-a medical review. *J R Army Med Corps*. 2015;161(2):94-99

Smith J, Greaves I. The use of chemical incapacitant sprays: a review. *J Trauma*. 2002;52(3):595-600

US Army Medical Center of Excellence. Available at: https://medcoe.army.mil/. Accessed February 18, 2022