REVIEW ARTICLE

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Hazardous Chemical Emergencies and Poisonings

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This article was updated on April 25, 2019, at NEJM.org.

N Engl J Med 2019;380:1638-55.
DOI: 10.1056/NEJMra1504690

Hazardous chemical emergencies and related poisonings result from various exposures, including inadvertent residential, industrial, occupational, or transportation mishaps; natural disasters; and hazardous-substance releases that are intended to cause harm.[1-3] Up to 100,000 industrial chemicals are used each day in the United States,[4] and federal authorities estimate that more than 10,000 potentially consequential releases of hazardous substances occur annually.[4,5] In addition, numerous compounds have been developed primarily as military weapons, with exceedingly high toxicity.[6-8] Both toxic industrial chemicals and military chemical weapons are capable of causing mass casualties in a substantive release and may be deployed intentionally in the context of chemical terrorism,[8-10] targeted assassination attempts,[8,11,12] or wartime attacks on civilian populations, as tragically shown in the current Syrian war.[13,14]

A toxidrome-based, emergency medical systems (EMS) approach to chemical weapons attacks was presented recently by Ciottone in the *Journal*.[8] (Toxidromes are constellations of clinical signs, particularly vital signs, mental status, and ocular, respiratory, neurologic, and skin findings, that are characteristic of general classes of poison.) A similar approach is useful for the myriad possible entities in nonintentional hazardous chemical incidents. We review the toxicology and hospital-based management of acute poisonings caused principally by dermal and inhalational exposure to several representative chemical-agent classes in incidents involving the release of hazardous substances or chemical attacks (Table 1). Cyanide and organophosphate poisonings are emphasized, since they can also affect individual patients in the more familiar contexts of occupational and residential exposures or ingestions with suicidal intent and since specific emergency antidotal therapy is crucial for good outcomes.

Overview of Hospital-Based Emergency Management

Incidents involving the release of hazardous chemicals may result in widespread chaos and confusion, affecting the EMS response and emergency department (ED) care.[2,8] A rapid influx of multiple critically ill victims with unfamiliar illnesses, as well as numerous low-risk but understandably anxious patients, potentially far outnumbering the seriously ill,[1] poses significant challenges to hospital-based emergency care providers. Patients may bypass prehospital care and arrive at the hospital unaware of or misinformed regarding the cause of their symptoms, with the potential to chemically contaminate bystanders and staff.[2,15-17] Thus, prompt recognition of the chemical event is important so that ED staff and hospital emergency management personnel can secure hospital entrances and decontaminate contami-

nated patients before they enter the ED, assisted as needed by providers garbed in appropriate personal protective equipment.

Consensus guidelines for hospital-based decontamination techniques and personal protective equipment are available.[18-21] Decontamination of skin, eyes, and wounds minimizes the risk of contact injury, reduces the dose that patients absorb, and improves their health outcomes, while reducing the risk of secondary contamination. Briefly, contaminated clothing is immediately removed and safely disposed of, followed by high-volume, low-pressure flushing of hair and skin with tepid water in most cases (exposure to reactive metals is one exception); gentle washing with liquid soap, water, and nonabrasive sponges or washcloths; and active drying. This approach has recently been validated in a simulation study with volunteers.[22]

Ocular decontamination is effected by removal of contact lenses (if present) and immediate, copious irrigation with balanced salt solution, lactated Ringer's solution, saline, or water.[23,24] Irrigation may be facilitated with the use of local anesthetic drops and Morgan lenses (contact lenses connected to tubing, allowing copious irrigation), if available, but should not be postponed in order to obtain these adjuncts. It is generally recommended that hospital decontamination teams don level C personal protective equipment, consisting of a hooded, chemical-resistant body suit with a face shield, air-purifying respirator, and double layers of chemical-resistant gloves and boots[18] (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Critically ill patients require immediate resuscitation before or concurrently with decontamination. Resuscitation, which is performed by emergency personnel wearing personal protective equipment, includes airway, breathing, and circulatory support (the ABCs), with empirical antidotal therapy provided when indicated. Additional treatment, such as anticonvulsant or other medications needed to maintain physiological homeostasis, is provided as soon as possible.

Chemical disasters pose a considerable risk of psychic trauma, and hospital management should include early involvement of mental health and risk-communication resources.[25,26] Victims may include children, pregnant women, and the elderly, raising additional concerns.[27,28] In particular, several physiological and developmental factors may increase the susceptibility of young children to poisoning and affect management (e.g., assistance with decontamination may be required, family separation issues need to be addressed, and antidote choices, formulations, and delivery devices must be considered carefully, with size-based dosing).[9,29,30]

An accurate history or laboratory confirmation of substances released may not be immediately available, forcing providers to make initial clinical decisions on the basis of incomplete or inaccurate information.[2,8] To help focus the initial evaluation and treatment in such cases, it is customary to look for a toxidrome.[2,8,31,32] A toxidrome nomenclature developed by the U.S. Department of Homeland Security and the National Library of Medicine is especially relevant to chemical incidents[33] (Table S1 in the Supplementary Appendix). Recognition of the characteristic features of opioid, cholinergic, and knockdown (asphyxiant) toxidromes may prompt hospital-based, empirical antidote administration. Routine hospital laboratory tests, including measurements of blood glucose, electrolytes, and lactate, as well as blood gas analysis and hemoglobin speciation, can help narrow the differential diagnosis. Just-in-time clinical guidance is also available from consultant medical toxicologists, regional poison control centers (telephone number, 800-222-1222), and internet-accessible tools such as the National Library of Medicine's Chemical Hazards Emergency Medical Management (CHEMM) website.[34] Ultimately, clinical or environmental laboratory results may confirm the responsible chemicals and allow for more targeted treatment and post-event communications.

TOXICOLOGIC PRINCIPLES

Chemicals exert toxicity primarily by reacting with specific target cellular macromolecules or creating critical alterations in the cellular microenvironment, leading to altered cellular function, structural injury, or damaged genetic material.[35] Clinical effects depend on several factors, including intrinsic toxicity, physical state, exposure route, and dose (with the dose–response principle, though oversimplified, stating that the amount of absorbed poison generally correlates

Table 1. Representative Hazardous Chemicals.*

Agent Class and Examples	Likely Contexts†‡	Primary Toxicologic Effects	Toxidrome	Laboratory Findings	Treatment Overview
Primary respiratory irritants					
High water solubility					
Ammonia, sulfur dioxide, hydrogen chloride	Hazmat, occupational, residential	Acid or base generation, cytotoxic injury, oxidant formation, inflammatory cascade	Irritant or corrosive (respiratory: central lung)	Potential hypoxemia	Remove from exposure; perform ABCs; decontaminate skin, eyes; supportive care
Intermediate water solubility					
Chlorine	Hazmat, occupational, residential, CWA	HCl generation; cytotoxic injury, oxidant formation, inflammatory cascade	Irritant or corrosive (respiratory: central and peripheral lung)	Potential hypoxemia	Remove from exposure; perform ABCs; decontaminate skin, eyes; supportive care
Low water solubility					
Oxides of nitrogen	Occupational (silo-filler's disease)	Cytotoxic injury, oxidant formation, inflammatory cascade	Irritant or corrosive (respiratory: peripheral lung)	Potential hypoxemia	Supportive care
Phosgene	Occupational, CWA	HCl generation; cytotoxic injury, oxidant formation, inflammatory cascade	Irritant or corrosive (respiratory: peripheral lung)	Potential hypoxemia	Supportive care
Vesicants					
Sulfur mustard	CWA, occupational	Alkylating agent; cytotoxic injury to skin, lung, mucous membranes of the eye, nose, and respiratory tract; "radiomimetic" systemic toxic effects	Irritant or corrosive (ocular, skin, lung injury; systemic effects, such as bone marrow suppression, with severe exposure)	Potential hypoxemia, neutropenia in severe cases	Decontaminate skin, eyes; supportive care; granulocyte colony-stimulating factor for neutropenia (typical dose, 5 μg/kg/day subcutaneously; hematology–oncology consultation recommended)
Asphyxiants					
Simple					
Methane, propane, nitrogen, helium, xenon, and other noble gases	Hazmat, occupational, residential	Displacement of oxygen	Knockdown (asphyxiant)	Low arterial oxygen pressure and saturation	Remove from exposure, perform ABCs, provide 100% oxygen
Carbon dioxide	Occupational, natural disaster	Displacement of oxygen, plus direct systemic effects (e.g., CNS depression, hyperventilation)	Knockdown (asphyxiant)	Low arterial oxygen pressure and saturation, with or without hypercarbia	Remove from exposure, perform ABCs, provide 100% oxygen
Systemic					

Methemoglobin inducers (e.g., nitrites and nitrates, products of combustion, multiple medications)	Hazmat, occupational, smoke from house fire, self-inflicted, adverse drug reaction	Methemoglobin induction, resultant interference with hemoglobin oxygen binding, leftward shift of oxyhemoglobin dissociation curve	Knockdown (asphyxiant); cyanosis unresponsive to oxygen administration	Normal arterial oxygen pressure and saturation (calculated), with or without metabolic acidosis, hyperlactatemia; elevated methemoglobin	Remove from exposure, perform ABCs, provide 100% oxygen; antidote: methylene blue (1–2 mg/kg IV, given slowly over a period of 5 min; may repeat in 30–60 min as needed)
Carbon monoxide	Hazmat, occupational, smoke from house fire, residential, self-inflicted	Carboxyhemoglobin production, resultant interference with hemoglobin binding, leftward shift of oxyhemoglobin dissociation curve, mitochondrial cytochrome oxidase inhibition	Knockdown (asphyxiant)	Normal arterial oxygen pressure and saturation (calculated), with or without metabolic acidosis, hyperlactatemia; elevated carboxyhemoglobin	Remove from exposure, perform ABCs, provide 100% oxygen; consider HBO‡
Cyanide	Hazmat, occupational, smoke from house fire, self-inflicted, adverse drug reaction, CWA	Mitochondrial cytochrome oxidase inhibition	Knockdown (asphyxiant) plus irritant	Normal arterial oxygen pressure and saturation (mild cases); elevated venous oxygen saturation; metabolic acidosis, hyperlactatemia; elevated blood cyanide level§	Remove from exposure, perform ABCs, provide 100% oxygen; correct acidosis; consider GI decontamination for ingested cyanogenic compounds; consider HBO; antidotes: hydroxocobalamin, sodium nitrite, sodium thiosulfate‡
Hydrogen sulfide	Occupational, natural disaster, self-inflicted, CWA	Mitochondrial cytochrome oxidase inhibition	Knockdown (asphyxiant) plus irritant	Normal arterial oxygen pressure and saturation (mild cases); elevated venous oxygen saturation; metabolic acidosis, hyperlactatemia	Remove from exposure (PPE for rescuers), perform ABCs, provide 100% oxygen, correct acidosis; consider HBO; antidotes: sodium nitrite, hydroxocobalamin (same dosing as for cyanide)‡
Cholinergic agents					
Organophosphate and carbamate insecticides	Hazmat, occupational, residential, self-inflicted	Cholinesterase inhibition at neural synapses	Cholinergic (muscarinic, nicotinic, CNS)	Low red-cell cholinesterase and serum cholinesterase levels§	Remove from exposure; decontaminate skin, eyes (PPE for providers); consider GI decontamination, as needed; antidotes: atropine, pralidoxime
Military nerve agents	CWA	Cholinesterase inhibition at neural synapses	Cholinergic (muscarinic, nicotinic, CNS)	Low red-cell cholinesterase and serum cholinesterase levels§	Remove from exposure; decontaminate skin, eyes (PPE for providers); antidotes: atropine, pralidoxime, diazepam

* ABCs denotes airway, breathing, and circulatory support, ARDS acute respiratory disease syndrome, CNS central nervous system, CWA chemical weapon attack, GI gastrointestinal, hazmat hazardous material, HBO hyperbaric oxygen therapy, HCl hydrochloric acid, IV intravenous, and PPE personal protective equipment.

† "Residential" refers to a residential, vehicular, or similar isolated event. Examples of a natural disaster are a volcano eruption and a gas-emitting lake.

‡ HBO for carbon monoxide poisoning is controversial but may mitigate neurocognitive sequelae and may be considered if readily available, particularly for patients with loss of consciousness, ischemic cardiac changes, neurologic deficits, and clinically significant metabolic acidosis. HBO for cyanide and hydrogen sulfide has been reported, but its efficacy is unproven, and it is not typically recommended.

§ Blood cyanide, red-cell cholinesterase, and serum cholinesterase tests are not available on an emergency basis in most hospitals.

with severity), as well as factors affecting host susceptibility (e.g., genetic factors, age, and coexisting conditions).[36] For dermal or inhalational exposures, the systemically absorbed dose varies with the concentration of the agent and the duration of exposure (contact time). Intrinsic toxicity is often expressed as the median lethal dose (LD_{50}, the dose that will cause death in 50% of persons) and is measured in milligrams per kilogram of body weight. For gases, the estimated median lethal dose (LCt_{50}) reflects both the concentration inhaled and the duration (t) of exposure and is typically expressed in milligrams × minutes per cubic meter inhaled.

CLASSES OF HAZARDOUS SUBSTANCES

PRIMARY RESPIRATORY IRRITANTS

Numerous agents that cause respiratory tract and pulmonary injury after inhalation exposure are among the most common substances involved in industrial incidents.[1,3] These primary respiratory irritants injure mucous membranes by various mechanisms, including liberation of acids (chlorine, phosgene, sulfur dioxide, and nitrogen oxides) and alkali (ammonia), oxidant formation, and inflammatory-cascade initiation.[37] Exposure to respiratory irritants leads to characteristic toxidromes that are based on the agent's water solubility.[37,38] Highly water-soluble chemicals (e.g., ammonia) cause immediate irritant symptoms (burning sensation, tearing, sneezing, rhinorrhea, and cough) from exposed mucous membranes. These immediate effects generally provide effective warning, limiting exposure. However, massive exposure or inability to flee may further involve the lower airway and gas-exchange surfaces. Severely affected patients present with airway obstruction, dyspnea, wheezing, and progressive acute lung injury. In 1984, the extraordinary industrial release of methyl isocyanate in Bhopal, India, exposed more than 200,000 people, causing an estimated 6000 deaths within 1 week.[39] Smaller-scale incidents involving other agents, such as moderately water-soluble chlorine, have occurred from railroad transport events,[40] the common household mixing of bleach and cleaning compounds, or exposure to chemicals used in swimming pools.[41,42] Chlorine was deployed as a weapon in World War I and has been used against civilians, with devastating consequences, in the current Syrian civil war.[13] Standard treatment of exposures to such water-soluble agents is supportive, including removal from exposure, decontamination, and provision of humidified oxygen and nebulized bronchodilators as indicated[37,38] (Table 2). Potentially salutary, but less established, interventions include inhaled or systemic glucocorticoids and nebulized sodium bicarbonate for chlorine inhalation.[37,42]

In contrast to water-soluble compounds, relatively water-insoluble respiratory irritants cause few symptoms or upper-airway signs before delayed-onset acute lung injury is manifested. Inciting agents include oxides of nitrogen (causing silo filler's disease) and phosgene.[37,38,43,44] Patients may be unaware of exposure, presenting hours to days later with increased sputum production, chest tightness, and dyspnea on exertion. Clinical findings include dyspnea, tachypnea, wheezes, and rales; pulse oximetry or blood gas analysis may show decreased oxygen saturation with activity. Imaging studies may suggest interstitial or central pulmonary edema. Treatment begins with prompt recognition and termination of exposure. Most experts recommend early administration of glucocorticoids, although the benefit of this treatment has not been proved. Additional therapies of potential benefit include inhaled beta-agonists and *N*-acetylcysteine, as well as ibuprofen.[37,38,43-45] After phosgene exposure, bed rest and close observation are recommended, with oxygen supplementation delayed until it is clinically required to prevent hypoxemia. If oxygen therapy is necessary, it should target oxygen saturation at the low end of the normal range in order to mitigate oxidant-induced injury.[43,44] Delayed or persistent effects of respiratory irritants include airway hyperreactivity, or reactive airways dysfunction syndrome, characterized by acute bronchoconstrictor responses to otherwise innocuous concentrations of inhaled agents,[46,47] as well as interstitial pulmonary fibrosis, emphysema, bronchiectasis, and bronchiolitis obliterans.[37,39,45]

VESICANTS

Vesicants, or blistering agents, are a distinct class of chemical warfare agents that were first used in World War I.[48] Initial identification through toxidrome recognition is challenging because the initial skin, eye, and respiratory symptoms from vesicants are similar to the symptoms caused by other irritant corrosive chemicals. However, ves-

Table 2. Emergency Care Guidelines for Toxic Inhalant Injury.*

Medication	Adult Dose	Pediatric Dose	Comments†
Prehospital (moderate-to-severe toxic injury)			
Albuterol MDI, 90 μg/actuation (use of spacer preferable)	4–8 actuations	Body weight, 5–10 kg: 4 actuations 11–20 kg: 6 actuations >20 kg: 8 actuations Add mask for young children	Repeat same dose every 20 min up to 3 times as needed for acute bronchospasm; active airway management required for worsening gas exchange or evidence of upper-airway obstruction
Hospital (moderate-to-severe toxic injury)			
Albuterol		Add mask for young children	Repeat same dose every 20 min up to 3 times as needed for acute bronchospasm; active airway management required for worsening gas exchange or evidence of upper-airway obstruction
Intermittent nebulization	2.5–5 mg	5–10 kg: 2.5 mg 11–20 kg: 3.75 mg >20 kg: 5 mg	
MDI, 90 μg/actuation (use of spacer preferable)	4–8 actuations	5–10 kg: 4 actuations 11–20 kg: 6 actuations >20 kg: 8 actuations	
Continuous nebulization	7.5–15 mg/hr	5–10 kg: 7.5 mg/hr 11–20 kg: 11.25 mg/hr >20 kg: 15 mg/hr	
Nebulized sodium bicarbonate, 3–4%‡	4 ml administered over a 20-min period	4 ml administered over a 20-min period	Repeat dose as needed if improvement noted; consider addition of nebulized sodium bicarbonate in selected cases (e.g., 1:1 dilution of 5 to 8.4% sodium bicarbonate stock solution with sterile saline provides approximately 3–4% sodium bicarbonate solution for inhalation)
Glucocorticoids			Consider glucocorticoids in addition to inhaled beta-agonist
Prednisone	40–80 mg orally	1–2 mg/kg, orally (maximum, 60 mg)	
Methylprednisolone	40–80 mg IV	1–2 mg/kg, IV (maximum, 60 mg)	

* In general, we recommend that initial supportive care and medications for bronchospasm due to acute chemical inhalational injury parallel that for acute exacerbations of asthma. The suggested medication regimens are adapted from our institutional preferences (e.g., Children's Hospital of Philadelphia's ED Pathway for Evaluation/Treatment of Children with Asthma [www.chop.edu/clinical-pathway/asthma-emergent-care-clinical-pathway]) and literature review (e.g., the National Institute of Health's Guidelines for the Diagnosis and Management of Asthma [www.nhlbi.nih.gov/files/docs/guidelines/asthgdln.pdf]). Prehospital and hospital care for mass casualties (e.g., in cases of injury from a hazmat exposure, an industrial terrorist incident, or a CWA) or care for individual patients (e.g., in cases of injury from home-based mixing of chemicals such as acid or ammonia and bleach, incidents related to swimming pool chemicals, small-scale industrial release of respiratory irritants, or occupational exposure to vesicants in discarded munitions) focuses on adequate oxygenation and decontamination. The recommended initial therapy is high-flow oxygen for dyspnea or low oxygen saturation; high-flow, low-pressure ocular irrigation with physiologic saline or water; beta-agonist metered-dose inhaler (MDI) or nebulized beta-agonists (e.g., albuterol) for wheezing or cough, with spacing device; early disrobing and water-based skin decontamination for liquid exposures, with particular attention to intertriginous areas for mustard exposure. Suspected exposure to phosgene is an exception to high-flow oxygen; in such cases, oxygen supplementation should be delayed until clinically necessary in order to avoid hypoxemia. Then oxygen supplementation should be used to target oxygen saturation at the low end of the normal range, since the pulmonary injury is primarily related to covalent binding by reactive oxygen to cellular macromolecules (nucleophilic attack), with loss of surfactant and alveolar injury. Measures that anticipate increasing dead space, hemoconcentration with incipient pulmonary edema, and application of positive-end respiratory pressure and oxygen supplementation, as required, take precedence over sympathomimetic and antiinflammatory medications.

† Consultation with a regional poison control center, medical toxicologist, or pulmonologist or intensivist is recommended for patients with persistent or worsening symptoms. Additional treatment approaches that might be considered for toxic inhalant–induced bronchospasm or acute lung injury include protective lung-ventilation strategies, inhaled glucocorticoids, antioxidants such as *N*-acetylcysteine, and antiinflammatory agents such as ibuprofen.

‡ For exposure to respiratory irritants based on the generation of hydrochloric acid (e.g., chloramine and chlorine), nebulized sodium bicarbonate may be considered if wheezing or cough persists after the patient has been removed from the source of exposure and one or two administrations of inhaled beta-agonists have been administered. If nebulized sodium bicarbonate is used, it should be administered separately from nebulized beta-agonists.

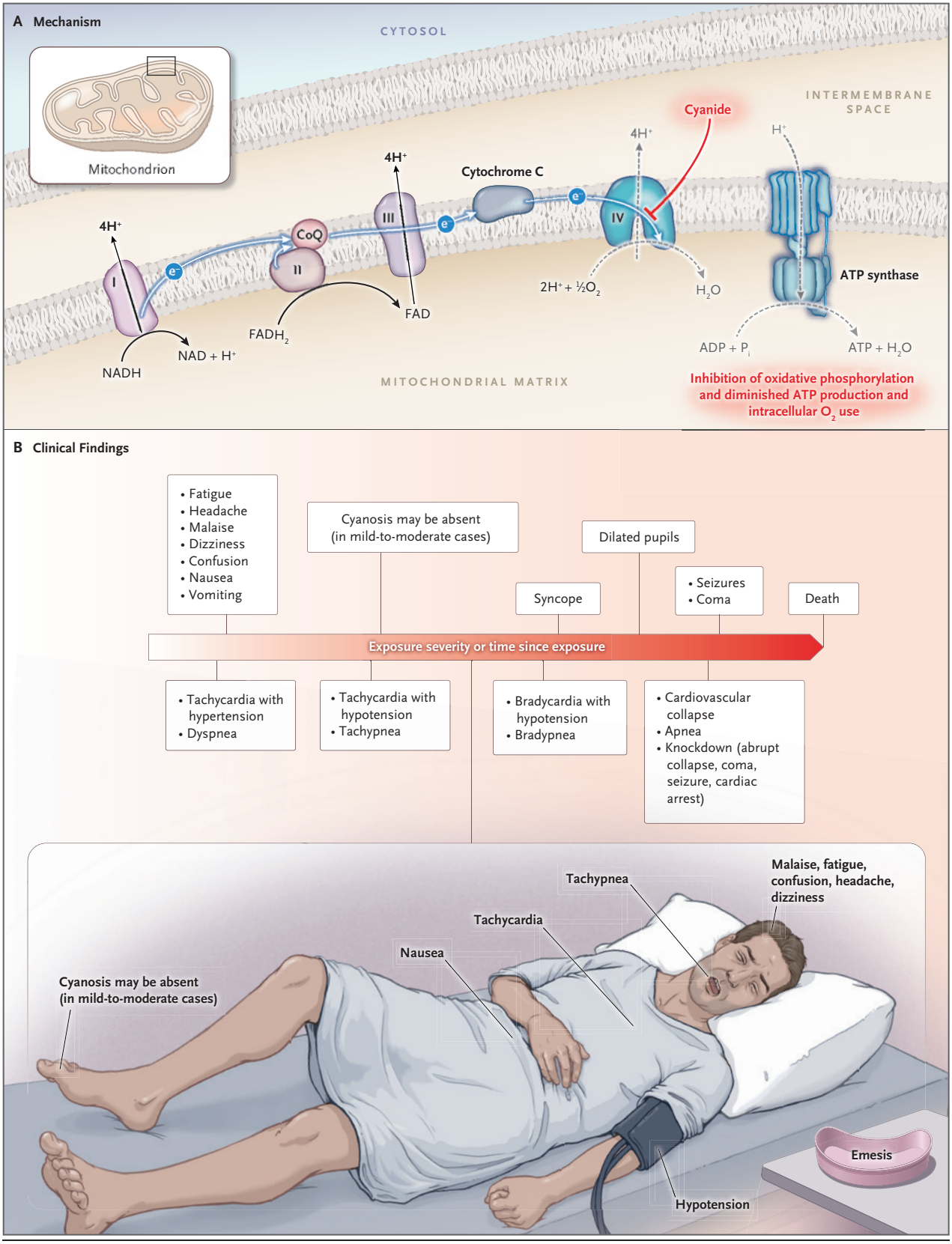

Figure 1 (facing page). Cyanide Poisoning.
Panel A shows the mechanism of cyanide poisoning at the level of the mitochondria, and Panel B shows the spectrum of clinical findings and a patient with moderate cyanide poisoning. ADP denotes adenosine diphosphate, CoQ coenzyme Q, e^- electron, FAD and $FADH_2$ oxidized and reduced flavin adenine dinucleotide, respectively, and P_i inorganic phosphate.

icant exposure may progress to more clinically significant injuries, with serious systemic effects. Although vesicants include nitrogen mustard, lewisite, and phosgene oxime, sulfur mustard is the greatest concern with respect to military and terrorist use. Casualties have been reported from the use of sulfur mustard in the 1980s Iran–Iraq conflict and attacks against civilians in the current Syrian conflict and have also been reported among fishermen exposed to munitions that were disposed of at sea and resurfaced in fishing dredges.[13,49,50]

Liquid mustard persists in the environment at room temperature and is primarily a dermal hazard.[48] Vapors, formed at higher ambient temperatures, or aerosolized liquids, are an inhalation hazard. Mustard is an alkylating agent, attacking cellular macromolecules and DNA and irreversibly damaging target tissues on contact, particularly skin, lung, and eye tissues. There is rapid formation of a highly reactive sulfonium ion, which forms cross-links with guanine in DNA, arresting the cell cycle, initiating apoptosis, generating oxidative stress, depleting glutathione and other antioxidants, and increasing inflammatory mediators.[51,52] Mustard injures basal keratinocytes in the epidermis, degrades adhesive proteins, and initiates intense inflammation, causing dermal–epidermal separation.[52,53] Skin injury is manifested 2 to 24 hours after exposure, initially as erythema and burning pain, with subsequent formation of vesicles, which coalesce into large bullae (Fig. S2 in the Supplementary Appendix).[48,49] Vapors penetrate clothes and concentrate in moist areas, which explains the high number of inguinal and axillary burns observed in battlefield casualties.[7] Mustard penetration of the dermis provides a route for systemic absorption and distant organ injury (e.g., lung and bone marrow injury).[48]

The lungs sustain cytotoxic injury and oxidative stress from inhaled mustard vapors or aerosol droplets or from systemically absorbed adducts after skin exposure.[48,54,55] Respiratory mucosal sloughing, casts and fibrin pseudomembrane formation in the airways, lung inflammation, and activation of the coagulation pathway may result in the acute respiratory distress syndrome, with high mortality. Symptoms include a delayed onset of burning pain in the nose and throat, nosebleeds, hoarse voice, productive cough, and dyspnea. Most deaths from mustard exposure are due to respiratory failure.[48] Chronic lung effects include bronchitis and bronchiolitis obliterans.

The eyes are most sensitive to mustard exposure, with red, irritated conjunctiva progressing to blepharospasm and lid edema, corneal ulcerations, and in extreme cases, corneal rupture.[48,56] The systemic toxic effects of mustard exposure are similar to those of chemotherapeutic agents: bone marrow suppression, neutropenia, and subsequent sepsis, mutagenesis, and carcinogenesis.[48,55]

The delayed onset of symptoms complicates triage, treatment, and disposition of potentially exposed patients. Management is mostly limited to rapid skin and ocular decontamination to limit the dose and prevent the spread of contamination, as well as to the provision of supportive respiratory, ophthalmic, and burn care[7,48] (Table 1). Hospital-based decontamination consists of immediate removal and safe disposal of clothing, the use of copious soap and water to wash skin and hair, and copious eye irrigation. Skin bullae contain no active mustard and may be débrided as indicated. Early instillation of combined antibiotic and glucocorticoid ophthalmic agents, with ophthalmologic consultation even for mild ocular injury, is recommended[48,56]; keratopathy attributable to impaired cellular regeneration can occur decades after a severe exposure. Management of systemic effects includes vigilant surveillance for and early treatment of infections and the use of granulocyte colony-stimulating factor for neutropenia (Table 1). Effective early treatments to prevent or lessen mustard injuries have been elusive, but new mechanism-based therapies are now showing promise. Recent studies suggest that antioxidants (e.g., *N*-acetylcysteine), anticoagulants (e.g., tissue plasminogen activator), and antiinflammatory therapies (e.g., dexamethasone), especially in combination, may be promising interven-

Table 3. Cyanide Antidotes.

Indication	Supportive Laboratory Findings	Medication	Adult Dose	Pediatric Dose	Comment
Smoke inhalation from house fire, with prehospital cardiorespiratory arrest or coma, hypotension	High-anion-gap metabolic acidosis, lactate level >10 mmol/liter (elevated carboxyhemoglobin level alone not typically associated with lactate level >10 mmol/liter)	Hydroxocobalamin* (sodium thiosulfate [25%]† if hydroxocobalamin not available)	5 g	70 mg/kg; maximum, 5 g	IV infusion over a 15-min period; repeat the same dose as needed in severe cases
Injury from occupational or hazmat exposure, nitroprusside, self-harm, or CWA; or suggestive toxidrome and severely ill patient	High-anion-gap metabolic acidosis, lactate level >8 mmol/liter; narrow arteriovenous oxygen saturation gap	Hydroxocobalamin* (sodium thiosulfate [25%]† plus sodium nitrite [3%]‡ if hydroxocobalamin not available)	5 g	70 mg/kg; maximum, 5 g	IV infusion over a 15-min period; repeat the same dose as needed in severe cases

* Hydroxocobalamin is the preferred cyanide antidote in all circumstances. Some practitioners recommend hydroxocobalamin followed by thiosulfate (administered through a separate or well-flushed catheter to avoid particulate formation) for severe cases, especially if evidence of toxic effects persists after the maximum dose of hydroxocobalamin has been administered, but the superiority of this combination over hydroxocobalamin alone has not been proved. If hydroxocobalamin is not available, sodium nitrite plus sodium thiosulfate may be substituted, except if clinically significant carbon monoxide toxic injury is also suspected, in which case thiosulfate alone is preferred. Immediate treatment with one of the indicated regimens is recommended for critically ill patients with suspected cyanide intoxication. We also recommend consultation with a medical toxicology service or poison control center for more specific guidance. Additional antidotes available outside the United States include dicobalt edetate and dimethylaminophenol.

† In patients with clinically significant concomitant carbon monoxide toxic effects, thiosulfate given alone will have some antidotal benefit if hydroxocobalamin is not available. Nitrites are contraindicated in such patients. For all indications, thiosulfate (25%) is administered at a dose of 12.5 g (50 ml) in adults and 412 mg per kilogram (maximum, 12.5 g) (1.65 ml per kilogram; maximum, 50 ml) in children, by IV infusion over a 30-minute period; repeat a half dose after 30 minutes as needed.

‡ Nitrites should generally be avoided in pregnant women, but if hydroxocobalamin is not available, the severity of the case must be considered. Amyl nitrite inhalation was previously recommended to precede sodium nitrite infusion in the prehospital setting and was included as part of the cyanide antidote kit, but this kit is no longer available. Sodium nitrite (3%) is administered at a dose of 300 mg (10 ml) in adults and 5.8 to 11.6 mg per kilogram (maximum, 300 mg) (0.19–0.39 ml per kilogram; maximum, 10 ml) in children, by IV infusion over a 5-minute period; repeat a half dose after 30 minutes as needed. Nitrite dose adjustments are recommended for children on the basis of expected or measured hemoglobin levels. For an estimated hemoglobin level of 12 g per deciliter, sodium nitrite (3%) at a dose of 10 mg per kilogram (maximum, 300 mg) (0.33 ml per kilogram; maximum, 10 ml) is recommended. Consultation with a toxicology service or poison control center is advised if dose adjustment is required.

tions.[51,52,54] Large numbers of mustard-exposed patients would place a tremendous burden on the health care system, requiring extensive ophthalmologic, burn unit, and critical care resources.

ASPHYXIANT AGENTS

Asphyxiant exposures cause tissue hypoxia, with profound neurologic and cardiovascular effects.[57,58] Simple asphyxiants (e.g., nitrogen and methane) act primarily through physical displacement of oxygen from inspired air, resulting in arterial hypoxemia. Some systemic or chemical asphyxiants (e.g., carbon monoxide and methemoglobin inducers) interfere with oxygen transport, and some (e.g., carbon monoxide, hydrogen sulfide, cyanide, phosphine, and azides) interfere with oxidative metabolism, leading to tissue hypoxia with a shift to anaerobic metabolism and resulting in metabolic acidosis and hyperlactatemia. Arterial oxygenation, as indicated by the partial pressure of arterial oxygen, may be preserved before respiratory depression and cardiovascular collapse ensue. Inadvertent environmental and occupational exposures to asphyxiants are numerous. Intentional poisonings also occur, including suicidal inhalation of carbon monoxide and hydrogen sulfide[59,60] and ingestion of azide or cyanide salts.[61,62] Some asphyxiants are considered to be potential terrorist threats.[57] In the most severe exposures, particularly with carbon monoxide, cyanide, and hydrogen sulfide, rapid knockdown may occur, with a sudden loss of consciousness, collapse, and progressive cardiovascular compromise. The asphyxiant (knockdown) toxidrome ranges from severe effects, such as seizures, coma, hypotension, bradycardia, and

apnea, to milder findings, including headache, dizziness, fatigue, tachycardia, dyspnea, nausea, and vomiting.

Excessive exposure to carbon monoxide occurs commonly from faulty heating systems, household combustion appliances, vehicle engine exhaust, and smoke from house fires, resulting in frequent unintentional and suicidal poisoning deaths and accounting for more than 50,000 ED visits in the United States each year.[59,63] Carbon monoxide interferes with the binding of oxygen to hemoglobin and inhibits mitochondrial cytochrome oxidase. The diagnosis of carbon monoxide exposure is supported by a characteristic exposure history, asphyxiant toxidrome, and elevated blood carboxyhemoglobin level. The carboxyhemoglobin level decreases after removal from exposure and decreases more rapidly with oxygen therapy, which is often applied by first responders, and it is thus best interpreted in the clinical context.[63,64]

Hydrogen sulfide, associated with a rotten-egg odor, is implicated in catastrophic occupational exposures involving workers (and unprotected coworkers attempting rescue) in sewers or other enclosed spaces.[58,65] Reports on suicides related to home production of hydrogen sulfide in Japan and the United States highlight the lethality of this gas, with an extremely high risk of injury to first responders.[60] Hydrogen sulfide has serious irritant effects on the mucous membranes of the eye (with characteristic "gas eye" corneal ulcerations), nose, and respiratory tract and causes acute lung injury.

Cyanide exposure is associated with inhalation of smoke from house fires; additional sources of exposure include industrial and laboratory accidents, sodium nitroprusside therapy, cyanogenic chemical and plant ingestion, suicide attempts, and criminal or terrorist activity.[57,58,66-69] Cyanide inhibits mitochondrial cytochrome oxidase and thus oxidative phosphorylation, with asphyxiant clinical effects, metabolic acidosis, and hyperlactatemia (Fig. 1). An elevated mixed venous oxygen saturation, which is uncharacteristic of many causes of cardiorespiratory compromise, may suggest the diagnosis.[58,69] Cherry-red skin and bitter-almond breath odor have been described, but these are uncommon findings and prone to misattribution.[70] Elevated blood cyanide levels would support the diagnosis, but the test is not available on an emergency basis. In critically ill persons with smoke inhalation, lactate levels above 10 mmol per liter are strongly associated with cyanide toxicity.[68]

Management of asphyxiant poisoning begins with removal to fresh air, dermal decontamination for liquid exposures, advanced life support with 100% oxygen as the respired gas, and correction of metabolic acidosis.[1,57,58,69] Gastrointestinal decontamination may be considered for cyanide and azide ingestion, particularly ingestion of cyanogenic compounds (e.g., acetonitrile and amygdalin). Oxygen, which is used for hypoxemia associated with simple asphyxiants, enhances carboxyhemoglobin elimination and, despite cytochrome oxidase inhibition, appears to be beneficial in managing the toxic effects of cyanide and hydrogen sulfide.[1,57,58] Hyperbaric oxygen therapy, if immediately available, may mitigate neurocognitive sequelae of clinically significant carbon monoxide toxicity[63,64,71] (Table 1).

The toxic effects of cyanide should be suspected in any potentially exposed or suicidal patient presenting with altered sensorium, cardiovascular collapse, and severe metabolic acidosis (especially with marked hyperlactatemia), unless another cause is readily apparent, and warrants antidote administration on an emergency basis.[58,70] Three antidotes for the toxic effects of cyanide are currently available in the United States[57,72] (Table 3). An older regimen (the cyanide antidote kit) consists of sequential administration of nitrite (forming methemoglobin, which dissociates cyanide from cytochrome oxidase, and inducing nitric oxide synthesis, which may have additional salutary effects) and thiosulfate (enhancing conversion of cyanide to thiocyanate, which is less toxic). A newer antidote, hydroxocobalamin, exchanges a hydroxyl group for cyanide, forming cyanocobalamin (vitamin B_{12}), which is nontoxic. The efficacy of hydroxocobalamin has been established in numerous experimental studies, case series, and one prospective clinical trial.[72,73] Hydroxocobalamin causes reddish coloration of the skin and body fluids, skews several colorimetric laboratory results (including the carboxyhemoglobin level), and causes false blood-leak alarms in some hemodialysis systems.[74-76] However, its use is not complicated by potential nitrite-induced hypotension or excessive methemo-

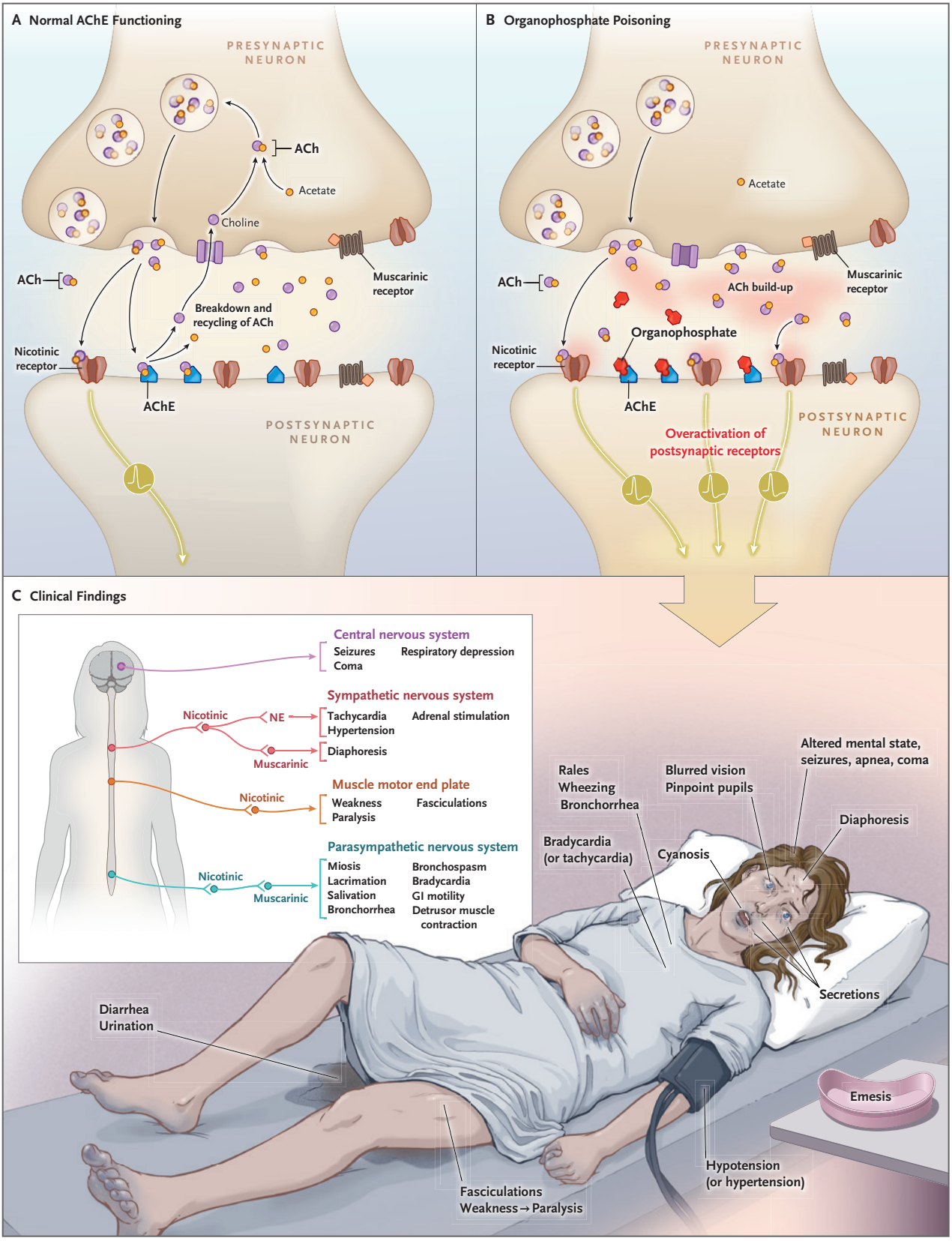

Figure 2 (facing page). Organophosphate Poisoning.
Panel A shows the cholinergic synapse. Both nicotinic and muscarinic receptors are shown for illustrative purposes. Panel B shows the inhibition of acetylcholinesterase (AChE) by organophosphate, resulting in overstimulation of nicotinic receptors and overexcitation of the postsynaptic neuron. Panel C shows clinical findings in a patient with moderate organophosphate poisoning. ACh denotes acetylcholine, GI gastrointestinal, and NE norepinephrine.

globinemia, and many authorities now consider hydroxocobalamin the antidote of choice,[58] particularly for patients with toxic effects of cyanide from smoke inhalation,[73] for children,[77] and for use in the prehospital setting.[73] Hydroxocobalamin combined with thiosulfate has shown synergistic efficacy in some[78] but not all[79] experimental models, and there is considerable clinical experience with its use in Europe.[73,80] Thus, initial hydroxocobalamin administration, followed by thiosulfate infusion (through a separate or well-flushed catheter), may be considered in severe cases.[80]

Robust research is under way to develop antidotes that have higher potency or that may be given intramuscularly or orally in the case of mass casualties (e.g., cobinamide, a hydroxocobalamin congener; sulfanegan, a sulfate donor; intramuscular nitrite and thiosulfate; and oral glycine or thiosulfate).[72,81,82] Hydrogen sulfide also binds to methemoglobin and cobalt compounds, and patients may benefit from the prompt administration of nitrite (without thiosulfate) or hydroxocobalamin.[58] In addition, cobinamide was shown to have antidotal efficacy on the toxic effects of hydrogen sulfide in a study in animals.[83]

CHOLINERGIC AGENTS

Cholinergic compounds include organophosphate and carbamate pesticides, military nerve agents, and several commonly used medications, including neostigmine and physostigmine.[7,84,85] We focus here on organophosphate pesticides (e.g., chlorpyrifos and diazinon) and nerve agents (e.g., sarin, soman, tabun, VX, and Novichok agents). Organophosphate pesticides, which are widely used in agriculture, are highly toxic and commonly ingested with suicidal intent in developing countries.[86] Sarin was deployed as a terrorist weapon in the 1995 Tokyo subway attack[15] and has been used in military conflicts against civilian populations in Iraq and Syria.[13,14] Nerve agents were also used in the widely publicized assassination attempts in Malaysia in 2017 and the United Kingdom in 2018.[11,12] The incident in the United Kingdom highlighted fourth-generation agents, also known as Novichok agents. These nerve agents persist on skin and environmental surfaces for many days, have a latency period of several hours after dermal exposure, and are extremely toxic, requiring prolonged intensive care. Guidance for first responders and health care workers is available at the CHEMM website[34] (https://chemm.nlm.nih.gov/nerveagents/FGA.htm).

Organophosphates act primarily by inhibiting acetylcholinesterase at neural junctions. Excess synaptic acetylcholine results in the cholinergic toxidrome involving the central nervous system (CNS), neuromuscular junction, and autonomic nervous system[84,85] (Fig. 2). This inhibition becomes irreversible after variable periods of time ("aging"). Severe poisonings probably also involve γ-aminobutyric acid and *N*-methyl-D-aspartate glutamate receptors, exacerbating toxic effects on the CNS.[84,87,88] In classic cases, muscarinic, nicotinic, and CNS effects ensue. Muscarinic effects result from parasympathetic overstimulation (miosis and blurred vision; excessive secretions, especially salivation, lacrimation, urination, defecation, gastric cramping, and emesis [SLUDGE]; and bronchorrhea, bronchospasm, and bradycardia). Nicotinic signs result from overstimulation of sympathetic ganglia (diaphoresis and tachycardia) and neuromuscular junctions (muscle fasciculation, profound muscle weakness, and paralysis). Finally, a spectrum of CNS dysfunction occurs, including confusion, coma, apnea, and seizures. Lethality is due primarily to respiratory compromise from central apnea, severe airway narrowing, excessive pulmonary secretions, and respiratory muscle paralysis. The onset and pattern of clinical findings may vary according to the agent and route of exposure (volatility correlates with inhalation hazard). Inhalation of nerve-agent vapor causes ocular, respiratory, and systemic effects in seconds to minutes, with an abrupt onset of seizures, paralysis, and respiratory arrest in severe cases.[85] Skin exposure to liquid agents leads to dermal absorption, with potential early localized effects such as diaphoresis and fasciculation, followed by systemic toxic effects in the period up to 48 hours

Table 4. Antidotes to Cholinergic Agents.*

Antidote	Adult Dose	Pediatric Dose	Comments
Prehospital, moderate-to-severe toxic injury			
Atropine	2 or 3 autoinjectors (2 mg each; total, 4–6 mg)	Age <3 yr: 0.05–0.10 mg/kg (IM) or use autoinjector† Age 3–7 yr: 1 autoinjector (total, 1–2 mg) Age 8–13 yr: 1 or 2 autoinjectors (2 mg each; total, 2–4 mg) Age >13 yr: 2 or 3 autoinjectors (2 mg each; total, 4–6 mg)	Repeat every 2–10 min as needed to achieve rapid atropinization, then as needed for maintenance‡
Pralidoxime	2 or 3 autoinjectors (600 mg each; total, 1200–1800 mg)	Age 3–7 yr: 1 autoinjector Age 8–13 yr: 2 autoinjectors Age >13 yr: 3 autoinjectors	Repeat every hr two more times in severe cases (if logistically possible, use weight-based dosing for children <3 yr of age)†
Diazepam	2 or 3 autoinjectors, (10 mg each; total, 20–30 mg)	0.2–0.5 mg/kg (maximum, 10 mg) IM§	Repeat as needed for seizure control
Hospital, moderate-to-severe toxic injury			
Atropine	1–3 mg IV	0.02–0.05 mg/kg (maximum, 3 mg) IV	Double the dose every 5 min as needed to achieve rapid atropinization, then administer infusion of 10–20% of total loading dose/hr‡
Pralidoxime	1–2 g IV over 30 min	25–50 mg/kg (maximum, 2 g) IV over 30-min period	After loading dose, administer infusion of 0.5–1.0 g/hr in adults and 10–20 mg/kg/hr (maximum, 0.5–1.0 g/hr) in children
Diazepam	5–10 mg IV as needed	0.2–0.5 mg/kg (maximum, 10 mg) IV or IM as needed	Repeat as needed for seizure control

* When prehospital care for mass casualties is needed (e.g., in cases of exposure to nerve agents), the recommended initial antidotal therapy is autoinjector doses of atropine, pralidoxime, and diazepam. When hospital care or care for individual patients is needed (e.g., in cases of pesticide exposure or exposure to nerve agents in patients who bypassed EMS or received initial field treatment), the recommended initial antidotal therapy is atropine (IV) plus pralidoxime (IV), with diazepam (IV) for nerve-agent toxic injury. On the basis of data from studies in animals, hypoxia should be corrected before IV atropine is administered, and a first dose of intramuscular (IM) atropine may be preferable in patients who have persistent hypoxia after initial resuscitation. However, this approach is controversial, and most authorities would not withhold atropine administration by any route in a critically ill patient.[86] Dosing guidelines are adapted and summarized from the Chemical Hazards Emergency Medical Management (CHEMM) website[34] (https://chemm.nlm.nih.gov/na_hospital_mmg.htm#top) for treatment of nerve-agent toxic effects and from Eddleston[86] for treatment of pesticide toxic effects. These resources provide detailed recommendations for antidotal and supportive care of patients who are critically ill from organophosphate poisoning. We recommend additional consultation with a medical toxicologist or regional poison control center (telephone number, 800-222-1222 in the United States) for specific case management.

† Pediatric atropine autoinjectors have been produced in 0.5-mg and 1-mg sizes (though they are currently of limited availability), and dosing guidelines have been established. Prehospital treatment of young children with pralidoxime is problematic, since pediatric pralidoxime autoinjectors are not currently available. Guidelines have been suggested for using adult-size pralidoxime autoinjectors for the treatment of nerve-agent exposure in children 3 years of age or older (weight, >13 kg) as part of prehospital care or management of mass casualties.[29] For infants, one might consider using conventionally administered intramuscular pralidoxime. This may be facilitated by discharging one or several autoinjectors into an emptied 10-ml sterile saline vial. The solution of 300 mg per milliliter can then be withdrawn through a filter needle into syringes suitable for small-volume intramuscular injections.[90] If no alternatives are available for critically ill children under the age of 3 years, a single adult-size pralidoxime autoinjector (600 mg) may be used .

‡ Goals for atropinization in patients with organophosphate toxic effects are primarily drying of secretions, relief of airway obstruction and dyspnea, and resolution of bradycardia and hypotension as soon as feasible, generally within the first 30 minutes or so of therapy.[86,89,91] The evidence base for this approach is most robust for the treatment of pesticide poisoning and probably applies to nerve-agent exposure as well. Atropine therapy is best provided as an IV regimen administered in the hospital, with bolus doses doubled every 5 minutes until atropinization has been achieved. For hospital-based care, most authorities recommend continuous infusions of atropine and pralidoxime after initial bolus dosing, with adjustment of the atropine infusion rate to maintain atropinization while avoiding the toxic effects of atropine (e.g., hyperthermia, delirium, ileus, and urinary retention).[86,89]

§ Benzodiazepines are the preferred anticonvulsant agents for nerve-agent toxic effects, but child-size autoinjectors are not currently available. For initial anticonvulsant therapy for nerve-agent–induced seizures in children, midazolam (0.15 mg per kilogram [maximum dose, 10 mg], IM) could be administered instead of diazepam.

after exposure. The toxic effects of pesticides overlap those of nerve agents but vary somewhat. The effects typically develop 30 to 90 minutes after ingestion and may persist for several days. Seizures are relatively uncommon, but cardiovascular collapse may complicate severe cases, and delayed syndromes may occur, including the "intermediate syndrome," with severe muscle weakness leading to respiratory failure 1 to 4 days after ingestion, and a peripheral neuropathy.[84,86,89] Pesticide ingestion may be complicated by the toxic effects of hydrocarbon solvents, particularly aspiration-related lung injury.[86,89]

The diagnosis depends on the history, toxidrome recognition, and the response to empirical antidotal therapy.[84,86] Organophosphate toxicity results in depression of serum and erythrocyte cholinesterase levels; however, neither emergency assays for these agents nor routine laboratory tests for organophosphate compounds are widely available. Management includes decontamination by personnel in appropriate personal protective equipment, with consideration of gastrointestinal decontamination in the case of pesticide ingestion[86]; meticulous supportive care, with special attention to clearing of airway secretions, supplemental oxygen, and early endotracheal intubation in severe cases; and rapid antidote administration (Table 4).

Atropine is administered for its antimuscarinic effects, particularly drying of pulmonary secretions, relief of bronchoconstriction, correction of hypotension and bradycardia, and potential mitigation of seizures. Organophosphate poisoning confers a relative tolerance to atropine; therefore, very large doses of atropine may be required.[86] Rapid attainment of muscarinic blockade with atropine reduced morbidity in one randomized trial[91] and is endorsed by many authorities.[84,89] Pralidoxime, an oxime acetylcholinesterase reactivator available in the United States, is widely recommended for the toxic effects of nerve agents.[84,85,87] Though robust demonstration of the efficacy of pralidoxime in the treatment of the toxic effects of organophosphate pesticides is lacking, especially in resource-poor settings,[92] most authorities currently recommend its administration for clinically significant pesticide toxic injury as well, with critical care support.[84,89] Autoinjectors containing both these antidotes are available for intramuscular administration in the case of mass casualties from exposure to nerve agents, though smaller pralidoxime autoinjectors for use in children are not available[90] (Table 4). Critically ill patients should also receive benzodiazepines for their anticonvulsant effects. Intravenous administration is the preferred treatment route, especially in severely ill hospitalized patients. A nerve agent attack with mass casualties might overwhelm resources, including antidote stocks, underscoring the need for alternative antidotes and alternative routes of administration, such as sublingual, inhaled, and intranasal options. Recently issued recommendations based on expert consensus suggest such contingency anticholinergic medications, benzodiazepine anticonvulsant agents, and routes of administration.[93,94] Therapeutic approaches under study include enzyme hydrolases such as human butyrylcholinesterase and paraoxenase; novel combinations of oximes, anticonvulsant agents, and anticholinergic agents; magnesium; beta-adrenergic agonists; neuromuscular blocking agents (e.g., rocuronium); and intravenous lipid emulsions.[89,95,96]

HOSPITAL, COMMUNITY, AND NATIONAL PREPAREDNESS

For large-scale chemical events, local communities would have to provide treatment of multiple casualties until federal resources could be mobilized.[97] Preparations for such incidents should include both hospital- and community-based chemical disaster planning and drills. An effective response requires multiple agencies (e.g., law enforcement, fire and hazardous-material [hazmat] services, EMS, hospitals, health care coalitions, and public health agencies) to coordinate effective information management and communications, set clear priorities, manage with limited resources, adapt to rapidly changing and complex situations, and provide clear, accurate, and timely public messaging.[97-99]

Even though local communities must provide the initial response, emergency planners must identify the regional, military, government, and international resources available for preplanning and during a response. The World Health Organization, several U.S. federal agencies, and many

professional societies support specific planning and training for responding to chemical incidents.[100-102] Emergency planners must recognize the limits of their community's capabilities and during a response must forecast needs, use defined triggers to rapidly mobilize additional assets, and activate preplanned strategies to coordinate with local and mutual aid resources. In the United States, numerous federal agencies provide resources for the development and deployment of medical measures against chemical threats,[100,101,103] specialized teams of health care providers,[100] and laboratory analysis[104] (Table S2 in the Supplementary Appendix). For example, hospitals must stock appropriate antidotes (especially for nerve agents and cyanide) in sufficient supplies for a first wave of casualties.[97,105,106] To augment local stockpiles, the Centers for Disease Control and Prevention (CDC) provides CHEMPACK, a system of regionally based caches that can be quickly mobilized during a chemical incident.[91,94] The National Guard has developed specialized support teams that can supplement the capabilities of local response teams during chemical emergencies.[100] In addition, during a response, identification of chemical agents can be expedited by the CDC's Laboratory Response Network for Chemical Threats, which can detect a number of toxic chemical agents and analyze samples from a large number of exposed patients.[104]

SUMMARY

Hazardous chemical emergencies include unintentional releases of hazardous substances and chemical attacks. Consequent poisonings may result in mass casualties, challenging community and hospital preparedness and response efforts. The relevant classes of chemicals reviewed here include respiratory irritants, vesicants, knockdown agents (asphyxiants, including cyanide), and cholinergic agents (organophosphate insecticides and military nerve agents). Cyanide and organophosphate poisonings are also encountered in individual patients after inadvertent or suicidal exposures and are treated with specific antidotal therapy provided on an emergency basis after toxidrome recognition.

The findings and conclusions are those of the authors and have not been formally disseminated by the Department of Homeland Security or the U.S. government and should not be construed as representing any agency determination or policy.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Vikhyat Bebarta and Stephen Borron for research-based insights regarding antidotal treatment of cyanide poisoning and Dr. Kevin Osterhoudt for a thoughtful critique of an earlier version of the manuscript.

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