

## CHAPTER 159

# INHALED TOXINS

Lewis S. Nelson and Robert S. Hoffman

Many airborne toxins produce local noxious effects on the airways and lungs as irritants. The respiratory tract can also serve as a portal of entry for systemic poisons as simple or systemic asphyxiants. Inhalational exposure can be covert and indolent (as in occupational exposure to asbestos or urban exposure to photochemical smog) or fulminant and obvious. The circumstances and location of the exposure, the presence of combustion or odors, and the number and condition of victims assist in the diagnosis. Despite the array of possible toxic inhalants, identification of a specific inhalant is generally unnecessary because therapy is based primarily on the clinical manifestations (Table 159-1).

### SIMPLE ASPHYXIANTS

#### Perspective

Most simple asphyxiations are workplace related and usually occur during the use of liquefied gas while the employee is breathing through an airline respirator or working in a confined space.<sup>1</sup> Since the advent of catalytic converters, most deaths from the intentional inhalation of automotive exhaust result from simple asphyxiation, due to hypoxia, and not from carbon monoxide (CO) poisoning.<sup>2</sup>

#### Principles of Disease

Most simple asphyxiants are inert and produce toxicity only by displacement of oxygen and lowering of the fraction of inspired oxygen ( $F_{iO_2}$ ). Exposed patients remain asymptomatic if the  $F_{iO_2}$  is normal. Carbon dioxide and nitrogen, both constituents of air, produce narcosis at elevated partial pressures, but their predominant toxicologic effect is simple asphyxiation.

#### Clinical Features

Acute effects occur within minutes of onset of hypoxia and are the manifestations of ischemia. A fall in the  $F_{iO_2}$  from normal, 0.21 (i.e., 21%), to 0.15 results in autonomic stimulation (e.g., tachycardia, tachypnea, and dyspnea) and cerebral hypoxia (e.g., ataxia, dizziness, incoordination, and confusion). Dyspnea is not an early finding because hypoxemia is not as potent a stimulus for this sensation, or for breathing, as are hypercarbia and acidosis. Lethargy from cerebral edema is expected as the  $F_{iO_2}$  falls below 0.1 (10%), and life is difficult to sustain at an  $F_{iO_2}$  below 0.06 (6%).<sup>3</sup> Because removal from exposure terminates the simple asphyxiation and allows restoration of oxygenation and clinical improvement, most patients present with resolving symptoms. However, failure

to improve suggests complications of ischemia (e.g., seizures, coma, and cardiac arrest) and is associated with a poor prognosis.

#### Diagnostic Strategies and Differential Considerations

A consistent history, an appropriate spectrum of complaints, and a rapid resolution on removal from exposure are generally sufficient to establish the diagnosis. Minimally symptomatic or asymptomatic patients do not require chest radiography or arterial blood gas (ABG) analysis. Definitive diagnosis ultimately requires scene investigation by a trained and suitably outfitted team. Determination of the exact nature of the gas is of limited clinical value but may have important public health implications. Because the presenting complaints offered by most exposed patients are nonspecific and protean (e.g., dizziness, syncope, and dyspnea), the differential diagnosis is extensive.

#### Management and Disposition

Management rarely requires specific therapy other than removal from exposure, supportive care, and possibly administration of supplemental oxygen. Neurologic injury or cardiorespiratory arrest should be managed with standard resuscitation protocols. Patients with manifestations of mild poisoning who recover after removal from the exposure can be observed briefly and discharged. Patients at risk for complications of hypoxia, such as those presenting with significant symptoms (e.g., coma) or with exacerbating medical conditions (e.g., cardiac disease), should be observed for the development or progression of posthypoxic complications.

### PULMONARY IRRITANTS

#### Perspective

The pulmonary irritant gases are a large group of agents that produce a common toxicologic syndrome when they are inhaled in moderate concentrations. Although many of these agents can be found in the home, significant poisoning from consumer products is uncommon because of restrictions designed to reduce their toxicity. However, catastrophes such as the 1984 release of methyl isocyanate in Bhopal, India, which resulted in more than 2000 fatalities and 250,000 injuries, remain as an environmental risk. On a different scale, industrialization has increased ambient levels of sulfur dioxide, ozone, and oxides of nitrogen. These irritant gases frequently exacerbate chronic pulmonary disease.

**Table 159-1 Common Inhaled Toxins**

INHALANT	SOURCE OR USE	PREDOMINANT CLASS
Acrolein	Combustion	Irritant, highly soluble
Ammonia	Fertilizer, combustion	Irritant, highly soluble
Carbon dioxide	Fermentation, complete combustion, fire extinguisher	Simple asphyxiant; systemic effects
Carbon monoxide	Incomplete combustion, methylene chloride	Chemical asphyxiant
Chloramine	Mixed cleaning products (e.g., hypochlorite bleach and ammonia)	Irritant, highly soluble
Chlorine	Swimming pool disinfectant, cleaning products	Irritant, intermediate solubility
Chlorobenzylidene malononitrile (CS), chloroacetophenone (CN)	Tear gas (Mace)	Pharmacologic irritant
Hydrogen chloride	Tanning and electroplating industry	Irritant, highly soluble
Hydrogen cyanide	Combustion of plastics, acidification of cyanide salts	Chemical asphyxiant
Hydrogen fluoride	Hydrofluoric acid	Irritant, highly soluble; systemic effects
Hydrogen sulfide	Decaying organic matter, oil industry, mines, asphalt	Chemical asphyxiant; irritant, highly soluble
Methane	Natural gas, swamp gas	Simple asphyxiant
Methylbromide	Fumigant	Chemical asphyxiant
Nitrogen	Mines, scuba diving (nitrogen narcosis, decompression sickness)	Simple asphyxiant; systemic effects
Nitrous oxide	Inhalant of abuse, whipping cream, racing fuel booster	Simple asphyxiant
Noble gases (e.g., helium)	Industry, laboratories	Simple asphyxiant
Oxides of nitrogen	Silos, anesthetics, combustion	Irritant, intermediate solubility
Oxygen	Medical use, hyperbaric conditions	Irritant, free radical; systemic effects
Ozone	Electrostatic energy	Irritant, free radical
Phosgene	Combustion of chlorinated hydrocarbons	Irritant, poorly soluble
Phosphine	Hydration of aluminum or zinc phosphide (fumigants)	Chemical asphyxiant
Smoke (varying composition)	Combustion	Variable, but may include all classes
Sulfur dioxide	Photochemical smog (fossil fuels)	Irritant, highly soluble

## Principles of Disease

Irritant gases dissolve in the respiratory tract mucus and alter the air-lung interface by invoking an irritant or inflammatory response. When these gases are dissolved, most of them produce an acid or alkaline product, but several generate oxygen-derived free radicals that produce direct cellular toxicity (Fig. 159-1). The clinical effects of pulmonary irritants can be predicted by their water solubility (see Table 159-1).

## Clinical Features

Highly water-soluble gases have their greatest impact on the mucous membranes of the eyes and upper airway. Exposure results in immediate irritation, with lacrimation, nasal burning, and cough. Although their pungent odors and rapid symptom onset tend to limit significant exposure, massive or prolonged exposure can result in life-threatening laryngeal edema, laryngospasm, bronchospasm, or acute respiratory distress syndrome (ARDS) (formerly known as noncardiogenic pulmonary edema).<sup>4</sup> Poorly water-soluble gases do not readily irritate the mucous membranes at low concentrations, and some have pleasant odors (e.g., phosgene's odor is similar to that of hay). Because there are no immediate symptoms, prolonged breathing in the toxic environment allows time for the gas to reach the alveoli. Even moderate exposure causes irritation of the lower airway, alveoli, and parenchyma and causes pulmonary endothelial injury after a 2- to

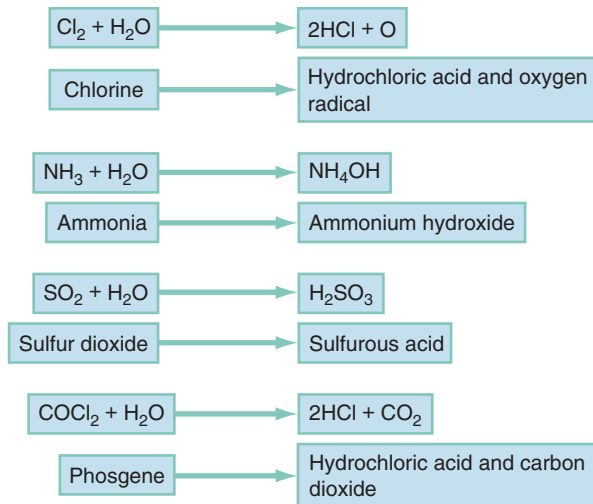
24-hour delay. Initial symptoms consistent with acute respiratory distress syndrome may be mild, only to progress to overt respiratory failure and acute respiratory distress syndrome during the ensuing 24 to 36 hours.<sup>5</sup>

Gases with intermediate water solubility tend to produce syndromes that are a composite of the clinical features manifested with the other gases, depending on the extent of exposure. Massive exposure is most often associated with rapid onset of upper airway irritation and more moderate exposure with delayed onset of lower airway symptoms.<sup>6</sup>

## Diagnostic Strategies and Differential Considerations

The evaluation of upper airway symptoms is usually done through physical examination but may require laryngoscopy. After exposure, swelling may occur rapidly or may be delayed, so normal findings on oropharyngeal or laryngeal evaluation may not exclude subsequent deterioration. Radiographic and laboratory studies have little role in the evaluation of upper airway symptoms.

Oxygenation and ventilation are assessed by serial chest auscultation, pulse oximetry, and capnometry supplemented as needed by chest radiography and ABGs in patients with cough, dyspnea, hypoxia, or abnormal findings on physical examination. No clinical test can identify the specific irritant, and identification is not generally necessary for patient care, although knowing the causative agent may allow refinement of the observation period.



**Figure 159-1.** Sample reactions of pulmonary irritants reacting with water in the lung.

Bronchospasm, cough, chest tightness, and acute conjunctival irritation frequently follow allergen exposure, but the history generally suggests the diagnosis. ARDS occurs after many physiologic insults, including trauma and sepsis, highlighting the need for accurate history taking.<sup>5</sup>

## Management

Signs of upper airway dysfunction (e.g., hoarseness and stridor) mandate direct visualization of the larynx and immediate airway stabilization, if necessary. Given the potential rapidity of airway deterioration, early and frequent reassessment should be performed.

Bronchospasm generally responds to inhaled beta-adrenergic agonists; the role of ipratropium is not yet defined. Other than as a standard treatment of a comorbid condition, such as asthma, there is no clear indication for corticosteroids.<sup>7</sup>

Patients exposed to chlorine or hydrogen chloride gas receive symptomatic relief from nebulized 2% sodium bicarbonate solution.<sup>6</sup> Because the inflammatory cascade is not altered, however, the component of lung injury mediated by free radicals probably continues and causes delayed deterioration. Patients receiving inhalational bicarbonate therapy require extensive discharge instructions for signs and symptoms of pulmonary irritation or admission to the hospital.

Diagnosis of acute respiratory distress syndrome indicates the need for aggressive supportive care, including manipulations of the patient's airway pressures (e.g., continuous positive airway pressure and positive end-expiratory pressure). Exogenous surfactant and nitric oxide may have a beneficial role in toxin-induced acute respiratory distress syndrome, despite little support for use in other forms of the syndrome.

## Disposition

Patients exposed to highly water-soluble gases can be discharged if they are asymptomatic or improve with symptomatic therapy. After exposure to intermediate or poorly water-soluble gases, asymptomatic patients should be observed for increasing dyspnea for several hours before final disposition. Patients with substantial exposure to these agents or those in high-risk situations (e.g., underlying pulmonary disease, extremes of age, and poor follow-up) should be observed for 24 hours and may require hos-

pitalization. All patients should be instructed to return if symptoms recur.

## SMOKE INHALATION

### Perspective

Annually, approximately 4000 people are injured or die in residential fires in the United States. Many of these casualties do not suffer serious cutaneous burns but rather die of smoke inhalation. This is a variant of irritant injury in which heated particulate matter and adsorbed toxins injure normal mucosa, similar to other irritant gases. In addition, CO and cyanide are systemic toxins often discussed with the smoke inhalation syndrome because of their common origin.

### Principles of Disease

Even at temperatures between 350 and 500° C, air has such a low heat capacity that it rarely produces lower airway damage. However, the greater heat capacity of steam (approximately 4000 times that of air) or heated soot suspended in air (i.e., smoke) can transfer heat and cause injury deep within the respiratory tract.

The nature of the fuel determines the composition of its smoke, and because fires involve variable fuels and burning conditions, the character of fire smoke is almost always undefined to the clinician. Irritant toxins produced by the fire are adsorbed onto carbonaceous particles that are deposited in the airways. The irritant substances damage the mucosa through mechanisms similar to those of the irritant gases, including generation of acids and free radical formation.

### Clinical Features

Most smoke-associated morbidity and mortality relate to respiratory tract damage. Thermal and irritant-induced laryngeal injury may produce cough or stridor, but these findings are often delayed. Soot and irritant toxins in the airways can produce early cough, dyspnea, and bronchospasm. Subsequently, a cascade of airway inflammation results in acute lung injury with failure of pulmonary gas exchange. The time between smoke exposure and the onset of clinical symptoms is highly variable and dependent on the degree and nature of the exposure. Singed nasal hairs and soot in the sputum suggest substantial exposure but are neither sufficiently sensitive nor specific to be practical.<sup>8</sup>

CO inhalation should be routinely considered in these patients. Patients who are exposed to filtered or distant smoke (e.g., in a different room) or to relatively smokeless combustion (e.g., engine exhaust) inhale predominantly CO, cyanide, and metabolic poisons and do not sustain smoke exposure.

### Diagnostic Strategies and Differential Considerations

With the obvious exposure history, the differential diagnosis is limited. Although it is often unclear whether inhalational injuries are thermal or irritant, the differentiation is clinically irrelevant. CO and cyanide should be considered in every case.

Early death is caused by asphyxia, airway compromise, or metabolic poisoning (e.g., CO). Airway patency should be evaluated early. If evidence of significant airway exposure is present, such as carbonaceous sputum or hoarse voice, the airway should be examined by direct or fiberoptic laryngoscopy. Simply observing the patient for deterioration can result in airway compromise requiring rapid and, by then, very difficult airway intervention. Signs of alveolar filling or hyperinflation on chest radiography, abnormal flow-volume loop or diffusing capacity for

CO on pulmonary function testing, or abnormal distribution and clearance of radiolabeled gas on ventilation scans can help predict lower airway injury.<sup>9</sup>

Metabolic acidosis, particularly when it is associated with a serum lactate level greater than 10 mmol/L, suggests concomitant cyanide poisoning.<sup>10</sup> Oxygenation should be assessed by co-oximetry because blood gas analysis and pulse oximetry may be inaccurate in CO-poisoned patients (see later).

## Management

The acute management of smoke inhalation is identical to that of other irritant inhalational injuries. Rapid assessment of the airway and early intubation, as indicated, are critical because deterioration may be occult and rapid. Inhaled beta-adrenergic agonists are widely used but without evidence supporting their benefit. Optimal supportive care and maintenance of adequate oxygenation (e.g., suctioning and pulmonary toilet) are the most important aspects of care. Bronchoscopy with bronchoalveolar lavage is frequently recommended to clear debris and toxins from the distal airways. Corticosteroids, whether they are inhaled or administered systemically, are not demonstrated to be helpful and are potentially harmful in patients with cutaneous burns.<sup>11</sup> Ibuprofen, antioxidants, exogenous surfactant, and high-frequency ventilation yield variably improved survival in experimental and clinical trials; none is considered standard care. Antibiotics should be used only in patients with suspected infection.

## Disposition

After the airway is examined and stabilized, patients with worrisome clinical findings (e.g., hoarseness and respiratory distress) and those at high risk of substantial exposure (e.g., closed-space exposure and carbonaceous sputum) should be admitted to a critical care unit or transferred to a burn center. This decision will vary on the basis of local resources, such as hospital capabilities and availability of a burn referral center.

## CYANIDE AND HYDROGEN SULFIDE

### Perspective

Inhalation can be the route of exposure for systemic poisons. Instead of directly affecting the airway and lungs, these poisons cause effects at the cellular level. Hydrogen cyanide is a gas with many commercial uses, particularly in synthetic fiber manufacture and fumigation. Hydrogen cyanide is occasionally noted to have the odor of bitter almonds. Cyanide in its salt form (e.g., sodium or potassium) is important in the metallurgic (e.g., jewelry) and photographic industries and is much safer to work with because of its low volatility. Cyanide salts do not have an odor under dry conditions. When cyanide salts are dissolved in water, hydrogen cyanide can leave the surface, particularly under acidic conditions. Cyanide is metabolically released in vivo from precursors (cyanogens) such as amygdalin, found in apricot and other *Prunus* species pits, and from nitriles, a group of chemicals with many commercial uses.

Hydrogen sulfide poisoning most often occurs in petroleum refinery and sewage storage tank workers. An Internet-derived means of suicide involves generation of hydrogen sulfide from sulfur-containing products, such as detergent, mixed with acids in an enclosed space, such as an automobile. On occasion, well-intentioned but hasty would-be rescuers become victims, emphasizing the need for proper training and equipment. Hydrogen sulfide has a noxious odor similar to rotten eggs, which becomes

unnoticeable with extremely high concentrations or prolonged exposure (*olfactory fatigue*).<sup>12</sup>

## Principles of Disease

Gaseous cyanide is rapidly absorbed after inhalation and is immediately distributed to the oxygen-using body tissues. Inhibition of oxidative metabolism by binding to complex IV of the electron transport chain within mitochondria occurs within seconds. The poisoned tissue rapidly depletes its adenosine triphosphate reserves and ceases to function (Fig. 159-2). Cyanide has no evident effect on other oxygen-binding enzyme systems, most notably hemoglobin. This is probably explained by the oxidation state of its iron moiety; cyanide binds only to oxidized iron ( $\text{Fe}^{3+}$ ), whereas deoxyhemoglobin contains reduced iron ( $\text{Fe}^{2+}$ ).

Hydrogen sulfide exerts its toxic effects both as a pulmonary irritant and as a cellular poison.<sup>12</sup> Its deadly metabolic effects are produced by a mechanism identical to that for cyanide poisoning. However, hydrogen sulfide's spontaneous dissociation from the mitochondrial cytochrome complex IV is rapid, allowing many patients to survive after brief exposure.

## Clinical Features

Tissue hypoxia occurs within minutes, with the exact onset dependent on the route, dose or concentration, and nature of the exposure. Dysfunction of the heart and the central nervous system—the organ systems most sensitive to hypoxia—is characteristic of cyanide poisoning, manifested as coma, seizures, dysrhythmias, and cardiovascular collapse. Metabolic acidosis develops as a result of diffuse cellular dysfunction and is associated with an elevated serum lactate concentration. Cyanosis is not characteristic but can be present in profoundly poisoned patients. Given the extreme toxicity of cyanide, mild acute poisoning is uncommon. Patients with acute hydrogen sulfide poisoning have similar clinical manifestations, although many are recovering by the time of arrival in the emergency department.

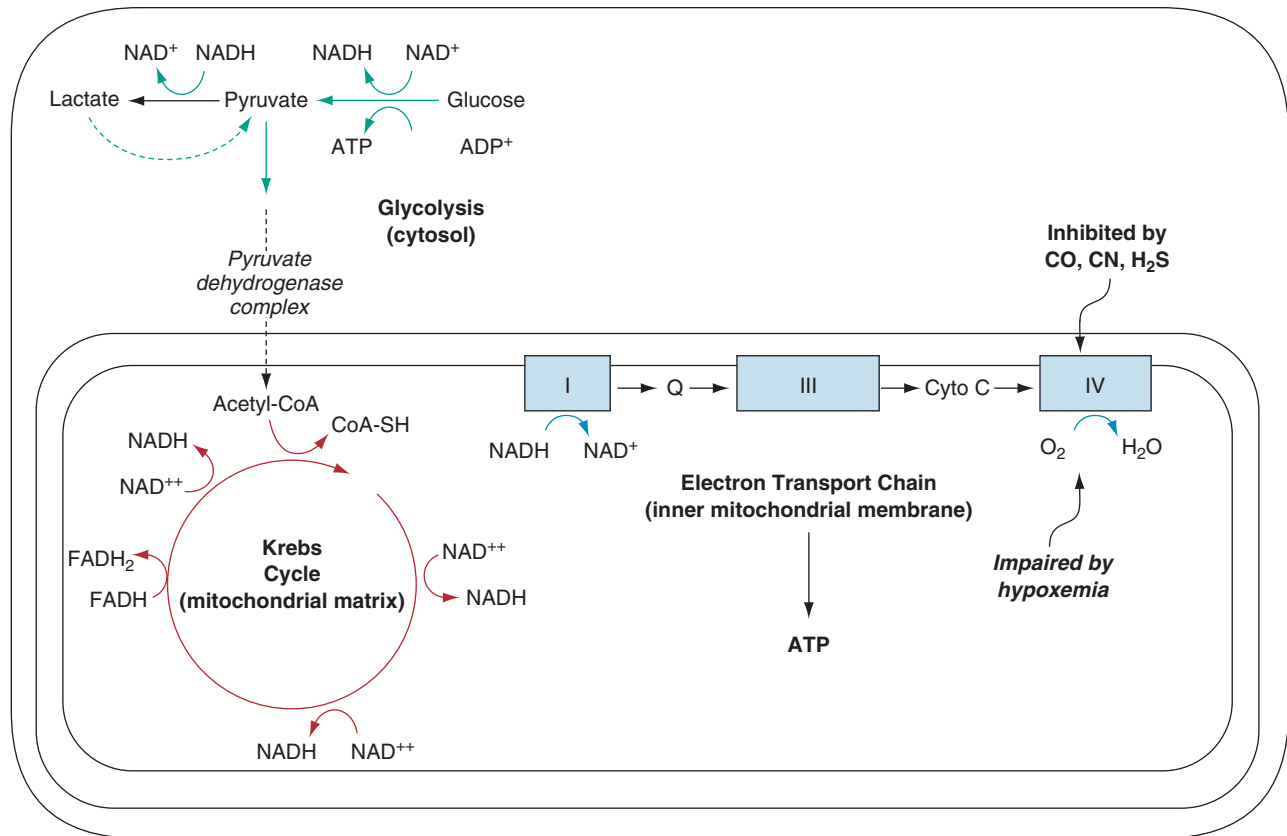
Because cyanide and hydrogen sulfide prevent tissue extraction of oxygen from the blood, the oxygen content of venous blood remains high, approaching that of arterial blood. Clinically, this may appear as the “arterialization” or brightening of venous blood to resemble arterial blood. A comparison of the measured venous (ideally but impractically mixed venous) and arterial oxygen contents may assist in the diagnosis of cyanide poisoning.<sup>13</sup> A low arterial-venous oxygen difference is suggestive of cyanide poisoning but is neither exclusionary nor pathognomonic for the diagnosis.

Patients surviving cyanide or hydrogen sulfide poisoning may have persistent or delayed-onset neurologic syndromes identical to those noted in patients with CO poisoning or cardiac arrest.<sup>14</sup>

## Diagnostic Strategies and Differential Considerations

The result of a blood cyanide determination is usually too delayed to be of use in the emergency department, but it can be useful for confirmation and documentation purposes. Technology exists for immediate cyanide determination but is not widely available. Rapid tests for hydrogen sulfide are not available.

In practice, the diagnosis is based on the circumstances of exposure and a corroborative physical examination. Rapid cardiovascular collapse, hypotension, bradycardia, ventricular dysrhythmias, and seizures in a fire victim should suggest cyanide poisoning but are also consistent with severe CO poisoning.<sup>10</sup> An elevated carboxyhemoglobin concentration in a fire victim may also suggest concomitant cyanide poisoning. However, the presence of these dramatic clinical findings with a low carboxyhemoglobin level is



**Figure 159-2.** The complete metabolism of a molecule of glucose to energy is complex but occurs in two broad steps. The first step, anaerobic glycolysis, which occurs in the absence of oxygen, generates pyruvate, NADH, and adenosine triphosphate (ATP). Pyruvate then enters the Krebs cycle to create potential energy in the second step, through the reduction of NAD<sup>+</sup> to NADH and FADH to FADH<sub>2</sub>. Similarly, fatty acid metabolism and protein metabolism produce FADH<sub>2</sub> and NADH, which also requires conversion to ATP. These conversions occur in the mitochondrial membrane, where oxidative phosphorylation is linked to the electron transport chain, the last phase of which involves the transfer of electrons to molecular oxygen to form water. Cyanide (CN), hydrogen sulfide (H<sub>2</sub>S), and carbon monoxide (CO) bind to and inhibit the last step, the Fe<sup>3+</sup>-containing cytochrome-aa<sub>3</sub> in complex IV, preventing further oxidation of NADH. This in turn hinders the Krebs cycle because the required regeneration of NAD<sup>+</sup> does not occur, and glucose metabolism is forced to end at pyruvate. For energy production to continue, NADH donates its electrons to pyruvate, creating lactate, and sufficient NAD<sup>+</sup> is regenerated for glycolysis to progress. Ultimately, energy failure and end-organ damage occur. CoA, coenzyme A; FAD, flavin adenine dinucleotide; NAD, nicotinamide adenine dinucleotide.

also concerning for cyanide poisoning. Pulse oximetry and ABG analysis are accurate in cases of isolated cyanide or hydrogen sulfide poisoning. An increased anion gap metabolic acidosis and elevated serum lactate concentration are usually present. A lactate concentration greater than 10 mmol/L in a fire victim is highly predictive of cyanide poisoning.<sup>10</sup> However, the carboxyhemoglobin level and other laboratory test results may take too long to be obtained, and the delay has important implications for the treatment of cyanide poisoning.

## Management

Patients exposed to cellular poisons, including hydrogen cyanide and hydrogen sulfide, require individualized and specific therapy. The diagnosis usually cannot be confirmed rapidly, and therapy is almost always empirical. Treatment should not be delayed in patients with suspected acute cyanide poisoning, and antidotal therapy should be administered immediately.

### Hydrogen Cyanide

The accepted goal of therapy is to reactivate the cytochrome oxidase system by providing an alternative binding site for the cyanide ion. There are two types of antidotal therapy for cyanide.

The cyanide antidote kit produces a high-affinity source of ferric ions (Fe<sup>3+</sup>) for cyanide to bind. The kit has three components, and although the best results are likely to be attained when the entire kit is used, this may be impractical or dangerous, particularly for nonhospital providers. Because animal models and clinical evidence in humans demonstrate that sodium thiosulfate alone (the “third” part of the kit), in combination with oxygen and sodium bicarbonate, offers substantial protection, this should be the initial therapy administered by paramedics and during mass poisoning events. Antidotes should not completely replace other resuscitation measures, including high-flow oxygen.

Methemoglobin (MetHb) formation is the goal of the first two parts of the kit. Inhaled amyl nitrite and intravenous sodium nitrite are both effective, but amyl nitrite should be administered to patients only before intravenous access. Caution should be taken to minimize the provider’s exposure to the volatile amyl nitrite because dizziness, hypotension, or syncope may occur. The dose of sodium nitrite for a previously healthy adult is 300 mg (10 mL of a 3% solution) given during 2 to 4 minutes, and dosing instructions for anemic patients and children are supplied with the kit. Sodium nitrite is a vasodilator, and hypotension may complicate a rapid infusion. Cyanide has a high affinity for MetHb and readily leaves cytochrome oxidase to form cyanmethemoglobin. Both free serum cyanide and cyanmethemoglobin are converted

by sulfur transferase (*rhodanese*) to thiocyanate, which is renally eliminated. Because the rate of rhodanese function increases with the availability of sulfur donor, the third part of the antidote kit is the sulfur-containing compound sodium thiosulfate. The adult dose is 12.5 g intravenously (IV), which is provided as 50 mL of a 25% solution (2 mL/kg of 25% sodium thiosulfate up to an adult dose in children). In general, few if any adverse effects are associated with proper doses. The nitrite components of the cyanide antidote kit should be avoided in fire victims with possible simultaneous CO and cyanide poisoning because both CO and MetHb reduce oxygen delivery to the tissues. The use of the thiosulfate component alone in this subset of patients is recommended.

Hydroxocobalamin is another antidotal therapy that takes advantage of the high affinity of cobalt for cyanide. On binding of cyanide, cyanocobalamin, or vitamin B<sub>12</sub>, is formed. The initial dose is 5 g IV during 15 minutes for adults and 70 mg/kg IV for children, up to an adult dose.<sup>15</sup> Thiosulfate, 12.5 g, can be coadministered if it is available. The known adverse effects of hydroxocobalamin are mild and include hypertension in those not cyanide poisoned and a bright red discoloration of the patient's skin. The drug's red color can interfere with certain spectrophotometric laboratory tests, including carboxyhemoglobin and possibly serum lactate, and blood samples should be obtained before the administration of the first dose of hydroxocobalamin.

There are insufficient clinical data to fully support the use of one cyanide antidote over the other.<sup>16</sup> However, hydroxocobalamin has been used for years and is largely replacing the cyanide antidote kit in the United States because of its ease of use and theoretic safety in CO-poisoned fire victims. Direct comparison to thiosulfate alone in this population has not been and likely never will be performed.<sup>17</sup>

Hyperbaric oxygen (HBO) therapy has been advocated but is of no proven benefit and is not routinely indicated for cyanide poisoning. In selected cases, when it is immediately available, its apparent value may lie in its ability to superoxygenate plasma and tissues, thus permitting higher levels of methemoglobinemia, particularly when CO poisoning is also present.

## Hydrogen Sulfide

Because the bond between hydrogen sulfide and cytochrome oxidase is rapidly reversible, removal from exposure and standard resuscitative techniques are usually sufficient to reverse hydrogen sulfide toxicity. Use of the nitrite portion of the cyanide antidote kit is suggested to create MetHb for patients with severe or prolonged toxicity.<sup>12</sup> Sodium thiosulfate is unnecessary because hydrogen sulfide is not detoxified by rhodanese. There is no defined role for hyperbaric oxygen therapy in cases of hydrogen sulfide toxicity.

## Disposition

All patients with symptomatic cyanide or hydrogen sulfide poisoning should be admitted to a critical care unit and observed for complications of tissue hypoxia. All patients should be observed for delayed neuropsychiatric findings.

## CARBON MONOXIDE

### Perspective

CO is the most common cause of acute poisoning death in developed nations and the most common cause of fire-related death.<sup>18</sup> CO is generated through incomplete combustion of virtually all carbon-containing products. Structure fires (e.g., wood), clogged vents for home heating units (e.g., methane), and use of gasoline-powered generators indoors are examples of the myriad means

through which patients are poisoned by CO. Appropriate public health authorities (e.g., fire department and Department of Health officials) should be informed immediately about any potential public health risks that are identified during the care of a CO-exposed patient.

## Principles of Disease

CO interacts with deoxyhemoglobin to form carboxyhemoglobin (COHb), which cannot carry oxygen. Hemoglobin binds CO tightly and forms a complex that is only slowly reversible. This allows the exposed individual to accumulate CO, even with exposure to low ambient concentrations. Although binding of hemoglobin is historically described as the mechanism of CO poisoning, it is relevant only in profoundly CO-poisoned patients because a simple reduction in oxygen-carrying capacity due, for example, to anemia would not cause similar symptoms. However, for pregnant patients, the fetus is at risk because it is relatively hypoxic compared with the mother. In muscle, CO binds myoglobin, preventing its normal function, and this probably explains the development of atraumatic rhabdomyolysis.

Most important, CO affects cellular oxygen use at the tissue level. CO, similar to cyanide, inhibits the final cytochrome complex involved in mitochondrial oxidative phosphorylation. This results in a switch to anaerobic metabolism and ultimately in cellular death.

Delayed-onset neurologic complications may be a manifestation of the hypoxic insult, although reperfusion injury and lipid peroxidation related to platelet-induced nitric oxide release may play a significant role.<sup>19</sup> By alteration of the platelet-associated nitric oxide cycle, the microvascular endothelium of the central nervous system undergoes free radical-mediated injury, resulting in localized inflammation and dysfunction. Animal models and human reports suggest that loss of consciousness during CO exposure may be necessary and is certainly a risk factor for the development of delayed neurologic sequelae.<sup>20</sup>

## Clinical Features

Severe CO toxicity and cyanide poisoning have identical clinical presentations of asphyxia: altered mental status, including coma and seizures; extremely abnormal vital signs, including hypotension and cardiac arrest; and metabolic acidosis. Unlike cyanide poisoning, however, mild CO poisoning occurs frequently, with headache, nausea, vomiting, dizziness, myalgia, and confusion as common presenting complaints. The neurologic assessment in these patients may yield normal findings or may demonstrate focal findings or subtle perceptual abnormalities. The often-touted cherry-red skin color in patients with cyanide or CO poisoning is a postmortem finding and is not noted in living patients.

Delayed neurologic sequelae are a well-documented phenomenon after CO exposure, although the frequency varies from 12 to 50%, depending on the definition and the sensitivity of the test used for their detection.<sup>21</sup> Patients have a variety of neurologic abnormalities after an asymptomatic period ranging from 2 to 40 days.<sup>20</sup> The delayed neurologic effects can be divided into those with readily identifiable neurologic syndromes (e.g., focal deficits and seizures) and those with primarily psychiatric or cognitive findings (e.g., apathy and memory deficits). Although the delayed neuropsychiatric sequelae require formal neuropsychiatric testing to be detected, the impact of these abnormalities on the patient's daily function may be significant. Risk factors that predict the development of delayed neurologic sequelae include age and loss of consciousness. Because most CO-poisoned patients reaching the emergency department survive, prevention of delayed neurologic and neuropsychiatric sequelae is the major goal of therapy.

## Diagnostic Strategies and Differential Considerations

Suspicion of CO poisoning relies on the history and physical examination findings. Co-oximetry, an inexpensive and readily available spectrophotometric laboratory method that can distinguish between the normal hemoglobins and COHb (and MetHb), confirms exposure to CO. Other laboratory tests only exclude other diagnoses. Severity of poisoning may not correlate with COHb levels because prolonged exposure to low levels can be fatal with a low measured COHb, but a brief, high-concentration exposure can produce a high COHb level with minimal symptoms.

The ABG analysis is a poor screening test for CO poisoning other than to identify the presence of a metabolic acidosis and a normal partial pressure of oxygen ( $P_{O_2}$ ). CO decreases oxygen bound to hemoglobin but does not affect the amount of oxygen dissolved in blood. Because the  $P_{O_2}$ , a measure of dissolved oxygen, is normal in patients with CO poisoning, the calculated oxygen saturation will be normal even in the presence of significant CO poisoning. Most pulse oximeters are unable to detect CO poisoning because COHb essentially is misinterpreted as oxyhemoglobin. Newer pulse co-oximeters are capable of noninvasively detecting COHb as well as methemoglobinemia, but the exact clinical utility of this test is not yet fully defined.<sup>22</sup>

Mild to moderate CO poisoning is a difficult diagnosis to establish clinically, and patients are easily misdiagnosed as having a benign headache syndrome or viral illness. CO poisoning should be suspected in every patient with persistent or recurrent headache, especially if a group of people have similar symptoms or if the headache improves soon after the person leaves an exposure site.

Patients with severe CO poisoning may present with coma or cardiovascular collapse, both of which have a broad toxicologic, metabolic, infectious, medical, and traumatic differential diagnosis. Many diagnoses are excluded by the medical history, physical examination, or standard laboratory testing. Given the relatively protean manifestations of CO poisoning, when it is being seriously considered, it should be excluded by co-oximetry of an arterial or venous blood sample or by newer pulse co-oximetry. Misdiagnosis can be catastrophic, particularly if the patient returns to the poisoned environment.

## Management

Treatment begins with oxygen therapy, which serves two purposes. First, the half-life of COHb is inversely related to the  $P_{O_2}$ ; it can be reduced from approximately 5 hours on room air to 1 hour by providing supplemental 100% oxygen. Hyperbaric oxygen (HBO) therapy further reduces the half-life to approximately 30 minutes. Alteration of the kinetics of COHb is applicable only to patients with extremely elevated COHb levels (e.g., 50%). Even then, only a minority of patients can be treated sufficiently rapidly for the HBO to be lifesaving. Second, a sufficient  $P_{O_2}$  can be achieved with HBO to sustain life in the absence of adequately functioning hemoglobin, but this is helpful only when the COHb is extremely elevated. Thus, the primary indication for HBO is not to prevent mortality but rather to prevent delayed neurologic sequelae.

There is controversy regarding the benefit of HBO because the effect is not immediate (as with life and death) but requires close follow-up and sophisticated testing. Several evidence-based reviews have suggested a limited role for HBO, although this conclusion is disputed.<sup>23-25</sup> A decrease of delayed neurologic sequelae from approximately 12% to less than 1% is associated with HBO.<sup>21</sup> When HBO administration is delayed more than 6 hours after exposure, its efficacy appears to decrease,<sup>26</sup> suggesting the need for rapid decision-making. Evidence also suggests that HBO positively affects the development of the delayed neuropsychiatric and

delayed neurologic sequelae after CO poisoning.<sup>27-29</sup> A randomized, double-blind study found that HBO therapy was superior to normobaric oxygen therapy at reducing the incidence of delayed neurologic sequelae at both 6 weeks and 1 year after poisoning.<sup>27</sup> However, another found no benefit of HBO on the development of delayed neurologic sequelae compared with extensive normobaric oxygen.<sup>28</sup> In this study, however, the majority of patients were suicidal and possibly depressed, which would interfere with performance on the neuropsychiatric testing needed to differentiate the two groups of patients. A recent trial found that in comatose patients, one HBO session was superior to two sessions; however, in patients with transient loss of consciousness (i.e., syncope), outcome after HBO therapy was equivalent to 6 hours of normobaric oxygen therapy.<sup>30</sup>

Given the implications of poor tissue oxygenation with COHb and the relative safety of HBO, a patient with a neurologic abnormality or cardiovascular instability (e.g., syncope, altered mental status, myocardial ischemia, and dysrhythmias) is a candidate for HBO. This should be tempered by the need for transport, sometimes long distances, for HBO therapy to be obtained. The decision about HBO therapy should not be strictly based on the COHb level, which correlates only weakly with toxicity. For example, patients with prolonged low-level exposure have a "soaking" phenomenon, in which extremely high tissue concentrations of CO occur with low COHb levels. Thus, patients with consequential clinical findings that are considered to be related to CO poisoning should receive HBO even though their COHb level is relatively low.

In addition to use of HBO in patients with obvious signs of tissue hypoxia, some institutions have set a conservative COHb level of 25% at which asymptomatic or minimally symptomatic patients will be referred for HBO therapy. Some institutions use COHb levels of 40%, and others refrain from specifying a number. The decision to perform HBO therapy should be considered in light of the transport and other medical requirements. Special consideration is given to pregnant women because of the relative hypoxia of the fetus. Because fetal CO poisoning is associated with dysfunction and death and HBO therapy appears to be safe in pregnancy, many institutions initiate HBO therapy in a pregnant woman to a COHb level of 15%.<sup>31</sup>

Further study is still needed to define the optimal duration, pressure, and frequency as well as the cost-benefit and risk-benefit relationships of HBO therapy. At this time, discussion with a regional HBO center or poison control center is advisable. Patients with elevated COHb levels who do not require HBO should be treated with normobaric oxygen delivered by a tight-fitting non-rebreather face mask until the symptoms resolve and the COHb levels fall. The total duration of such therapy is undefined, and although 3 days was suggested in one study,<sup>28</sup> most mildly CO-poisoned patients probably require no more than 6 hours of therapy.<sup>32</sup>

## Simultaneous Carbon Monoxide and Cyanide Poisoning (Fire Victim)

Concurrent toxicity from CO and cyanide is widely reported and a major factor in the mortality associated with smoke.<sup>10,33</sup> Smoke inhalation victims who present with coma and metabolic acidosis can have severe CO poisoning, cyanide poisoning, or both. Nitrite-induced methemoglobinemia, which further reduces the tissue oxygen delivery, may be detrimental to patients with elevated COHb levels or otherwise impaired oxygen delivery.

Sodium thiosulfate, administered without nitrites,<sup>34</sup> or hydroxocobalamin should be given to all smoke inhalation victims with coma, hypotension, severe acidosis, or cardiovascular collapse in whom cyanide poisoning cannot be rapidly excluded. If the COHb level is known to be low and the patient has persistent acidosis or

hemodynamic instability, the complete cyanide antidote kit, including the nitrites, can be administered. Patients with high COHb levels undergoing HBO therapy can also receive nitrite therapy while pressurized with little concern of decreasing the oxygen-carrying capacity. Alternatively, hydroxocobalamin, with or without sodium thiosulfate, can be administered in either of these last two situations.

## Disposition

The decision to transfer a patient to an HBO facility must consider the time delay to therapy, patient issues (e.g., burns and age), and potential transport-related complications.<sup>35</sup> At a minimum, prolonged normobaric oxygen therapy should be administered, although the benefit of this remains undefined. Admission decisions should be based on the patient's clinical condition. All patients exposed to CO require close follow-up for delayed neurologic sequelae.

## KEY CONCEPTS

### Simple Asphyxiants

- Any gas can be a simple asphyxiant if it displaces sufficient oxygen from the breathable air.
- Appropriate therapy for simple asphyxiation includes removal from exposure, supplemental oxygen, and supportive care.

### Pulmonary Irritants

- Highly water-soluble gases produce rapid irritation and predominantly upper respiratory tract symptoms, such as bronchospasm.
- Poorly water-soluble gases often produce delayed lower respiratory tract findings, such as acute respiratory distress syndrome.

### Smoke Inhalation

- Smoke inhalation injury is typically irritant in nature.
- Early assessment, often including visualization of the airway, is essential. Early intubation before deterioration is critical if damage is present.
- Consider carbon monoxide and cyanide in patients with smoke inhalation.

### Cyanide and Hydrogen Sulfide

- An antidote for cyanide poisoning optimally be administered early.
- The sodium thiosulfate portion of the cyanide antidote kit and hydroxocobalamin are safe for empirical administration in any patient in whom cyanide poisoning is possible, including fire victims.
- Patients with hydrogen sulfide poisoning generally respond to removal from exposure and ventilatory support.

### Carbon Monoxide

- Carbon monoxide poisoning is common and has important public health implications.
- Carbon monoxide poisoning can be covert and difficult to diagnose; it should be investigated with co-oximetry.
- Because the role of hyperbaric oxygen therapy in carbon monoxide poisoning is controversial, consultation with a hyperbaric oxygen facility, poison control center, or medical toxicologist may be helpful.

*The references for this chapter can be found online by accessing the accompanying Expert Consult website.*



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