Asphyxiants

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KEYWORDS

• Asphyxiants • Cyanide • Hydrogen sulfide • Carbon monoxide • Hydrazoic acid • Azide • Methemoglobinemia • Antidote

KEY POINTS

- Asphyxiants deprive the body of needed oxygen via displacement (simple asphyxiants) or by interfering with transport or use of oxygen within tissues and organs (systemic asphyxiants).
- Asphyxiants may be gases, liquids, or solids and may enter the body by multiple routes.
- Bedside clinical diagnosis is essential, because confirmatory tests are often delayed or unavailable.
- The asphyxiant toxidrome, supported by a careful history and search for distinguishing clinical features, helps to narrow the differential diagnosis.
- Aggressive supportive care is often lifesaving in these poisonings.
- Early use of appropriate antidotal therapy is effective against severe carbon monoxide, cyanide, and opioid poisonings and toxicant-induced methemoglobinemia.

INTRODUCTION

Asphyxia is defined as impaired or absent exchange of oxygen and carbon dioxide on a ventilatory basis; combined hypercapnia and hypoxia or anoxia. Stedman's further defines an asphyxiant as "anything, especially a gas that produces asphyxia."[1] Although people tend to think of highly, toxic gases when discussing asphyxiation, it is particularly important for the emergency physician to keep in mind that asphyxiants may be gases, liquids, or solids, and can potentially enter the body not only by inhalation but also by skin absorption, ingestion, or injection. The speed of onset of symptoms is determined not only by the substance's inherent toxicity and physical characteristics, such as water solubility, but by its propensity for metabolism to toxic

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byproducts. Thus, although inhalation of hydrogen sulfide gas in high concentrations may result in immediate knockdown and apnea, symptoms of asphyxia after ingestion of sodium azide may lag by an hour or so,[2] and symptoms of cyanide poisoning after ingestion of acetonitrile by half a day or more.[3] Failure to recognize the role of active metabolism of cyanogens to cyanide or of dichloromethane to carbon monoxide (CO) may contribute to avoidable deaths.

Mechanisms of Asphyxia

Asphyxia may occur through several mechanisms. First, oxygen in inspired air may be replaced by other gases, depriving the body of sufficient atmospheric oxygen. Such gases need not have intrinsic toxicity. Even inhalation of inert gases, such as helium or argon, may lead to death.[4] The condition of (near) death resulting from inadequate atmospheric oxygen is referred to as simple asphyxia. Another form of simple asphyxia results from inability of oxygen to reach the pulmonary capillaries for exchange with carbon dioxide. This condition may occur after exposure to irritant or corrosive gases resulting in upper airway obstruction, bronchospasm, pulmonary edema, or hemorrhage. See the article by Tovar and Leikin in this issue.

In contrast, systemic asphyxia results from exposure to a compound that directly impairs either transport of oxygen via hemoglobin (CO, methemoglobin inducers) or interferes with the efficient use of oxygen at the tissue level via inhibition of oxidative phosphorylation (azides, CO, cyanides, sulfides; **Fig. 1**). There have been significant advances in recent years in understanding of the inhibition of cytochrome-c oxidase by CO, hydrogen cyanide, hydrogen sulfide, and nitric oxide (NO). Physiologic roles for these compounds, as well as their toxicity, have been described by Cooper and Brown.[5]

CIRCUMSTANCES

Unintentional

The circumstances leading to asphyxia are manifold. Most cases are unintentional. CO is the leading cause of unintentional poisoning deaths in the United States.[6] Household exposures to CO may derive from defective furnaces, improper indoor use of generators, and charcoal cooking devices, among others. On average, there are 430 non–fire-related CO deaths per year in the United States.[7] The number of injuries attributable to CO is far greater. Some 68,316 CO exposures were reported to poison centers during 2000 to 2009. Of these, 36,691 people required treatment in a health care facility, with 9625 having moderate to major effects.[6] Industry is responsible for a concerning number of unintentional deaths from asphyxiation. On average, 22 workers die on the job each year from CO poisoning in the United States.[8] Many additional workers seek care in emergency departments after CO exposures.

Another source of industrial asphyxiation is improper confined space entry. The Occupational Safety and Health Administration describe confined spaces as areas not necessarily designed for continuous occupancy, with limited or restricted means for entry or exit. Confined spaces include, but are not limited to, tanks, vessels, silos, storage bins, hoppers, vaults, pits, manholes, tunnels, equipment housings, ductwork, and pipelines.[9] Such areas by their nature are conducive to depletion of atmospheric oxygen (with occupancy) and concentration of gases that are lighter (silo) or heavier (sewer) than air. Notorious industrial multiple casualty incidents involving asphyxiant gases have been reported. A synopsis of federal and state confined space incident investigations can be found at the Web site of the National Chemical Safety Program and in a review by Dorevitch and colleagues.[10,11]

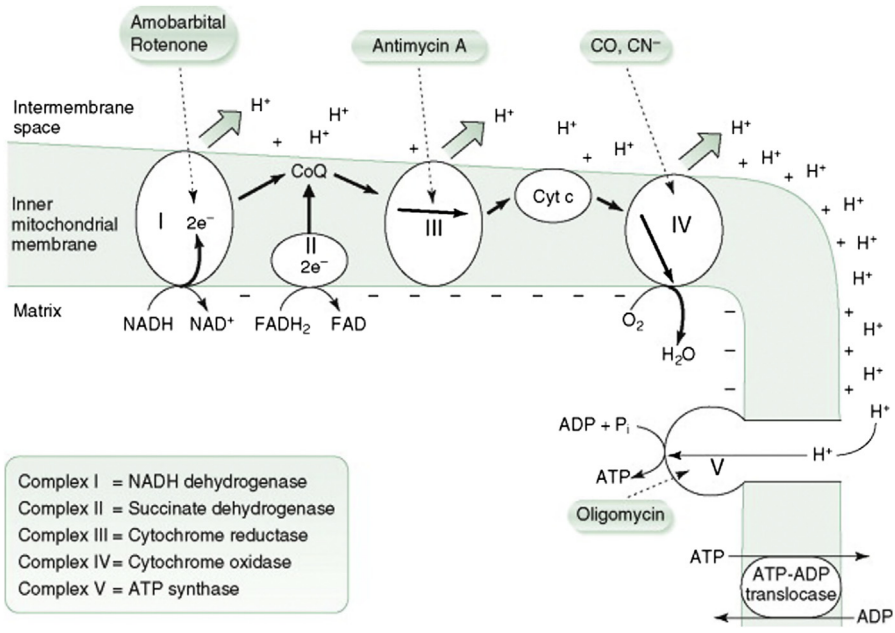

Fig. 1. Electron transport and its inhibition. Overview of oxidative phosphorylation in the inner mitochondrial membrane. Electron flow (*thick arrows*) through complexes I, III, and IV provides energy to pump H^+ ions from the matrix to the intermembrane space (*thick arrows*) against the proton electrochemical gradient. The downhill movement of H^+ ions back into the matrix provides the energy for ATP synthesis by means of complex V. Preferential export of ATP from the matrix by ATP-ADP translocase (an antiport) maintains a high ADP/ATP ratio in the matrix. Inhibitors block electron flow through the indicated complexes (*dashed arrows*); as a result, ATP synthesis also ceases. CN, cyanide; CoQ, coenzyme Q; Cyt c, cytochrome-c; FAD, flavin adenine dinucleotide; FADH2, flavin adenine dinucleotide, reduced form; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide, reduced form. (*From* Pelley JW, Goljan EF. Generation of energy from dietary fuels. In: Pelley JW, editor. Rapid review biochemistry. Philadelphia: Elsevier/Mosby; 2011; with permission.)

Inhalation of products of combustion (fire smoke) is responsible for the largest number of asphyxiant deaths and injuries. The Federal Emergency Management Administration reports that 2450 persons lost their lives and 13,900 were injured in some 364,500 residential building fires occurring in 2011.[12] Structure fires may lead to asphyxia from combined exposures to CO, cyanide, obstruction of alveoli by soot, and a variety of irritant gases and vapors. Although deaths from smoke inhalation are gradually declining, the rate of injuries has remained steady.

Intentional

Asphyxiant poisoning remains a common form of suicide, although related statistics are unclear, because some incidents are classified by vital statistics experts as suffocation and others as poisoning. In 2010, suffocation (which includes people putting plastic bags filled with helium over their heads) was responsible for 9493 deaths, second only to firearms as a method of suicide. Suicide by poisoning (which includes death by CO), was a close third at 6599 deaths.[13] With the uncertainty surrounding autoerotic suffocation,[14] inhalant abuse,[15] or self-poisoning by opioids (arguably an

asphyxiant death), the statistics become even more muddled. In recent years, a disturbing trend of self-poisoning by hydrogen sulfide has been described.[16,17] Suicide by asphyxiation therefore remains an important cause of death.

Statistics for homicide by asphyxiation are equally difficult to discern. For 2010, for example, some of the 544 deaths by homicidal suffocation may be attributable to asphyxiation, as are a portion of the 79 homicides by poisoning.[13]

Use of asphyxiants for the purpose of terrorism is a major concern of federal officials.[18] Both hydrogen cyanide and cyanogen chloride are recognized as chemical warfare agents.[19] In May 1995, operatives of Aum Shinrikyo placed bags of sulfuric acid and sodium cyanide in the restroom of a Tokyo subway station. When mixed, these 2 substances produce deadly hydrogen cyanide (HCN) gas. Injuries in this instance were limited to 4 patients with throat irritation and respiratory problems.[20] In 2012, newspapers reported that Al Qaeda was planning to launch an attack on the Summer Olympics in London using hand cream contaminated with cyanide.[21] As a consequence of hydrogen sulfide suicides, the New York Department of Homeland Security issued an alert in 2008 raising concerns that the potential existed for hydrogen sulfide to be used as a chemical weapon in a terrorist attack.[22] In general, asphyxiant gases have not been highly efficacious as chemical weapons, because of their tendency to disperse on the open battlefield.[23] Nonetheless, there are concerns that such agents could be released in confined spaces with greater risk to the exposed. Such was the case when one or more aerosolized fentanyl derivatives were disseminated by Russian counterterrorist forces through the ventilation system in an opera house in 2002. Although the exact circumstances remain unclear, 125 hostages experienced fatal asphyxia caused by the diffusion of these opioids in an attempt to terminate a hostage situation.[24,25]

To reiterate, asphyxiants need not be in gaseous form to create havoc. In 1978, more than 900 followers of Jim Jones died in a murder/suicide incident involving cyanide-laced Kool-Aid at the People's Temple in Jonestown, Guyana. In 1982, Tylenol capsules were laced with cyanide, causing numerous deaths in the Chicago area. With little imagination and minimal resources, a terrorist group could incite significant societal disruption by targeting open foods in self-serve restaurants in several cities and contaminating them with a potent systemic asphyxiant like potassium cyanide. Although terroristic intentions have not been established in this case, an incident involving presumably intentional contamination, with sodium azide, of iced tea in a restaurant has been reported[26,27] (discussed elsewhere in this issue).

Imagined

In addition, not all apparent collective asphyxiant poisonings are what they seem. Nordt and colleagues[28] describe an event involving 22 patients initially thought to have CO poisoning. Subsequent testing revealed this to be a case of mass sociogenic illness. As the investigators point out, this is a diagnosis of exclusion.

AGENTS OF TOXICITY

Simple Asphyxiants

Virtually any gas not described as a systemic asphyxiant may cause simple asphyxia. Many are physiologically inert, such as nitrogen, helium, argon, and the other noble gases. Others, such as carbon dioxide, Freon, methane, and propane, have some physiologic effects. Nonetheless, in most cases, significant injury or death is thought to occur primarily through oxygen deprivation.

Carbon dioxide, in addition to acting as a simple asphyxiant, has physiologic effects depending on its concentration in air. As the concentration increases, the individual's respiratory rate and heart rate increase. Cardiac arrhythmias and alteration in consciousness may occur. Concentrations greater than 10% may lead to seizures, coma, and death.[29] Carbon dioxide poisoning may also be a contributor to deaths often initially assumed to be caused by hydrogen sulfide,[30] and has been implicated in mass casualty incidents.[31]

In addition to their roles in intentional inhalant abuse,[15] hydrocarbons and fluorocarbons are responsible for industrial incidents, including deaths.[11,32]

Systemic Asphyxiants

Azides

Azides are used as detonators for car airbags, primers, shell detonators, broad-spectrum biocides, and laboratory reagents.[33,34] Azides that are commonly available include sodium azide (NaN_3), lead azide ($Pb[N_3]_2$), and hydrazoic acid (HN_3); HN_3 is formed when sodium azide comes into contact with sulfuric acid. A systematic review of sodium azide exposures found that most industrial exposures occurred by inhalation, whereas laboratory exposures and suicide attempts typically involved ingestion.[33]

Carbon monoxide

Each year, nearly 500 Americans die from unintentional CO poisoning, about 15,000 visit the emergency department, and more than 4000 are hospitalized because of CO poisoning.[6,35] Mass exposures to CO are occasionally reported.[36] In the workplace, approximately 22 deaths each year are recorded to have been caused by unintentional non–fire-related CO poisoning. In most cases, motor vehicles are the exposure source, followed by heaters and generators.[8] Another source of both industrial and home hobbyist exposure includes dichloromethane (also known as methylene chloride), a common ingredient of paint strippers that is metabolized to CO.[37,38]

Cyanides and cyanogens

Cyanides pose risks from intentional exposures, occupational exposures, structural fires, and as a terrorist threat. The National Poison Center Data System annually reports more deaths from cyanide in the United States than from methanol, digoxin, and pesticides combined.[39] Ingestion of cyanide is more common than is generally supposed and is potentially deadly. Mastication and ingestion of seeds of the *Prunus* species (apricots, bitter almonds, choke cherry, peaches) can release amygdalin, which is biotransformed by β-D-glucosidase to cyanide, glucose, and aldehyde.[40] Laetrile, a semisynthetic congener of amygdalin, sold in health food stores as vitamin B_{17}, as a putative but unproven treatment of cancer, has similar potential for cyanide toxicity.[41,42] Collective deaths caused by hydrogen cyanide poisoning have occurred in industry.[43] Cyanogenic (cyanide-producing) industrial solvents, such as acetonitrile and propionitrile, have limited inherent toxicity, but are biotransformed via cytochrome P450 to release cyanide (**Box 1**).[3,44–46] Although structural fires comprise the most common cyanide exposures, another major concern for cyanide toxicity comes from its use as a terrorism weapon. At least 6 European cyanide terrorist plots and 2 US plots have been foiled in recent years.[47]

Smoke inhalation

Fire smoke contains multiple products of combustion, including multiple toxic gases, chief among them CO, cyanide, and carbon dioxide, as well as irritant vapors and soot

Box 1
Common cyanides and cyanogens

Substance	Characteristics and Uses
Acetonitrile, CH_3CN	Common laboratory reagent and solvent. Slowly metabolized to cyanide in the body. Multiple pediatric deaths in past caused by household use as artificial fingernail remover; fewer suicidal and industrial poisonings[3,44,46,53–58]
Acrylonitrile, CH_2CHCN	Used in the manufacture of plastics, adhesives, and rubber. Slowly metabolized to cyanide in the body. Also has inherent toxicity unrelated to cyanide metabolism[59–61]
Calcium cyanide, $Ca(CN)_2$	Water-soluble salt converted to HCN by addition of water or acid. Used as cement stabilizer, fumigant
Cyanogen, NCCN	Colorless gas, heavier than air, soluble in water. Used for welding, cutting metals, rocket propellant. Potential rapid onset of toxicity[62]
Cyanogen bromide, CNBr	Heavy, extremely irritant gas metabolized to cyanide. Used as a fumigant[62]
Cyanogen chloride, CNCl	Heavy, extremely irritant gas metabolized to cyanide. Used as a fumigant. Prohibited chemical warfare agent[62]
Gold cyanide, AuCN	Poorly water-soluble cyanide salt. Delayed onset of toxicity after ingestion[63,64]
Hydrogen cyanide, HCN	Gas or volatile liquid used in electroplating, metallurgy. Common component of fire smoke. Susceptible to use in terrorism. Prohibited chemical warfare agent[49–52,65–67]
Mercuric cyanide, $Hg(CN)_2$	Poorly water-soluble cyanide salt; bactericide, disinfectant. Delayed onset of toxicity after ingestion. Mercury poisoning also possible[68,69]
Potassium cyanide, KCN	Water-soluble salt converted to HCN by addition of water or acid. Used in electroplating, mining, metallurgy[70–73]
Propionitrile, CH_3CH_2CN	Used as solvent, chemical intermediate. Slowly metabolized to cyanide in the body[45,74]
Silver cyanide, AgCN	Poorly water-soluble cyanide salt. Delayed onset of toxicity after ingestion. Used for silver plating[75]
Sodium cyanide, NaCN	Water-soluble salt converted to HCN by addition of water or acid. Used in electroplating, mining, metallurgy[76–78]

comprising a deadly asphyxiant mixture. The National Fire Protection Association reports that 1,375,000 fires occurred in the United States in 2012, resulting in 16,500 civilian injuries and 2855 civilian deaths. Analyses of death certificates from 2003 to 2007 indicate that 51% of fire deaths were attributable to smoke inhalation only, with an additional 23% of deaths caused by smoke inhalation and burns. Burns alone have been responsible for only 25% of deaths in recent years.[48] Of the deaths that occur immediately after exposure or that are caused by cardiac arrest, a substantial number are attributable to cyanide or combined cyanide and CO toxicity.[49–52]

Hydrogen sulfide

Hydrogen sulfide is produced from decomposition of sulfur-containing organic material and is a reagent and/or byproduct of several industrial processes. It is found in sour crude oil and petroleum workers are commonly exposed to it. The boom in natural gas production by hydraulic fracturing has raised concerns about increased releases of hydrogen sulfide.[79] Hydrogen sulfide is also produced in sulfur springs, caves, and other underground fields of natural gas. It is often present in compost pits and sewers. Hydrogen sulfide has been responsible for numerous deaths in and around manure

pits.[80] It can also be released from combining household chemicals with toilet bowl cleaners.[81] This form of so-called cookbook chemistry has been a mechanism for suicide in Japan and other countries[16,17,82] and has raised concerns for potential terrorist use.

Methemoglobin-inducing substances

Like CO, methemoglobinemia decreases the oxygen-carrying capacity of hemoglobin. By oxidizing the iron in hemoglobin to the ferric state, methemoglobin inducers render hemoglobin incapable of carrying oxygen, which is instead replaced by water. A small percentage of hemoglobin is normally in the form of methemoglobin (1%–3%). This amount is well tolerated. However, as the percentage of methemoglobin increases and the oxygen saturation decreases, symptoms ensue, depending in part on the underlying health of the person exposed. A large number of compounds have been reported to induce methemoglobinemia, including prescription and nonprescription drugs and industrial chemicals. A nonexhaustive list of methemoglobin-inducing compounds is given in **Table 1**. The pathophysiology of methemoglobin formation is described by Percy and colleagues.[83] A comprehensive review of occupational methemoglobinemia has been given by Bradberry.[84]

Opioids

Opiates and opioids easily meet the definition of an asphyxiant because they impair exchange of oxygen and carbon dioxide on a ventilatory basis, although before the use of fentanyl derivatives by Russian Special Forces in the 2002 Dubrovka theater incident in Moscow, few authorities would have classified them under the rubric of hazardous materials or agents of opportunity for chemical terrorism. Nonetheless, this catastrophic decision resulted in the deaths of 125 hostages.[24] Although speculation remains regarding the exact combination of agents used by the Special Forces, the Russian Ministry of Health admitted several days later that a derivative of fentanyl was used to neutralize the terrorists.[25] Riches and colleagues[24] were able to definitively identify carfentanil and remifentanil in extracts of clothing from casualties of the assault. If they can be used for the purpose of counterterrorism, these readily accessible agents might be equally suited for purposes of terrorism, particularly given their demonstrated lethality.

CLINICAL MANIFESTATIONS

General

Timely historical details are often lacking in cases of asphyxiation, particularly in mass casualty events, so clinicians must rely on toxic syndromes (toxidromes) for rapid decision making. Numerous descriptions exist for the asphyxiant toxidrome. Markel and colleagues[85] identified 4 toxidromes applicable to toxicologic mass casualty events, one of which is an asphyxiant toxidrome, comprising headache, fatigue, dizziness, nausea, anxiety, dyspnea, altered mental status, cardiac ischemia, syncope, coma, and seizures. Kunisaki and Godwin[86] described 2 asphyxiant toxidromes. The simple asphyxiant toxidrome consists of shortness of breath, altered mental status, seizures, and coma. The toxidrome for systemic asphyxiants includes the signs and symptoms listed previously, in addition to metabolic acidosis, cardiovascular collapse, and shock.[86] Although toxidromes (**Box 2**) are helpful to direct the clinician to initial management, the clinical manifestations produced by individual compounds are often unique; asphyxiants do not always follow the rules. Physicians should be aware of subtle distinctions in presentations. Pertinent details of the exposure, a directed physical examination, and selected point-of-care testing, may help astute

Table 1
Substances reported to induce clinically relevant methemoglobinemia

Substance	Category	References
5,6-Methylenedioxy-2-aminoindane, 2-aminoindane	Amphetamine analogues, substances of abuse	148
Aluminum phosphide	Pesticide	149–151
Amyl nitrite, butyl nitrite, iso-amyl nitrite	Medication, substances of abuse	152–154
Aniline	Dyestuff	155
Arginine alpha-ketoglutarate	Dietary supplement, NO booster	156
Automobile exhaust (nitrogen oxides)	Automobile exhaust	157,158
Benzocaine	Medication, local anesthetic	97,159–161
Chlorate salts	Matches, explosives	91,162,163
Cocaine	Medication, substance of abuse	164
Copper sulfate	Pesticide	165
Dapsone	Medication	161,166–169
Dinitrophenol	Dye, chemical intermediate	91
Holi colors	Synthetic dyes	170–172
Indoxacarb	Pesticide	173,174
Lidocaine	Medication, local anesthetic	175
Linuron	Herbicide	155
Mephedrone	Substance of abuse	107
Metaflumizone	Pesticide	176
Methylene blue	Medication, antidote	177,178
Metoclopramide	Medication, antiemetic	179,180
NO	Medication, cellular messenger	181
Nitrobenzene	Organic solvent	91,182
Nitroethane	Organic solvent	182
Phenazopyridine	Medication, urinary anesthetic	183
Phenylenediamine	Dye	91
Prilocaine	Medication, local anesthetic	184,185
Primaquine	Medication, antiinfective	161
Recombinant urate oxidase	Medication, antihyperuricemic	186
Sodium nitrite	Medication, preservative	187–189
Sulfamethoxazole-trimethoprim	Medication, antiinfective	190,191
Tetracaine	Medication, local anesthetic	192
Toluidine	Medication, dye	91
Trinitrotoluene	Explosive	91
Zinc phosphide	Pesticide	151

emergency medicine physicians to narrow the differential diagnosis, further facilitating the choice of treatment options, specifically antidotes.

Specific

Table 2 shows some of the differences in presentations of poisonings by the various asphyxiants. The reported variability comes from review articles and case series and is not intended to be definitive, but may be useful in narrowing the differential diagnosis.

Box 2
The asphyxiant toxidrome

Severity and Time	Central Nervous System	Cardiovascular System	Respiratory System	Gastrointestinal System
	Headache and fatigue	Tachycardia	Dyspnea	Nausea and vomiting
	Dizziness	Hypertension	Tachypnea	—
	Altered mental status	Myocardial ischemia	Bradypnea	—
	Syncope	Hypotension	Apnea	—
	Seizures	Bradycardia	—	—
	Coma	Cardiovascular collapse	—	—

Azides

Other than as a component of airbags, azides are not a common household product. Poisonings are likely to occur in laboratories by ingestion and in industry by inhalation.[33] Regardless of the route of exposure, the most commonly reported health effect is hypotension. Although it is counterintuitive, hypotension occurring early (less than 1 hour) is considered to indicate a pharmacologic response predicting a benign outcome. Patients with late hypotension (greater than 1 hour) are considered at high risk of death. Hypotension lasting more than 1 hour has been reported as uniformly lethal. Severe signs and symptoms included altered mental status, seizure, coma, arrhythmias, tachypnea, pulmonary edema, metabolic acidosis, and cardiorespiratory arrest.[33] Patients have survived high-dose exposures with only supportive care.[87] There are no known effective antidotes to azide.[88]

Carbon monoxide

Baud[89] reviewed cases and series of CO and cyanide poisonings with the goal of identifying differences in their clinical presentations. He emphasized the frequent muddling of clinical descriptions in the literature of what should be appreciated as 3 distinct forms of CO poisoning: (1) pure CO, such as from faulty propane and butane heaters and furnaces; (2) automobile exhaust; and (3) smoke inhalation. He then performed comparisons of non–fire-related CO (excluding automobile exhaust) and non–fire-related cyanide poisonings. Baud[89] found that, although there are significant similarities between pure CO and pure cyanide poisonings, particularly in milder poisonings, there are also some substantial differences that are emphasized in poisonings of greater severity. For example, transient loss of consciousness and/or improvement in mental status with oxygen administration alone is common with even severe CO poisoning. Transient loss of consciousness was not found in his review of cyanide poisoning. Dilated pupils were found to be very rare in CO poisoning but frequent in cyanide-induced coma. Seizures were noted also to be more frequent in cyanide poisonings. He also pointed out differences in the cardiovascular effects of the 2 agents: CO rarely presents with hypotension or bradycardia. In contrast, cyanide poisoning begins with early and transient tachycardia and hypertension followed by tachycardia and hypotension, and finally by bradycardia and hypotension preceding cardiac arrest. In addition, there are significant differences in the respiratory effects of these 2 toxicants. The most common effect on breathing in pure CO poisoning is an increase in frequency, whereas severe cyanide poisoning starts with tachypnea but ultimately leads to bradypnea and even central apnea.[89]

Table 2
Signs and symptoms of acute severe asphyxiant poisoning[a]

Signs/ Symptoms	Azides	Carbon Monoxide[b]	Cyanide	Hydrogen Sulfide	Methemoglobin Inducers
Symptoms					
Vision trouble, temporary	++	++			
Signs					
Apnea	+++	+	+++	+++	
Cyanosis	+++	+	+	+++	+++
Hypertension			+++		
Hypotension	+++	+	+++	+++	+++
Knockdown/ precipitous collapse	+++	+	+++	+++	+
Lacrimation/ red eye	+	–		+++	
Loss of consciousness, transient	+++	++	–	+++	
Odor, breath or body			++	+++	+++
Pulmonary edema	++		+	+++	
Seizures	+++	++	+++	+	+++
Diagnostic Studies					
Lactic acidosis	+++	++ Usually ≤6 mmol/L in "pure" CO poisoning[b]	+++ Usually ≥8 mmol/L in "pure" CN poisoning	+++	+
Methemoglobin	+	–[b]	–[b]	+	+++ Usually >30%. Impaired consciousness and seizures at concentrations >60%. >80% is life-threatening.
Selected References	33,91	89,90,115,193	89,142,194	96,195,196	84,91

–, Not Reported or limited data.
+, Rarely Reported.
++, Occasionally Reported.
+++, Frequently Reported.

[a] All asphyxiants share the capacity to induce signs and symptoms of hypoxia, including dizziness and headache, coma, chest pain, dyspnea, and gastrointestinal signs. The role of this table is to point out some distinguishing features of various asphyxiants, to aid in their identification.

[b] Excludes smoke inhalation.

The importance of the source of CO, as pointed out by Baud,[89] is elegantly shown by the study of Chou and colleagues,[90] who compared presentations of 150 children, 90 with CO poisoning (from CO sources 1 and 2 listed earlier), and 60 with smoke inhalation (CO source 3). The differences in clinical findings are astounding (**Table 3**). Although carboxyhemoglobin levels did not differ significantly between the two groups, there was no mortality or respiratory arrests in the CO group. In contrast, the smoke inhalation group had 20% mortality and 68.5% incidence of respiratory arrest. It is therefore inappropriate to group smoke inhalation with CO poisoning of other sources. Additional toxicants are clearly at work in smoke inhalation. There is growing evidence that cyanide contributes to smoke inhalation morbidity and mortality.[49–52] The combination of soot in the mouth, nose, or secretions with altered level of consciousness in a fire involving a confined space strongly suggests cyanide as a contributing toxicant.[49,50] A plasma lactate level greater than 10 mmol/L in the setting of smoke inhalation is an even more sensitive sign of the presence of significant exposure to cyanide.[49]

Cyanide

Cyanide poisoning should be suspected in the setting of sudden collapse of laboratory and health care workers,[91,92] textile workers[71] and jewelers.[71,93] Bradypnea and/or central apnea occurring suddenly after collapse should also suggest the possibility of cyanide poisoning.[89] A plasma lactate level greater than or equal to 8 mmol/L in the setting of clinical suspicion of pure cyanide poisoning is both sensitive and specific.[94]

Hydrogen sulfide

Hydrogen sulfide is easily identified by its smell of rotten eggs, detection of which is diminished with prolonged exposure (olfactory fatigue). It is also an irritant to the

Table 3
Clinical and laboratory findings among 150 children with exposure to CO without or with accompanying smoke inhalation. Although carboxyhemoglobin levels are similar, clinical findings and outcomes are markedly different, showing that smoke inhalation is not simply CO poisoning

	Category of Poisoning		
Measure	**CO Alone**	**CO + Smoke**	***P***
Death (n, %)	81, 0	53, 20.3	<.001
Initial GCS (n, mean)	17, 14.7	18, 6.7	<.001
Depressed MS in ED (n, %)	83, 13.6	57, 76.3	<.001
Initial pH (n, mean)	43, 7.4	44, 7.2	<.001
Respiratory arrest (n, %)	80, 0	54, 68.5	<.001
Cardiac arrest (n, %)	80, 0	54, 25.9	<.001
Median time to ED (n, min)	27, 40	10, 25	.04
Median time to HBO (n, min)	69, 70	47, 50	.23
Mean COHb level (n, % ± SD)	85, 23.5 ± 11.53	59, 27.6 ± 16.25	.07

n in each row is the sample available for analysis.

Abbreviations: COHb, carboxyhemoglobin; ED, emergency department; GCS, Glasgow coma score; HBO, hyperbaric oxygen therapy; MS, mental status; SD, standard deviation.

From Chou KJ, Fisher JL, Silver EJ. Characteristics and outcome of children with carbon monoxide poisoning with and without smoke exposure referred for hyperbaric oxygen therapy. Pediatr Emerg Care 2000;16(3):152. Table 1; with permission.

eyes and mucous membranes. Hydrogen sulfide is most closely associated with the phenomenon of knockdown, which may occur immediately after high-dose exposure.[95,96] Workplace monitoring of hydrogen sulfide concentrations in ambient air may also simplify the diagnosis.

Toxicant-induced methemoglobinemia

Cyanosis is the hallmark of significant methemoglobinemia, caused by the production of chocolate-brown blood. The cyanosis is distinct for 2 reasons: it does not improve substantially with adequate oxygenation and ventilation, and the degree of cyanosis may be marked without accompanying respiratory distress. A quick bedside test placing venous blood from the cyanotic patient alongside venous blood from a nonpoisoned patient on a piece of filter paper may reveal the chocolate-brown color. Bedside pulse co-oximetry by specialized devices such as the Rad-57 may be useful[97,98]; laboratory-based co-oximetry provides a definitive answer.

MANAGEMENT

The general management of asphyxiant exposures requires rapid bedside decision making, aided by limited diagnostic studies, principally performed at the point of care. Definitive identification of substances other than CO is almost never available in a clinically relevant timeframe.

Supportive care starts with essential airway management and supplementation of oxygenation. Adequate ventilation and oxygenation may be lifesaving in serious asphyxiant exposure, even in the absence of specific antidotes.[99] Secure the patient's airway with endotracheal intubation and provide mechanical ventilation if the patient is comatose or unable to protect the airway. Treat shock initially with crystalloid infusion. If there is not a rapid hemodynamic response, administer direct vasopressors such as norepinephrine, epinephrine, or phenylephrine. Address cardiac dysrhythmias first with oxygenation and ventilation, and secondarily with antidysrhythmic drug administration in accordance with advanced cardiac life support guidelines. If seizures occur, immediately obtain a blood glucose measurement at the point of care. Treat refractory seizures with benzodiazepines, barbiturates, propofol, and/or specific antidotes. Correct acidemia promptly with parenteral bicarbonate or hyperventilation. Several of the asphyxiants are weak acids. Acidemia favors the nonionized state of these compounds, which allows absorption across membranes including the blood-brain barrier.[100] Therefore, target a blood arterial pH of 7.45 to 7.5 in these patients. Persistent acidemia may require extracorporeal therapies. Administer specific antidotes as indicated, without waiting for confirmation of poisoning.

Diagnostic Studies

Place asphyxiated patients on a cardiac monitor. Obtain a 12-lead electrocardiogram to detect signs of myocardial ischemia or alterations in electrolytes, such as hyperkalemia or hypocalcemia. ST segment elevation on the electrocardiogram may predict subsequent hypotension.[101] Pulse oximetry may be impossible to interpret in the setting of asphyxiant poisoning, depending on the exposure and the pulse oximeter. Conventional pulse oximetry measures total hemoglobin, oxyhemoglobin, and deoxyhemoglobin, providing an estimate of oxygen saturation based on the ratio of oxyhemoglobin to total hemoglobin.[102] Methemoglobin cannot be detected by conventional pulse oximetry and measurements of hypoxemia may not be accurate.[103] Carboxyhemoglobinemia has been shown to falsely increase displayed oxygen saturation on conventional pulse oximetry.[104] Cyanide poisoning results in an increase in

oxyhemoglobin saturation, which may lead to unwarranted reassurance. In short, conventional pulse oximetry has a limited role in asphyxiant poisoning management.

The recent development of pulse co-oximetry, which measures 12 rather than 2 wavelengths of light, permits transcutaneous measurement not only of oxyhemoglobin, deoxyhemoglobin, and total hemoglobin but also of carboxyhemoglobin and methemoglobin. Initial enthusiasm for the device[102,105] has been tempered by other recent studies that have raised concerns about inaccuracy of methemoglobin detection in the presence of hypoxia.[103,106] Although pulse co-oximetry offers advantages compared with conventional pulse oximetry, undue dependence on these devices is not encouraged. When in doubt, co-oximetry by laboratory analysis is advised.[103,107,108]

Blood Gases with Co-oximetry

Severe metabolic acidosis is a constant feature in the setting of cyanide[94] and sodium azide poisonings.[2,33,88,109–111] In the absence of respiratory distress or hemodynamic instability, significant alterations in acid-base balance are rare in CO poisoning.[89] The value of arterial blood gases in CO poisoning has previously been questioned.[112,113] A venous blood gas test with co-oximetry is appropriate in most cases of CO poisoning. In cyanide poisoning, simultaneous arterial and venous blood gases may reveal a narrowed arterial-venous oxygen saturation difference, which suggests inhibition of oxidative phosphorylation.[114]

Lactate

Plasma lactate level is more mildly increased in even severe CO poisoning compared with cyanide poisoning.[94,115] In the setting of suspected pure cyanide poisoning, a plasma lactate level greater than or equal to 8 mmol/L is a sensitive and specific finding suggesting cyanide poisoning.[94] In the setting of smoke inhalation, a plasma lactate level greater than 10 mmol/L strongly suggests cyanide poisoning.[49] Azide poisonings and hydrogen sulfide poisonings are also frequently associated with lactic acidosis, although predictive values of lactate have not been established for these two poisonings.

Laboratory and Point-of-care Confirmation of Poisoning

As previously mentioned, laboratory confirmation of asphyxiant poisoning is elusive. Confirmation of methemoglobinemia and carboxyhemoglobinemia by co-oximetry is obtainable in most major hospitals. Blood cyanide is a reference laboratory study that may not yield results for days.

Antidotes

Specific antidotes comprise an important adjunct to aggressive supportive care in poisoning. Baud and colleagues[116] defined an antidote as, “a drug whose mechanisms of action have been determined, which is able to modify either the toxicokinetics or the toxicodynamics of the poison and whose administration to the poisoned patient reliably induces a significant benefit.” With the possible exception of chemical mass casualties, in whom the use of an antidote autoinjector may gain time to perform other lifesaving procedures, the administration of an antidote should almost never be the treatment of first intention. Rather, antidotes should be given after institution of, or concurrently with, supportive care measures. A list of commonly available antidotes for asphyxiant poisonings is shown in **Table 4**. A more comprehensive list of antidotes that should be stocked by hospitals is provided by Dart and colleagues.[117] However, many hospitals stock inadequate amounts of antidotes, because of cost and other

Table 4
Antidotes to consider for selected asphyxiants

Antidote	Initial Adult | Pediatric Doses	Azides	CO	Cyanides and Nitriles	Fire Smoke Inhalation (CO/CN)	Hydrogen Sulfide
Hydroxocobalamin	5g IV/IO over 15 min | 70 mg/kg IV/IO over 15 min	T[2]	No	Yes	Yes	T[131]
Oxygen	Normobaric at 100% by mask or hyperbaric at 3 ATA for 1 h | same as adult	Yes	Yes	Yes	Yes	Yes
Sodium nitrite	300 mg IV/IO over >5 min | 0.2 mL/kg (6 mg/kg) IV/IO over >5 min	No	No	Yes	Yes[a]	Yes
Sodium thiosulfate	12.5 g of 25% solution IV/IO slowly | 1 mL/kg (250 mg/kg) IV/IO slowly	No	No	Yes	Yes[b]	No

Availability of an antidote does not constitute an indication for its use. Study the indications, contraindications, and adverse effects carefully before use; consult with a regional poison center or medical toxicologist if in doubt. Hyperbaric oxygen therapy remains controversial for all poisonings; consult a regional poison center or medical toxicologist for advice.

Abbreviations: ATA, atmospheres absolute; IO, intraosseous; IV, intravenous; T, of theoretic benefit.

[a] Caution: not generally recommended; considered by some clinicians to be relatively contraindicated in this setting. Induces methemoglobinemia, which may worsen CO-associated and CN-associated tissue hypoxia.

[b] Limited data for sodium thiosulfate used alone for this indication. Considered safe.

considerations. Gasco and colleagues[118] reported that, among 286 US hospital pharmacy managers, only 38 of 234 (16%) hospitals had sufficient stocking of cyanide antidotes. The shortage of cyanide antidotes may explain in part why they are rarely used even when cyanide poisoning is suspected.[39] In contrast, hydroxocobalamin has been subject to increasing use since its introduction in 2006. There is a widely held perception that it is safer than the previous cyanide antidote kit,[119] which may increase the otherwise low use of antidotal therapy for cyanide toxicity by providers.[39]

Oxygen

Administer high-flow oxygen to all patients with asphyxiant poisoning by tight-fitting nonrebreather mask, if respirations are sufficient, or via endotracheal tube. Elimination of respiratory toxicants by adequate ventilation is elemental in their management. In many cases of CO poisoning, administration of normobaric oxygen may be all that is needed (**Fig. 2**). Hyperbaric oxygen therapy has been advocated for poisoning by CO, cyanide, and hydrogen sulfide, and in toxicant-induced methemoglobinemia.[120–123] Its use remains controversial and a review of the pros and cons is beyond the scope of this article. The decision to use hyperbaric oxygen in asphyxiant poisoning should be determined from local norms, patient condition, and nearby availability of a suitable chamber. Administration of oxygen in the setting of inhibition of oxidative phosphorylation should theoretically be superfluous (the cells cannot use the oxygen that is already transported to the mitochondria) but oxygen administration is empirically beneficial in this setting nonetheless. Both experimental studies and clinical cases have shown a direct benefit of oxygen in cyanide poisoning.

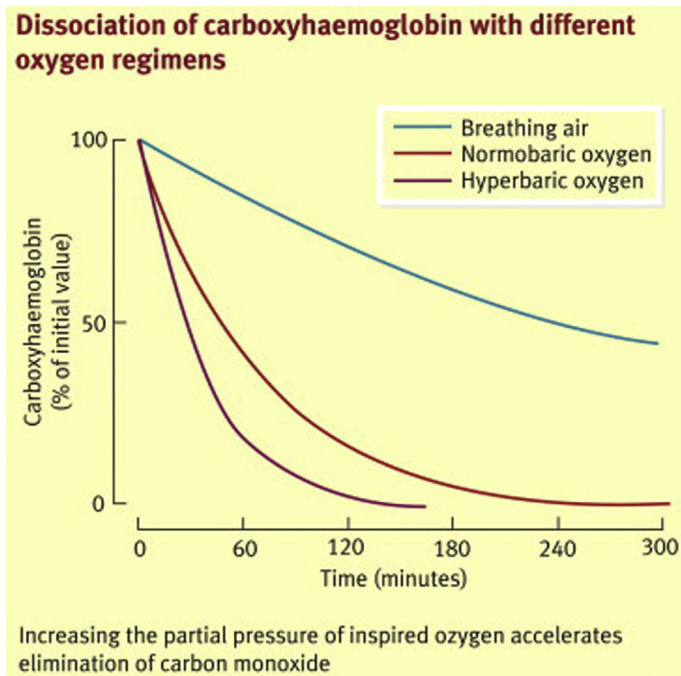

Fig. 2. Elimination of CO with various forms of oxygen therapy. (*From* Bateman DM. Carbon monoxide. Medicine 2012;40:116; with permission.)

Hydroxocobalamin

Hydroxocobalamin (vitamin B_{12a}) has been in use in Europe as a cyanide antidote since the 1980s and was approved as a cyanide antidote (Cyanokit) by the US Food and Drug Administration (FDA) in 2006. It rapidly and essentially irreversibly binds with the cyanide anion to form cyanocobalamin (vitamin B_{12}), a compound of low toxicity that is eliminated in the urine. In addition, it acts as a scavenger of NO, increasing blood pressure, which is a desired effect in a severely hypotensive patient.[124,125]

No randomized clinical trials of human efficacy of any cyanide antidote have been undertaken. Published experience with hydroxocobalamin has included case reports and series,[49,70,126] an open-labeled clinical trial in smoke inhalation,[50] a human safety evaluation,[127] and a placebo-controlled good-laboratory-practice trial in beagle dogs.[128] Several large-animal studies have evaluated hydroxocobalamin in clinically relevant cyanide models of toxicity following its approval by the FDA. Hydroxocobalamin was as effective as sodium thiosulfate/sodium nitrite in critically ill subjects.[129] In addition, hydroxocobalamin alone was superior to sodium thiosulfate alone (92% vs 0% survival).[124] Hydroxocobalamin produced a survival of 73% in cyanide-induced cardiac arrest and the effect was seen when infused over less than 5 minutes in critically ill subjects in several swine models of cyanide toxicity.[124,129,130] Hydroxocobalamin use has also been reported for hydrogen sulfide toxicity in a case report and in an animal model, with limited results.[131,132] It may be administered intravenously (IV) or intraosseously with similar outcomes and no additional adverse events.[133] The initial dose in suspected cyanide poisoning is 5 g IV over 15 minutes in adults and may be repeated, based on response, not to exceed 15 g total. The dose in children is 70 mg/kg IV over 15 minutes (off-label use). It is category C in pregnancy. Common adverse effects include reddish discoloration of skin, urine, and plasma; transient increase of blood pressure; and reversible acneiform rash. Rare allergic reactions have been reported. The reddish coloration of plasma and urine may result in unreliable laboratory testing for some common laboratory parameters during the 24 to 48 hours after administration. The plasma discoloration may trigger a blood-leak alarm, hindering certain hemodialysis machines.[134–136]

Sodium nitrite

Sodium nitrite has been widely used as a cyanide antidote since the classic work of Chen and colleagues in the 1930s. It has also been proposed for use in hydrogen sulfide poisoning[137] but has been found to be ineffective in sodium azide poisoning.[88] The antidotal mechanism of action of sodium nitrite is incompletely understood. It has been known for many years to induce a certain percentage of methemoglobinemia. Methemoglobin is able to reversibly bind cyanide and sulfide ions, extracting them from their binding sites on cytochrome-c oxidase. This process was long assumed to be the principal mechanism of its antidotal efficacy. In recent years, sodium nitrite has been shown to be a donor of NO. NO is now known to competitively inhibit the binding of cyanide by cytochrome-c oxidase and may serve as an endogenous cyanide antidote.[138] Supplementation of NO by administration of sodium nitrite may serve as an additional mechanism of antidotal action. Sodium nitrite was for many years packaged with amyl nitrite for inhalation and sodium thiosulfate for injection as a cyanide antidote kit. This specific kit was never approved by the FDA. However, a kit containing only sodium nitrite and sodium thiosulfate was recently approved by the FDA.[139]

The efficacy of sodium nitrite, both alone and in combination with sodium thiosulfate, has been well established in animal models. Human experience has been limited

to case reports and series, but these also strongly suggest its efficacy. The initial dose of sodium nitrite is 300 mg by slow intravenous injection in adults. The pediatric dose is 6 mg/kg IV at 2.5 to 5 mL/min, not to exceed 300 mg. It is category C in pregnancy. Principal side effects include hypotension[57,140] and excess methemoglobinemia.[73] Although measureable methemoglobinemia greater than 10% is uncommon,[141] cyanmethemoglobin (which also does not carry oxygen) is not detected by co-oximetry, therefore the amount of methemoglobin after treatment with sodium nitrite in the setting of cyanide poisoning may be grossly underrepresented. Thus, the practice of following serial methemoglobin levels as a means of assessing sodium nitrate therapy should be strongly discouraged. The presence of any measurable (unbound) methemoglobin after sodium nitrate therapy indicates that available cyanide has been bound and that no additional nitrate therapy is likely to be beneficial. Because sodium nitrite induces a degree of methemoglobinemia (which does not carry oxygen), most toxicologists do not recommend it use in treatment of cyanide poisoning in the setting of smoke inhalation, which results in multiple forms of hypoxia.[142]

Sodium thiosulfate

Thiosulfate sulfurtransferase (previously known as rhodanese), is an endogenous enzymatic converter of cyanide to less toxic thiocyanate found in the liver. This enzyme is effective at detoxifying cyanide, but is quickly depleted of sulfane sulfur. Sodium thiosulfate serves as a substrate for the enzyme and therefore as an effective antidote. As mentioned earlier, sodium thiosulfate has historically been packaged and used along with sodium nitrite. There are limited studies of its efficacy used alone. It has been stated that sodium thiosulfate is a slow-acting antidote,[143] although this assertion has been questioned.[144,145] The dose of sodium thiosulfate is 50 mL of a 25% solution (12.5 g) by slow intravenous bolus or infusion in adults. The pediatric dose is 1 mL/kg body weight of the 25% solution, not to exceed 12.5 g. It is category C in pregnancy. Sodium thiosulfate may be of benefit in cyanide poisoning caused by smoke inhalation,[144] but recent data in a pig model suggest that sodium thiosulfate alone is not an effective antidote.[124,146] Unlike sodium nitrite, sodium thiosulfate does not interfere with oxygenation and has minimal side effects. Although sodium nitrite has been proposed as an antidote for sulfide poisoning, sodium thiosulfate is of no theoretic benefit.

Methylene blue

Methylene blue is the antidote of choice for treatment of excessive or symptomatic toxicant-induced methemoglobinemia. Methylene blue reduces methemoglobin, in the presence of adequate NADPH (nicotine adenine dinucleotide phosphate) and the enzyme methemoglobin reductase, to hemoglobin. Methylene blue is converted in the process to leucomethylene blue. Because methylene blue is eliminated in the urine, it is contraindicated in renal failure. It is also contraindicated in G6PD (glucose-6-phosphate dehydrogenase) deficiency, in which inadequate NADPH is available and hemolysis may occur. Treatment with methylene blue is generally recommended when there are significant symptoms of hypoxia or when the methemoglobin concentration is more than 30%.[84] The recommended dose of methylene blue for children and adults is 1 to 2 mg/kg body weight given IV over 5 minutes. It is pregnancy category C. Other important adverse effects of methylene blue therapy include formation of methemoglobin at high doses, fecal and urine discoloration, and interference with co-oximetry.[147]

Naloxone

Emergency physicians are familiar with naloxone for opioid poisonings, thus its use is not further described here except to encourage emergency planners to consider

sufficient stocking of naloxone to deal with a terrorist event such as that reported in the Russian theater incident.

SUMMARY

Asphyxiants are responsible for a large number of deaths and serious injuries each year. Smoke inhalation poses the greatest threat from the point of view of incidence, exacting substantial morbidity and mortality. Long referred to as CO poisoning, it is now appreciated that smoke inhalation is a complex form of asphyxiation involving not only CO but cyanide, volatile organic compounds, carbon dioxide, and soot, all of which affect oxygenation and ventilation. CO in its pure form is another frequently encountered asphyxiant, both in the home in the workplace. Another common form of asphyxiation is caused by toxicants that induce methemoglobinemia, including many drugs and industrial compounds. Rarer are poisonings by azides and hydrogen sulfide, but they continue to take an important toll in agricultural and industrial settings. The treatment of all of these poisonings is, first and foremost, aggressive supportive therapy with oxygen, mechanical ventilation, crystalloids, and when necessary vasopressors. Specific antidotes can be lifesaving, but serve as adjuncts to supportive care. It is incumbent on emergency physicians to recognize these poisonings quickly and to act quickly. The asphyxiant toxidrome, aided by careful history and examination, leads emergency physicians in the appropriate treatment direction.

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