87 Carbon Monoxide Poisoning

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At a Glance...

- Carboxyhemoglobin levels confirm the diagnosis of carbon monoxide poisoning, but severity of illness, rather than levels, determines the type and intensity of treatment.
- Treatment consists of patient removal from exposure environment and administration of high-flow, high-concentration oxygen at normobaric or hyperbaric pressure.
- Hyperbaric oxygen therapy is most likely to benefit patients with severe carbon monoxide poisoning, such as those with loss of consciousness, persistent altered mental status, seizures, ataxia, hypotension, myocardial injury, and significant symptoms that do not resolve with surface pressure oxygen.
- Pregnant patients with acute carbon monoxide poisoning should be treated with hyperbaric oxygen therapy if they meet criteria defined for nonpregnant patients or if there are signs of fetal distress; treatment with normobaric oxygen should be prolonged because of the slower elimination of carbon monoxide from the fetus.

INTRODUCTION AND RELEVANT HISTORY

Carbon monoxide (CO), a colorless, odorless, nonirritating gas created by incomplete burning of carbonaceous fossil fuels, is a ubiquitous toxin. Mild CO poisoning often masquerades as nonspecific headache or is misdiagnosed as viral illness, whereas moderate to severe CO poisoning produces significant morbidity (e.g., delayed neurologic dysfunction) and mortality and provokes treatment controversy. With more than 2000 annual deaths and at least 15,000 to 40,000 diagnosed cases of nonfatal acute CO poisoning occurring annually in the United States, this poison affects the practice of all physicians.

EPIDEMIOLOGY

Carbon monoxide poisoning is the third leading cause of accidental poisoning death in the United States.[1] Although CO death rates have declined by 80% since the introduction of the catalytic converter in 1975, CO was still responsible for 2379 deaths in the United States in 1998.[2] Most of these deaths were due to suicide, but a large number of accidental poisonings also occurred (Tables 87-1 and 87-2). In addition to those listed, common sources of accidental CO poisoning include small engines (i.e., electrical generators and power washers), propane-powered fork lifts, boats, ice skating rink resurfacers (Zambonis), paint strippers (methylene chloride), and fires (i.e., victims of smoke inhalation).[3,4] About 40,000 people are diagnosed with CO poisoning in emergency departments in the United States annually.[3] Among emergency department patients with headache or "flulike symptoms," the incidence of occult CO poisoning (defined as venous carboxyhemoglobin [COHb] level of 10%) may range from 0.2% to 23.6%.[5-11] Outbreaks of CO poisoning occur after storm-related power outages, in both warm and cold weather.[12] During these outages, charcoal and electrical generators predominate as sources of CO. Poor and immigrant populations are at highest risk.

STRUCTURE AND STRUCTURE–ACTIVITY RELATIONSHIPS

Carbon monoxide is colorless, odorless, and tasteless. Because it has almost the same density as air, CO dis-

TABLE 87-1 Sources of Carbon Monoxide in Fatal Poisoning, 1998

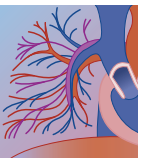
CARBON MONOXIDE	NO. OF FATALITIES
All carbon monoxide–related deaths	**2379**
Unintentional deaths	***491***
Motor vehicle related	238
Non–motor vehicle related	93
Mechanism undetermined	160
Suicide deaths	***1747***
Motor vehicle related	1330
Non–motor vehicle related	4
Mechanism undetermined	413
Homicides and deaths of undetermined or other intent	***141***

Modified from Mott JA, Wolfe MI, Alverson CJ, et al: National vehicle emissions policies and practice and declining US Carbon monoxide-related mortality. JAMA 2002;288:988–995.

TABLE 87-2 Sources of Carbon Monoxide in Unintentional, Nonfire Carbon Monoxide Poisoning Deaths Due to Consumer Products, 1994–2000

CARBON MONOXIDE	PERCENT AGE OF FATALITIES
Heating systems	52
Engine-powered tools	16
Charcoal grills and charcoal	12
Other or multiple appliances	9
Gas ranges and ovens	8
Camp stoves and lanterns	6
Gas water heaters	2

Modified from Vagts SA: Non-fire Carbon Monoxide Deaths Associated with the Use of Consumer Products: 1999 and 2000 Annual Estimates. Bethesda, MD, U.S. Consumer Products Safety Commission, 2003.



tributes equally throughout an enclosed area. Because CO is a small, nonpolar molecule, it penetrates through standard drywall and can disperse throughout separate units of a multifamily dwelling.

PHARMACOLOGY

Pathophysiology

Carbon monoxide enters the body through the lungs, where it binds to hemoglobin with an affinity 200 to 240 times that of oxygen.[13] The binding of CO to one of the four binding sites on the hemoglobin tetramer shifts hemoglobin to its high-affinity conformation. This shifts the oxyhemoglobin dissociation curve to the left, greatly impairing the ability of hemoglobin to deliver oxygen to tissues. This enhanced affinity and impaired unloading of oxygen is referred to as the *Haldane effect*.

COHb plays only a partial role in the pathogenesis of CO poisoning. This is suggested by the clinical observation that COHb levels do not correlate with the severity of clinical effects and can be low in the face of coma from CO poisoning.[14] Further evidence is provided by a canine study that revealed markedly differing mortality rates for dogs with similar blood COHb levels but differing tissue CO levels.[15] In this study, death occurred uniformly in dogs that breathed air containing 13% CO for 15 minutes resulting in COHb blood levels of about 65%. In contrast, death did not occur in other groups of dogs that were transfused with enough COHb red blood cells to produce blood COHb levels of 60%. In addition, death did not occur in a third group of dogs that had their blood hemoglobin content reduced by 68% through phlebotomy. Thus, animals spontaneously breathing CO had a higher total-body content of CO from its tissue redistribution. Redistributed or "tissue" CO accounts for 10% to 15% of total-body CO stores but is critical to the pathophysiology of CO.[16]

CO produces tissue toxicity from its avid binding to other heme proteins (cytochromes), such as myoglobin, the cytochrome a-a_3 complex (cytochrome oxidase) of the mitochondrial respiratory chain, and guanylate cyclase. Myoglobin's affinity for CO is about 30 to 60 times greater than that for oxygen.[17] CO binding to myoglobin impairs myocardial oxygen uptake from blood into the mitochondria of tissues. Binding of CO to cytochrome oxidase disrupts cellular respiration and oxygen utilization in all tissues, including the brain. Although cytochrome oxidase binds oxygen with greater affinity than CO, CO competes with oxygen for binding sites under conditions of cellular hypoxia and dissociates slowly from cytochrome oxidase once binding has occurred.[18]

In addition to direct cytochrome oxidase blockade, CO promotes the production of reactive nitrogen species that further inhibit cellular cytochrome oxidase and electron transport.[19,20] Cellular hypoxia causes free radical release from vascular endothelial cells and platelets. Concurrently, CO displaces nitric oxide (NO) from heme-containing proteins in endothelial cells and platelets.[21] Once released from cells, NO reacts with free radicals to produce peroxynitrate ($ONOO^-$), which further inhibits cytochrome oxidase, injures DNA and cell membranes, and triggers apoptosis in neuronal tissue.[19,21]

In addition to cellular hypoxia, CO produces smooth muscle relaxation and vasodilation. CO binds to and stimulates the activity of the heme protein, guanylate cyclase.[22] This results in an increased production of the smooth muscle relaxant, cyclic guanosine monophosphate (cGMP). The displacement of NO from platelets and endothelial cells by CO also results in vasodilation.[21,23] NO, also known as *endothelial derived relaxation factor*, is a potent smooth muscle relaxant. Headache from CO poisoning is likely mediated by extracerebral and intracerebral vasodilation. Hypotension and syncope from CO poisoning may be mediated by some combination of peripheral vasodilation, with COHb-induced myocardial ischemia, direct myocardial depressant effects, and loss of central control of vasomotor tone. Clinically, hypotension and syncope (even if transient) signify serious CO exposure and are ominous predictors of serious neurologic sequelae.[24,25] Brain areas that have high oxygen requirements or are watershed regions of perfusion (e.g., basal ganglia, hippocampus, and subcortical white matter) are particularly susceptible to CO-mediated injury. In monkeys, cerebral white matter lesions correlated better with decreases in blood pressure than with COHb levels, and it has been suggested that an episode of hypotension may be required for severe neurologic deficits to occur.[26] In essence, cellular hypoxia is often accompanied by tissue ischemia. These primary CO-induced pathophysiologic processes (hypoxia and ischemia) induce a cascade of secondary events (ischemia reperfusion effects) that are integral to short- and long-term central nervous system (CNS) toxicity associated with CO.

The histopathology of CO poisoning is similar to that of postanoxic encephalopathy, or so-called reperfusion injury. Brain reperfusion injury patterns are largely mediated by oxidative damage initiated by oxygen free radicals and sustained by second-generation lipid radicals. Current evidence suggests that xanthine oxidase activity is largely responsible for the generation of free radicals associated with CO-mediated lipid peroxidation and brain injury.[27] When CO exposure is associated with tissue hypoxia, adenosine dinucleotide triphosphate (ATP) stores are depleted in tissues. Simultaneously, the cells have a greatly increased demand for ATP to repair oxidative damage. In a series of steps, ATP is converted to uric acid and an oxygen free radical.

Investigations by Thom and colleagues indicate that significant CO exposure produces a cascade of biochemical events responsible for delayed neurologic sequelae.[19,21,23,24,27] Significant CO exposure promotes release of NO from endothelial cells and platelets. Concurrently, impaired mitochondrial function and oxidative stress promotes production and release of oxygen free radicals from these cells. NO reacts with oxygen radicals to form peroxynitrite. Peroxynitrite binds to perivascular tissue proteins causing endothelial

injury. Endothelial injury provokes expression of adherence molecules (e.g., β-integrin) on cell surfaces, which promotes leukocyte binding to injured endothelial cells. Leukocytes release proteases that further augment the activity of xanthine oxidase and production of oxygen free radicals. Subsequently, brain lipid peroxidation and delayed CNS toxicity ensue. Brain injury is also mediated by additional mechanisms, such as activation of excitatory amino acids (e.g., glutamate) and apoptosis-related enzymes (e.g., caspase-1).[23,28]

Pharmacokinetics

Carbon monoxide uptake and elimination occur through the lungs and are dependent on minute volume. Only a small amount of CO is metabolized by oxidation to carbon dioxide. Because CO diffusion through the alveoli is rapid and complete, the amount of CO dissolved in arterial blood is directly related to the concentration of CO in the air of the patient's environment. Depending on conditions, whole-body equilibrium may only be reached after 4 to 6 hours of exposure. Conversely, measurements of CO concentration in expired air correlate well with venous CO levels. Overall, the amount of CO absorbed by the body depends on ambient air CO and oxygen concentrations, minute ventilation, and duration of exposure. In human volunteer studies, the elimination of CO in room air (21% oxygen) ranges from 249 to 320 minutes.[29,30] Administration of 100% oxygen shortens the elimination half-life to 47 to 80 minutes at normal atmospheric pressure and to about 20 minutes at 2.5 to 3 atmospheric pressure.[31,32]

Methylene chloride (see Chapter 93), found in paint strippers, degreasers, and other solvents, is another potential source of CO poisoning. It is readily absorbed from the lungs and gastrointestinal tract; lesser amounts may also be absorbed from the skin. Once absorbed, methylene chloride is slowly metabolized in the liver to CO and carbon dioxide. Peak CO levels from methylene chloride depend on the route of exposure but may not occur for over 8 hours. Because of ongoing CO production through metabolism of methylene chloride, the half-life of CO may appear to be prolonged, up to 13 hours, in these cases.[33,34]

Special Populations

Because of their rapid respiratory rate, children may be more susceptible to CO poisoning than adults. Advanced age may be a risk factor for adverse neurologic outcomes after CO poisoning.[35]

Although fetal hemoglobin has a higher affinity for CO than hemoglobin A in similar pH and Po_2 conditions, this effect is largely counteracted by the acidemic, hypoxic milieu of the normal fetus. As a result, fetal COHb levels are expected to be within 10% of maternal levels.[36] Based on animal data and mathematical models, the elimination half-life of fetal COHb is significantly longer (up to 3.5 times greater) than that of adult COHb.[37,38]

TOXICOLOGY

Clinical Manifestations

ACUTE EFFECTS

Signs and symptoms of mild CO poisoning include headache, nausea, vomiting, diarrhea, dizziness, weakness, dyspnea, and fatigue (Table 87-3). Misdiagnoses, such as viral illness and benign headache, are common. In one study, the diagnosis of CO poisoning was initially missed in up to 30% of cases; the most common incorrect diagnosis, "food poisoning" was made in 43% of these cases. The diagnosis of CO poisoning should be considered for patients presenting with one or more of the listed symptoms in the absence of fever.[39] A history of exposure to possible CO sources (e.g., fossil fuel heat, engines, propane and natural gas appliances, grills) or groups of patients with similar complaints should suggest occult CO poisoning and prompt blood or breath testing for CO.[8] With more severe exposure, patients can present with signs of neurologic, cardiovascular, and pulmonary dysfunction. These effects include confusion, irritability, ataxia, coma, focal neurologic deficits, seizures, syncope, hypotension, arrhythmias, myocardial ischemia or infarction, tachycardia, tachypnea, noncardiogenic and cardiogenic pulmonary edema, and respiratory and cardiac arrest.

In general, any organ can be affected by CO. Table 87-4 lists the spectrum of complications that can be associated with CO poisoning. Unusual complications include retinal hemorrhages, compartment syndromes, rhabdomyolysis and renal failure, skin blisters, bowel ischemia, and peripheral neuropathy. Although patients with more severe signs of acute CO poisoning (e.g., syncope, hypotension, coma) are more likely to develop delayed and long-lasting morbidity, this is not uniformly true. Patients with mild toxicity may develop delayed neurologic sequelae, and those with severe toxicity may have complete recovery.

CHRONIC EFFECTS

Some CO-poisoned patients develop lasting signs of brain injury, most commonly cognitive and personality

TABLE 87-3 Acute Symptoms in 1144 Patients with Carbon Monoxide Poisoning

SYMPTOM	PERCENTAGE OF PATIENTS
Headache	85
Dizziness	69
Fatigue or generalized weakness	67
Nausea or vomiting	52
Trouble thinking or confusion	37
Loss of consciousness	35*
Dyspnea	7
Chest pain	2

*Patients with loss of consciousness (LOC) were excluded from Thom's series (*N* = 65 without LOC; number with LOC excluded not stated).
Data from references 35, 41–43, 64, 68, and 90.

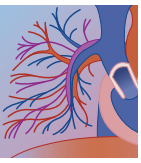


TABLE 87-4 Spectrum of Complications Due to Carbon Monoxide Poisoning

SYSTEM	COMPLICATIONS
Central nervous	Impaired cognition, memory dysfunction, vertigo, ataxia, parkinsonism, muscle rigidity, gait disturbance, disorientation, mutism, urinary incontinence, fecal incontinence, cortical blindness, hearing loss, tinnitus, nystagmus, seizures, coma, electroencephalographic abnormalities, cerebral edema, leukoencephalopathy, diabetes insipidus, globus pallidus necrosis
Psychiatric	Personality changes, depression, flattened affect, Tourette's syndrome, anxiety, agitation, poor impulse control
Cardiovascular	Tachycardia, easy fatigue, hypotension, ischemic electrocardiographic changes, arrhythmias, new-onset angina or exacerbation of existing angina, myocardial infarction
Pulmonary	Shortness of breath, pulmonary edema, hemoptysis
Gastrointestinal	Nausea, vomiting, abdominal cramps, diarrhea, gastrointestinal bleeding
Ophthalmologic	Decreased acuity, retrobulbar neuritis, paracentral scotomata, papilledema, flame-shaped retinal hemorrhages
Dermatologic	Erythematous patches, cherry-red skin, bullae, alopecia, sweat gland necrosis
Muscular	Rhabdomyolysis, compartment syndrome
Hematologic	Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, leukocytosis
Metabolic	Lactic acidosis, hyperglycemia, hypocalcemia, hyperamylasemia (salivary origin)

changes and parkinsonism. These may develop at the time of CO poisoning and continue (persistent neurologic sequelae) or develop after an asymptomatic interval of 3 to 21 days (delayed neurologic sequelae, or DNS). Longer latent periods have been reported. DNS manifest with a variety of neurologic and psychiatric signs and symptoms. Commonly described findings include memory loss, confusion, ataxia, incontinence, emotional lability, hallucinations, personality changes, blindness, and parkinsonism. There are no established diagnostic criteria for this disorder, and the observed incidence varies widely, from 12% to 74% for CO poisoning victims in recently published clinical trials.[35,40–45] One recent study, which paired 32 CO poisoning victims (8 of whom had loss of consciousness and 24 of whom received hyperbaric oxygen [HBO]) with gender, age, and educationally matched controls, found no evidence of the syndrome at all.[44] Many patients recover to normal over several weeks to months.[45,46]

DIAGNOSIS

Laboratory Testing

The diagnosis of CO poisoning is based on suggestive history and physical findings coupled with confirmatory COHb testing (Table 87-5). CO levels can be tested in either whole blood or exhaled air. In hospitals, the most commonly used technique is to measure COHb as a percentage of total hemoglobin using a multiple wavelength spectrophotometer. Blood is collected in a closed, heparinized container (a blood gas syringe or "green-top" tube) and analyzed on a co-oximeter. Because there is no significant difference between venous and arterial COHb levels, either type of sample is appropriate.[47] Because of endogenous CO production, some COHb is present in the blood of healthy subjects. Normal COHb levels are 0.5% to 2% in nonsmokers and up to 10% to 12% in smokers. Levels are somewhat higher in pregnant women, infants, and patients with hemolytic anemia. COHb is often misinterpreted as oxyhemoglobin by simple bedside pulse oximetry. Pulse oximetry overestimates oxyhemoglobin measurements by the approximate amount of COHb that is present.[48] Thus, co-oximetry is required to measure COHb levels accurately.

TABLE 87-5 Relationship of Carbon Monoxide Levels in Air and Carboxyhemoglobin Levels at Steady State

CARBON MONOXIDE CONCENTRATION IN AIR (PPM)	CARBOXYHEMOGLOBIN (%) ACHIEVED AT STEADY STATE	NOTES
10	1.5	Approximate upper limit of normal in nonsmokers
35	5	NIOSH-recommended exposure level for 8-hr workday
50	7	Current OSHA 8-hr permissible exposure level for 8-hr workday
70	10	Approximate upper limit of normal in smokers
350	35	NIOSH recommends supplied-air respirator use
1200	65	Immediately dangerous to life and health level (NIOSH)

NIOSH, National Institute of Occupational Safety and Health; OSHA, Occupational Safety and Health Administration. Calculated from formulas in reference 36, assuming adult patients with normal hemoglobin. Interindividual variability exists.

An alternative method, more commonly used in Europe, is to measure CO directly. A blood sample is diluted and mixed with a reagent to liberate CO from hemoglobin. The CO content of head-space gas is then measured with gas chromatography or infrared spectrophotometry.[49,50] Although this method is more accurate for measuring low CO levels, there is no clear advantage in the assessment of acute poisoning.

COHb "spot tests," performed by adding sodium hydroxide or ammonia to a tube of blood and observing for a persistent pink color, are neither sensitive nor specific.[51]

Breath analysis is a valid alternative to blood testing.[52,53] However, because patient cooperation is necessary, breath analysis may be impractical in young children and patients with significantly altered mental status. Models vary greatly in their ease of use, and some give false-positive results in the presence of ethanol. Normal levels of CO in exhaled air are 0 to 6 ppm in nonsmokers and up to 70 ppm in smokers. Most analyzers automatically convert these levels to predicted COHb levels for medical use.

A promising new technology is noninvasive pulse co-oximetry. These devices, which are essentially a technological improvement on pulse oximetry, use multiple wavelengths of light to directly measure oxyhemoglobin, deoxyhemoglobin, and COHb (and, in some models, methemoglobin) through a probe applied to the finger or ear. Because this procedure is rapid and noninvasive and does not require patient cooperation, it has the potential to replace exhaled breath and blood co-oximetry analysis for the diagnosis of CO poisoning.

COHb levels do not correlate well with clinical severity, outcome, or response to therapy.[41-43,46,54] The role of a COHb measurement is to confirm or exclude that a CO exposure has occurred. The diagnosis of CO poisoning is made when an elevated COHb level is documented concurrently with history, signs, and symptoms suggestive of poisoning. In order to interpret COHb measurements, it is important to know the time since cessation of exposure and whether the patient was on oxygen during this time. Although COHb elimination varies considerably between individuals, a reasonable estimate is to assume that COHb levels fall by half every 4 to 5 hours in patients breathing air and every 1 hour in patients breathing oxygen by mask. If calculations reveal a "predicted peak" COHb level of less than 10%, symptomatic CO poisoning is unlikely, and an alternative diagnosis should be sought. If the diagnosis of CO poisoning is confirmed, the history and physical examination guide the choice of therapy. Depending on the route of exposure, patients with methylene chloride poisoning may need serial measurements of blood COHb to rule out significant CO poisoning.

Arterial blood gas measurements are not useful to make the diagnosis of CO poisoning. They provide useful information with regard to the adequacy of ventilation and presence and degree of metabolic acidosis.[55]

Although elevated blood lactate levels may occur in severe CO poisoning, most patients in published case series have normal lactate levels. It is not clear whether elevated lactate is an independent risk factor in CO victims who otherwise appear well. CO poisoning rarely causes a lactate level greater than 4 mmol/L; an alternate explanation for lactic acidosis, such as cyanide poisoning or shock, should be sought. In particular, the measurement of blood lactate may be a useful surrogate for cyanide poisoning for smoke inhalation victims (see Chapters 86 and 88).

Carbon monoxide poisoning can cause myocardial infarction. In one case series, patients who demonstrated clinical evidence of myocardial injury (elevated CK-MB, elevated troponin I, and/or diagnostic ECG changes) were followed prospectively.[56] Survivors had a significant increase in cardiac and all-cause mortality over several years after the poisoning, compared with CO-poisoned patients who did not have myocardial injury.

Unfortunately, it is difficult to extrapolate from this study to a management strategy for patients with CO-induced myocardial infarction. All patients in this study were treated with HBO; HBO did not prevent the increased mortality, and it is speculative to say whether the rate would have been different had HBO not been employed. Patients with myocardial infarction were older and more severely poisoned than those without such injury, potentially confounding these results. Because CO can cause diffuse myocardial injury in the absence of coronary artery disease, it unclear whether evidence of myocardial infarction indicates a need for coronary angiography in the CO-poisoned patient or whether cardiac stress testing is safe or accurate in the immediate aftermath of CO poisoning.

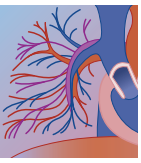
Any patient who suffers a prolonged period of unconsciousness or shock may develop complications such as rhabdomyolysis, compartment syndrome, renal failure, or disseminated intravascular coagulopathy. Testing for these conditions should be performed when clinical suspicion is high.

Other Diagnostic Testing

All women with childbearing potential who are suspected of having CO poisoning should have a pregnancy test. Although this topic is controversial, many experts recommend a prolonged period of oxygen therapy and a lower threshold for hyperbaric oxygen treatment if the CO poisoning victim is pregnant. An assessment of fetal status, such as a fetal heart rate, nonstress test, or ultrasound, should be performed when practical.

An ECG should be performed on individuals with a history of chest pain, dyspnea, or hypotension. Other testing, such as head computed tomography (CT) or lumbar puncture, may be needed to exclude other causes of altered mental status when the diagnosis of CO poisoning is inconclusive.

A special neuropsychological battery has been developed to detect subtle impairment in CO poisoning victims that might be missed by routine neurologic testing.[57] Performance on this battery is altered with CO poisoning and improves with therapy. However, the test is designed only to detect neuropsychological impairment and does not distinguish CO poisoning from other



causes of encephalopathy, including alcohol. The battery is somewhat cumbersome, requires 30 to 45 minutes to administer, must be administered in a quiet area, requires fluency and literacy in English, assumes normal intelligence, is not valid for children younger than 15 years, and does not predict patients at risk for developing delayed neurologic sequelae.[43,57] A standard focused neurologic examination, including mini-mental status examination and testing for ataxia, is adequate for routine clinical use.

Chest radiography is recommended for all seriously poisoned patients and those with cardiopulmonary signs and symptoms. Noncardiogenic pulmonary edema may be evident on chest radiograph. Brain CT is recommended for seriously poisoned patients. Brain CT may show signs of cerebral infarction secondary to hypoxia or ischemia. Symmetric low-density lesions of the globus pallidus, putamen, and caudate may be detected as early as 12 hours after CO poisoning and are associated with a poorer prognosis.[58,59] Brain magnetic resonance imaging (MRI) is able to detect basal ganglia lesions with greater sensitivity than head CT. In addition, other abnormal findings demonstrated on head MRI in CO-poisoned patients include diffuse, symmetric white matter lesions of the periventricular areas.[60]

Differential Diagnosis

Just as CO poisoning can mimic other illnesses, many other conditions cause encephalopathy, headache, nausea, weakness, or hypotension. When the diagnosis of CO poisoning is excluded or uncertain, testing for occult trauma, stroke, infection, drug intoxication, or metabolic derangement may be necessary. Rapid bedside tests should be used to exclude hypoglycemia and hypoxemia in almost all patients. Victims of smoke inhalation who have significant lactic acidosis should be suspected of having associated cyanide poisoning.

MANAGEMENT

Supportive Measures

All patients should receive aggressive supportive care while the diagnosis of CO poisoning is established. Patients with significant CNS or respiratory depression should have their airway protected, breathing assisted, and cardiovascular support provided as necessary. The administration of high-concentration, high-flow oxygen by tight-fitting face mask or endotracheal tube is fundamental. Severely poisoned patients should have continuous cardiac monitoring, an intravenous (IV) line established, and an ECG performed. Continuous pulse oximetry and parenteral thiamine, dextrose (or rapid fingerstick glucose determination), and naloxone should be considered for patients with altered mental status or seizures because of the potential for concurrent illness. Hypotension may be treated with IV fluids and, if necessary, vasoactive infusions.

Decontamination

Immediate removal from the contaminated environment is critical. Except for methylene chloride exposures, CO absorption ceases as soon as the patient is removed from the poisoned environment. Although CO victims have elevated amounts of CO in exhaled air, the amount involved poses no danger to health care workers. Although placing the patient on oxygen speeds the elimination of CO from the body, no form of decontamination is required.

Laboratory Monitoring

Serial measurements of COHb or breath CO are not helpful in management unless the exposure was to methylene chloride. Once the diagnosis of CO poisoning is established, further lab monitoring is only indicated as required by other medical conditions (e.g., cyanide poisoning, shock, trauma, and metabolic acidosis).

Antidotes

The antidote for CO poisoning is oxygen, which should be administered at a concentration as close to fiO_2 1.0 as reasonably achievable and for a period of at least 4 hours. High-concentration oxygen is delivered by a tight-fitting, reservoir-containing (non-rebreather) facemask or by endotracheal tube. Oxygen is delivered at ambient (atmospheric) pressure or elevated ambient pressure. Although the practice of administering oxygen has never been tested to see if it improves outcome, oxygen therapy is safe, inexpensive, and convenient and greatly improves the rate of CO elimination. The 4-hour duration of therapy is chosen for practicality and because it allows even the most severely poisoned patients (i.e., COHb > 40%) to eliminate CO to negligible levels.

Many experts recommend HBO or administration of oxygen at 2 to 3 atmospheres pressure absolute (ATA) in a hyperbaric chamber. Although HBO is reasonably safe, it is considerably more expensive and less convenient than administration of oxygen at ambient pressure ("normobaric" oxygen, or NBO), particularly if transfer to another facility is required.

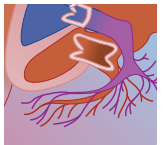
In experimental animal models of severe CO poisoning, HBO therapy decreases brain injury by a variety of mechanisms, including improved mitochondrial oxidative metabolism, inhibition of leukocyte adherence to injured vasculature, and reduced lipid peroxidation. In this setting, HBO has a paradoxical, and beneficial, antioxidant effect.[23,28,61-63] However, although treatment with HBO eliminated hippocampal cell death in a mouse model of CO poisoning, there was no difference in learning and memory testing.[64]

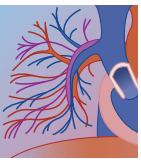
At least seven case series and nonrandomized clinical trials of HBO for CO poisoning have been published.[65-71] Few of these studies assessed outcomes by objective measures, and none were blinded. All reported a benefit from HBO over standard NBO therapy. five randomized clinical trials studying the effect of HBO on neuropsychological outcomes have been published and are listed in Table 87-6. Three of these trials reported a

TABLE 87-6 Randomized Trials of Neuropsychological Outcomes in Carbon Monoxide Poisoning Treated with HBO versus Normobaric Oxygen

STUDY	PATIENTS INCLUDED	BLINDED?	NEUROPSYCHOLOGICAL TESTS?	NO. OF TREATMENTS	LOST TO FOLLOW-UP (%)	NO. NBO PATIENTS	NO. (%) NBO PATIENTS WITH POOR OUTCOME*	NO. HBO PATIENTS	NO. (%) HBO PATIENTS WITH POOR OUTCOME*	HBO BENEFIT REPORTED	NO. NEEDED TO TREAT TO BENEFIT ONE PATIENT
Raphael, 1989[41]	No LOC	No	No	1	10	170	58 (34)	173	55 (32)	No	50.0
Thom, 1995[43]	No LOC	No	Yes	1	14	30	7 (22)	30	0 (0)	Yes	4.5
Mathieu, 1996[45]	Non-comatose	No	No	1	Unk.	276	42 (15)	299	26 (9)	Yes	15.4
Scheinkestel, 1999[42]	All	Yes	Yes	3–6	54	87	59 (68)	104	82 (79)	No (trend toward harm)	N/A (harm: 1 in 9.1)
Weaver, 2002[35]	All	Yes	Yes	3	3	76	35 (46)	76	19 (25)	Yes	2.9
Total*						639	201 (31)	682	182 (27)		21.0

*Some authors did not report the number of patients lost to follow-up by treatment group, making totals approximate.
LOC, loss of consciousness; NBO, normobaric oxygen; Unk., unknown.





benefit to HBO, and two showed NBO to be equally efficacious. These trials have differed greatly in entry criteria, blinding, time from poisoning to experimental therapy, and outcome measures studied. Only two were double-blinded, employed sham "hyperbaric" therapy in the NBO arm, and measured outcomes by objective neuropsychological testing.[42,43] These studies produced conflicting results; one study found a strong advantage to HBO, whereas the other showed no benefit and a nonsignificant trend toward harm. A fifth randomized trial used a nonclinical end point, which makes interpretation of results and extrapolation to clinical practice virtually impossible.[54] Methodologic differences between studies and missing data make formal meta-analysis of these trials impossible. A crude summary of the results suggests that HBO provides an advantage over NBO that is nearly statistically significant ($P = 0.056$; Chi-squared, 1 degree of freedom), but clinically very modest; only 1 of every 21 patients receiving HBO appeared to benefit from the therapy.

If HBO does prevent neurologic injury, it must do so by a mechanism other than enhancing CO elimination from the blood. In all trials for which the data are reported, COHb had declined to negligible levels in almost all patients by the time HBO therapy could be initiated, and COHb levels did not correlate with neurologic outcome or response to therapy. From animal studies, HBO appears to displace CO from mitochondrial cytochromes, has antioxidant effects that minimize ischemic-reperfusion injury, and prevents cellular apoptosis.

Although expensive and inconvenient, HBO therapy is reasonably safe; chamber-related complications occur in 0 to 8% of patients.[35,43,72] Complications include middle ear or sinus barotrauma (most common), seizures (1%), pneumothorax, gas embolism, and intolerable claustrophobia. HBO therapy is not available in most American hospitals. Transport to a center that can deliver HBO may contribute greatly to expense, inconvenience, and treatment delay.

Unfortunately, no single or combination of factors has been shown to reliably predict which CO poisoning patients will develop DNS. Most CO-poisoned patients recover completely with NBO alone, and therefore would not benefit from or need HBO therapy. In addition, no trial of HBO therapy has included children. Although outcomes are generally worse in elderly people, regardless of treatment, it is unclear whether the benefits of HBO are any greater in this group. Despite the lack of reliably identifying patients with CO poisoning at high risk for developing DNS, criteria have been proposed to use as indications for HBO in patients with CO poisoning[73,74] (Box 87-1). These indications have not been prospectively evaluated and validated, but their presence should provoke strong consideration for HBO treatment.

Almost all experts recommend HBO therapy for pregnant women with significant CO poisoning, regardless of stage of pregnancy or severity of clinical signs and symptoms. A landmark study in pregnant ewes showed that COHb levels in the fetus rise more slowly than in the mother, ultimately reaching a level 98% higher than the maternal level.[75] When CO exposure was discontinued, CO was eliminated from the fetus at about half the maternal rate. However, these results cannot be extrapolated directly to humans. Sheep hemoglobin A has a lower affinity for CO than human hemoglobin A, whereas sheep fetal hemoglobin has a much higher affinity for CO than human fetal hemoglobin.[76] During human poisoning, the peak fetal COHb percentage should be within 1% to 4% of maternal peak levels.[36,76] CO poisoning interferes with oxygen delivery to the fetus, but because the normal fetus is profoundly hypoxic and acidotic by postnatal standards, it unclear at what threshold this would lead to injury. Although unclear, pregnant patients likely need longer treatment with oxygen because of the slower elimination of CO across the placenta, particularly when the CO exposure occurred over several hours or more.[75]

It is known that severe maternal CO poisoning can cause intrauterine fetal demise, limb and vertebral anomalies, cranial deformities, brain injury, transient hepatomegaly, and congestive heart failure in the newborn.[77-79] It is unclear, however, whether mild to moderate maternal CO poisoning can produce adverse fetal outcomes. Three case series have examined pregnancy outcomes in CO-poisoned women.[77-79] In all cases, women with minor CO poisoning (no loss of consciousness and normal mental status) delivered healthy babies, despite not receiving HBO. Animal studies suggest that a single CO exposure can lead to intrauterine hypoxia, fetal brain injury, and increased rates of fetal death.[80-82] It is unclear from these studies, however, whether exposures that lead to adverse fetal

BOX 87-1 INDICATIONS AND CONSIDERATIONS FOR HYPERBARIC OXYGEN TREATMENT IN CARBON MONOXIDE POISONING

Accepted Indications

Altered mental status
History of loss of consciousness or syncope
Coma
Seizures
Focal neurologic deficits
Pregnancy with evidence of fetal distress

Considerations

Metabolic acidosis
Cardiac end-organ effects (severe arrhythmia, ischemia, or infarction)
Extremes of age
COHb level > 25%–40%
Abnormal neuropsychometric testing
Persistent neurologic symptoms after 4–6 hr of high-flow normobaric oxygen
Pregnancy with COHb level > 15%–20%

COHb, carboxyhemoglobin.
Adapted from references 73, 74, and 85.

outcome can occur in the absence of significant maternal poisoning. The efficacy of NBO or HBO for preventing adverse fetal outcomes for pregnant patients with CO poisoning has not been determined. To date, pregnant women have been excluded from all published trials of HBO in CO poisoning.

HBO is generally considered safe for the fetus and has been used safely in pregnant women with CO poisoning.[83] The results in these patients were similar to those of the pregnant women treated without HBO. When the mothers had normal mentation, the fetuses universally did well, whereas maternal coma or loss of consciousness carried a poor prognosis despite HBO.

Patients who develop cardiac arrest as a result of CO poisoning have very poor outcomes. In one series of such patients, none (0 of 18) survived to hospital discharge despite aggressive therapy, including HBO.[84]

A reasonable algorithm for managing CO-poisoned patients is presented in Figure 87-1. This management strategy is in keeping with a recent position statement of the Undersea and Hyperbaric Medical Society and the consensus report of a panel of CO-poisoning experts.[73,85] Unresolved issues include which subgroups of CO poisoned patients are most likely to benefit from HBO, the optimum HBO treatment pressure and number of sessions, the necessary intensity of NBO therapy in patients not receiving HBO, and the "window of opportunity" after which brain injury is irreversible even with therapy.[73]

In addition to oxygen therapy, several novel neuroprotective strategies have been evaluated in a mouse model of CO poisoning. Glutamate antagonists (riluzole), caspase-inhibitors (disulfiram), nitric oxide synthase inhibitors (*N*-nitro-L-arginine methyl ester, or L-NAME), adenosine agonists (2-chloro-N^6-cylopentyl-adenosine, or CCPA), and adenosine deaminase inhibitors (erythro-9-2-hydroxy-3-nonyl-adenine, or EHNA), have all been shown to prevent hippocampal damage and learning and memory defects in mice.[86-88] HBO did not prevent neurologic injury in the same model.[64] Although riluzole and disulfiram have been found to be safe and effective treatment for other human diseases, neither has been tested in human victims of CO poisoning.

Elimination

DISPOSITION

Victims of CO poisoning can be released from the hospital after 4 to 6 hours of oxygen therapy (whether NBO or a combination of HBO) if they are neurologically normal, have no more than mild symptoms, and have no unmet medical or psychiatric needs. NBO may be discontinued before 4 hours for patients with mild CO poisoning whose symptoms have resolved and who have COHb levels below 5%.[89] Patients who do not recover fully after initial therapy should receive further high-flow oxygen treatment and consideration for HBO referral and treatment. Patients with moderate to severe CO poisoning should be considered for HBO treatment upon arrival and subsequently admitted to the hospital, preferably to an intensive care unit.

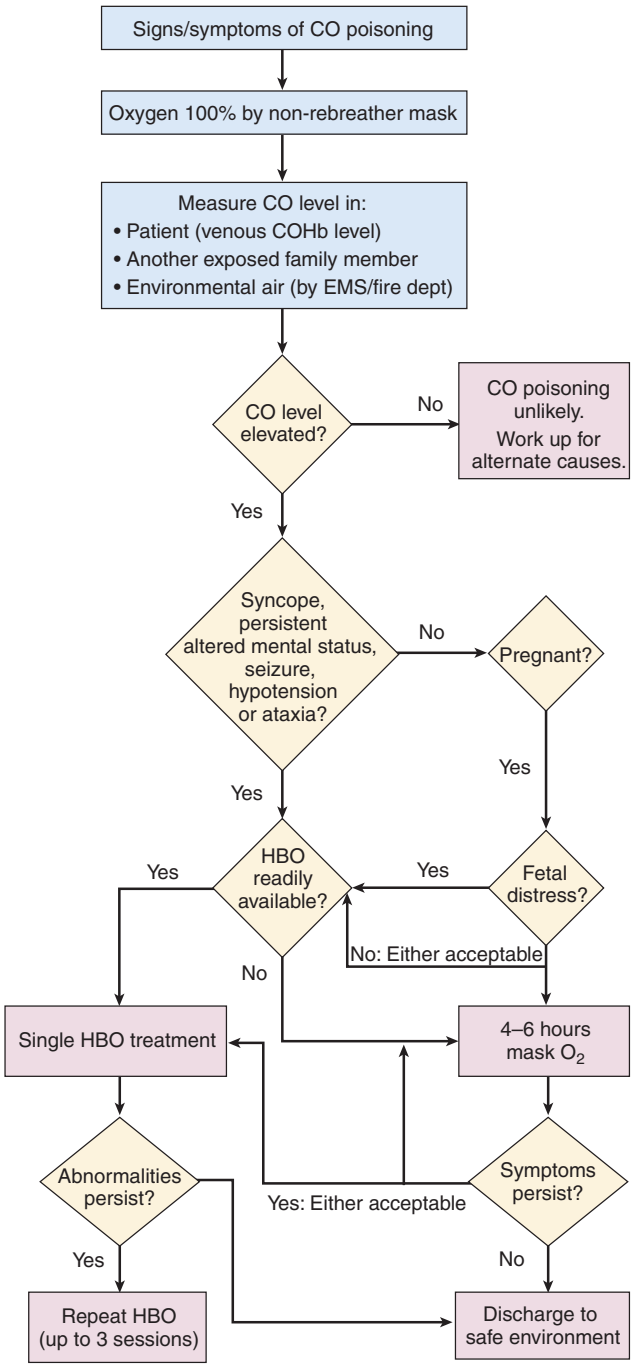
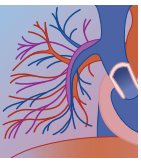


FIGURE 87-1 Suggested management algorithm for carbon monoxide poisoning.

Upon hospital discharge, patients should be warned of the possibility of delayed neuropsychological complications and provided with instructions about what to do if these occur. All patients diagnosed with CO poisoning who are discharged from the emergency department after NBO treatment should also have mandatory medical follow-up within 1 to 2 weeks so that repeat neurologic evaluation can be conducted. Most



patients return to normal within 3 to 12 months.[13,21] Because of the increased risk of cardiovascular mortality, patients who suffer myocardial infarction due to CO poisoning should have long-term follow-up and cardiac risk assessment performed.[56]

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88 Cyanide and Related Compounds—Sodium Azide

ALAN H. HALL, MD

At a Glance...

- Severe acute cyanide poisoning can be seen in a wide variety of settings, including enclosed-space fire smoke inhalation.
- Cyanide is a credible toxic terrorism threat agent.
- Whole-blood cyanide levels require several hours or longer to obtain.
- Emergent suspicion of the diagnosis and the decision to administer specific antidotes must be made on clinical and screening laboratory grounds.
- Elevated plasma lactate levels are a specific and sensitive indicator of the presence of significant cyanide poisoning in both smoke inhalation and pure cyanide poisoning cases.
- Several specific cyanide antidotes are available throughout the world.
- In the United States, only the cyanide antidote kit containing amyl nitrite for inhalation administration and sodium nitrite/sodium thiosulfate for intravenous administration is available as of June 2006.
- Amyl nitrite inhalation is an effective first-aid measure, especially in cases of hydrogen cyanide gas exposure.
- Growing evidence indicates that hydroxocobalamin may be the cyanide antidote of choice because of its efficacy and superior safety and adverse effects profile.
- The nitrite and thiosulfate antidote kit is not efficacious for sodium azide poisoning; hydroxocobalamin may be of theoretical benefit based on limited in vitro data.

INTRODUCTION AND RELEVANT HISTORY

Cyanide poisoning may be encountered in a wide variety of settings. Cyanide salts and hydrocyanic acid are used in common industrial processes such as electroplating, jewelry and metal cleaning, precious metal extraction, laboratory assays, and photographic processes.[1-4] Hydrogen cyanide is a chemical intermediate for the manufacture of synthetic fibers, plastics, and nitriles.[5] Criminal tampering by replacement of the ingredients in over-the-counter capsules with cyanide salts has resulted in a number of deaths.[6,7] Victims of enclosed-space fire-smoke inhalation may have both cyanide and carbon monoxide poisoning.[8,9]

Cyanide and carbon monoxide are synergistic toxicants[10] (see Chapters 86 and 87). Nontraumatic deaths in aircraft accidents may be due to inhalation of carbon monoxide and cyanide combustion products.[11] A number of compounds can liberate cyanide on spontaneous or thermal decomposition or by chemical reaction with acids (e.g., cyanogen, cyanogen bromide, cyanogen iodide, cyanogen chloride, calcium cyanide).[1] Cyanogen halides and hydrogen cyanide are potential chemical warfare agents.[12] At low concentrations, however, cyanogen halides are primarily lacrimating and pulmonary irritant agents.[3]

Cyanogenic compounds (laetrile, amygdalin from plant sources, nitrile compounds such as acetonitrile or propionitrile) can release cyanide during metabolism, chemical reaction in the gut, or bacterial degradation after ingestion.[3,13-17] Acute cyanide poisoning from apricot or peach kernels is unusual because the pits are usually swallowed whole and simply pass through the gastrointestinal tract; rare cases have been reported.[18] Severe or fatal cyanide poisoning with symptom onset delay of several hours has followed accidental acetonitrile ingestion from glue-on artificial nail–removing compounds.[19,20]

Acrylonitrile is a special case. After inhalation or dermal exposure, it both undergoes hepatic metabolism releasing cyanide and is itself hepatotoxic. Whole blood cyanide levels as high as 4.3 µg/mL have been found in patients with acrylonitrile poisoning.[17] In addition to supportive care and cyanide antidotes, treatment with *N*-acetylcysteine in a manner similar to that for acetaminophen poisoning has been recommended to prevent hepatotoxicity[17] (see Chapter 47).

Sodium nitroprusside releases cyanide during metabolism, which can result in elevated whole blood cyanide levels, and, occasionally, clinical cyanide poisoning.[21-24]

Coadministration of sodium thiosulfate or hydroxocobalamin can prevent cyanide toxicity, especially in patients receiving sodium nitroprusside infusions at rates greater than 2 µg/kg/minute[24,25] (see Chapter 61).

The frequent lack of correlation between blood cyanide levels and cyanide poisoning symptoms during nitroprusside administration suggests that the decision of whether to administer antidote therapy must be made on clinical grounds (e.g., presence of lactic acidosis or signs and symptoms consistent with cyanide poisoning). Clinical symptoms in this setting may, however, be due to thiocyanate accumulation.[26]

Chronic exposure to low levels of cyanide has been postulated to cause retrobulbar optic atrophy (in heavy smokers) and ataxic peripheral neuropathy (tropical ataxic neuropathy), as well as konzo (spastic upper motor neuron paraparesis) in people who consume large amounts of improperly prepared cassava, which contains the cyanogenic glycosides linamarin and lotaustralin in both roots and leaves.[27,28] Development of these neuropathies seems to require both chronic low-level cyanide exposure and either a deficiency of the endogenous cyanide-detoxifying enzyme rhodanese or protein-calorie malnutrition with dietary sulfur deficiency. A condition resembling acute cyanide poisoning treatable with hydroxocobalamin has resulted from acute ingestion of improperly prepared cassava.[29]