Carbon Monoxide Poisoning

Jorge A. Guzman, MD

KEYWORDS
- Carbon monoxide  •  Carboxyhemoglobin  •  Poisoning

KEY POINTS
- Carbon monoxide (CO) poisoning is the leading cause of death as a result of unintentional poisoning in the United States.
- Because of their higher metabolic rates, the cardiovascular and nervous systems are most frequently affected in severe intoxications.
- Diagnosis is made by prompt measurement of carboxyhemoglobin levels performed by spectrophotometric CO-oximetry (>3% in nonsmokers and >10% in smokers confirms CO exposure, but levels correlate poorly with the clinical picture).
- Treatment consists of the patient’s removal from the source of exposure and the immediate administration of 100% supplemental oxygen in addition to aggressive supportive measures.

INTRODUCTION
Carbon monoxide (CO) poisoning is common. Unintentional, non–fire-related CO poisoning is responsible for approximately 15,000 emergency department (ED) visits and nearly 500 deaths annually in the United States.\(^1,2\) CO is frequently unrecognized because the signs and symptoms are relatively nonspecific; consequently, the true incidence of CO poisoning remains unknown. Mortality rates range between 1% and 31%.\(^3\)

EPIDEMIOLOGY
CO is an odorless, colorless gas that usually remains undetectable until exposure results in injury or death. CO poisoning occurs both as the result of routine domestic, occupational, and recreational activities and in the wake of large-scale disasters such as those caused by hurricanes,\(^4\) floods,\(^5\) and winter storms.\(^6,7\)

Sources of CO include faulty furnaces, inadequate ventilation of flame-based heating sources, exposure to internal combustion engine exhaust (bus exhaust from attached garages, nearby roads, or parking areas can also be a source), and tobacco smoke.\(^8,9\) Additionally, endogenous sources have been cited (eg, hemolytic anemia and sepsis), although they rarely reach concerning levels.\(^3,10\)
It is estimated that each year in the United States at least 15,200 individuals seek medical attention in an ED or miss at least 1 day of work as a result of CO poisoning. However, this estimate does not account for the full burden of illness because the toxic effects of CO exposure are nonspecific, easily misdiagnosed, and underreported; as a result, many people with mild exposure may not seek medical attention or may be treated in the field.

According to a recent report from the US Centers for Disease Control and Prevention using data from the Nation Poison Data System, there has been a steady decline in CO exposures during the past few years. Most victims of unintentional non–fire-related exposures were treated at a health care facility. However, a significant proportion (45.1%) were managed at the site of exposure with instructions received by telephone from poison center personnel. CO exposures most frequently occurred among female victims, among those younger than 17 years, and during winter months, particularly in the Midwest region of the United States. In 2005, there were 24,891 CO-related hospitalizations nationwide: 17% were confirmed, 1% was probable, and 82% were suspected CO-poisoning cases. Of the confirmed cases (1.42/100,000 population), the highest hospitalization rates occurred among male victims, older adults (aged ≥85 years), and Midwestern US residents.

**MECHANISMS OF TOXICITY/PATHOPHYSIOLOGY**

CO toxicity is the result of a combination of tissue hypoxia-ischemia secondary to carboxyhemoglobin (COHb) formation and direct CO-mediated damage at a cellular level (Fig. 1).

CO binds hemoglobin (Hb) to form COHb with an affinity that is more than 200 times greater than that of oxygen. The amount of COHb formed depends on the duration of the exposure to CO, the concentration of CO in the inspired air, and alveolar ventilation. Additionally, bound CO ligand at any of the 4 oxygen-binding sites of Hb results in the complex having a greater affinity for oxygen at the remaining binding sites. Therefore, oxygen bound to COHb produces a complex that impairs the release of oxygen to peripheral tissues and causes a leftward shift in the oxygen-Hb dissociation curve. The increased affinity for oxygen by the COHb complex is known as the Haldane effect. The aforementioned effects of CO on the Hb complex ultimately cause a decrease in oxygen availability to the tissues with resultant tissue hypoxia.

CO also binds to heme-containing proteins other than Hb. The binding to cytochrome c oxidase impairs mitochondrial function, thereby worsening tissue hypoxia. This disturbance in electron transport increases the production of reactive oxygen species and induces oxidative stress, which in turn worsens tissue hypoxia. Additionally, CO binds myoglobin with an affinity 40 times greater than that for oxygen, and this high affinity is even more pronounced for cardiac myoglobin. The high-affinity binding to myoglobin may further reduce oxygen availability to the myocardial cells and may be responsible for arrhythmias and cardiac dysfunction.

Furthermore, CO binds to platelet hemoproteins, and the competition with intraplatelet nitric oxide (NO) increases NO release. Excess NO produces peroxynitrite, which further impairs mitochondrial function and worsens tissue hypoxia.

Intravascularly, CO causes platelet-to-neutrophil aggregation and release of myeloperoxidase, proteases, and reactive oxygen species, leading to oxidative stress, lipid peroxidation, and apoptosis. These effects seem to be more pronounced within the central nervous system, where NO-mediated vasodilatation and oxidative damage may explain the clinical syndrome of delayed neurologic damage.
Fig. 1. Pathophysiology of CO poisoning. CO diffuses rapidly into the blood after entering through the lungs. CO causes hypoxia through the formation of COHb and a leftward shift of the oxyhemoglobin dissociation curve and the binding to heme-containing proteins, particularly cytochrome c oxidase and myoglobin. CO also causes inflammation by increasing cytosolic heme levels and the heme oxygenase-1 protein, resulting in increased intracellular oxidative stress. CO binds to platelet heme protein, causing the release of NO. Excess NO produces peroxynitrite (ONOO), which in turns impairs mitochondrial function and worsens tissue hypoxia. CO induces platelet-neutrophil aggregation and neutrophil degranulation; release of myeloperoxidase, proteases, and reactive oxygen species, which contribute to oxidative stress; lipid peroxidation; and apoptosis. The interaction of proteases with xanthine dehydrogenase in endothelial cells forms xanthine oxidase, which inhibits endogenous mechanisms against oxidative stress. Additionally, CO-induced hypoxia activates hypoxia-inducible factor 1a, which can stimulate either protective or injurious gene regulation depending on the CO dose and host factors. (From Weaver LK. Clinical practice. Carbon monoxide poisoning. N Engl J Med 2009;360(12):1217–25, Fig 1; with permission).
CLINICAL PRESENTATION

The spectrum of symptoms depends on the duration of the exposure and the levels of CO. The clinical effects of CO are diverse and symptoms are nonspecific and can be easily confused with other illnesses; therefore, a high index of suspicion is crucial for an appropriate and early diagnosis.\textsuperscript{9,20} The severity ranges from mild flulike symptoms to coma and death. Because of their higher metabolic rate, the brain and the heart are most susceptible to CO toxicity.\textsuperscript{21} Common CO-induced manifestations are listed in Table 1.

Headache is one of the most common presenting symptoms of CO poisoning. It is described as frontal, it can be dull or throbbing, it is present in up to 84% of victims, and its intensity does not correlate with COHb levels. Dizziness is a frequent companion of the headache and can be seen in as many as 92% of CO victims.\textsuperscript{21} Increased CO exposure produces more severe neurologic manifestations, including confusion, syncope, seizures, acute strokelike syndromes, and coma.\textsuperscript{9} Additionally, CO poisoning may result in neurologic sequelae, neurobehavioral changes, and cognitive impairment including reduced memory, attention disorders, impaired executive function, slow mental processing speed, and significant depression and anxiety that may persist for 12 months or longer.\textsuperscript{22–24} Loss of consciousness, age of 36 years or older, and COHb levels of 25% or greater have been identified as risk factors for the development of cognitive sequelae and criteria for potential candidacy for hyperbaric oxygen (HBO) treatment.\textsuperscript{25} A delayed neuropsychiatric syndrome (DNS) may occur in patients 7 to 240 days after the acute CO exposure.\textsuperscript{26} Clinical features of DNS vary from subtle cognitive deficits to severe dementia, hallucinations, incontinence, parkinsonism, and other motor disturbances. It is more commonly seen in patients who present with a more symptomatic initial picture, and it resolves in up to 75% of the patients without additional specific treatments.\textsuperscript{9,21,26,27} HBO has been used to prevent and treat DNS with contrasting results.\textsuperscript{28,29} Neuropathologic abnormalities on brain imaging have also been described following CO poisoning.

\begin{table}[h]
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\hline
\textbf{Severity} & \textbf{Signs and Symptoms} \\
\hline
Mild & Fatigue, malaise \\
 & Headache \\
 & Dizziness \\
 & Confusion, disorientation \\
 & Blurred vision \\
 & Nausea, vomiting \\
\hline
Moderate & Ataxia \\
 & Syncope \\
 & Tachypnea, dyspnea \\
 & Palpitations, chest pain \\
 & Rhabdomyolysis \\
\hline
Severe & Hypotension \\
 & Cardiac arrhythmias \\
 & Myocardial ischemia \\
 & Coma \\
 & Respiratory depression \\
 & Noncardiogenic pulmonary edema \\
 & Seizures \\
\hline
\end{tabular}
\caption{Clinical signs and symptoms of CO poisoning}
\end{table}
involving the basal ganglia (particularly globus pallidus lesions in cases of severe poisoning) and delayed atrophy of the corpus callosum.\textsuperscript{22,30–32}

Cardiovascular effects of CO poisoning are common. Following acute exposure, tachycardia is frequently observed and considered a compensatory response to systemic hypoxia and cardiac dysfunction.\textsuperscript{18} COHb, even at low levels, exacerbates myocardial ischemia, and cardiac necrosis can occur even in the absence of cardiac symptoms.\textsuperscript{33} Conversely, elevations of cardiac biomarkers with normal coronary arteries are frequently observed in response to an acute CO exposure. Additionally, mild to moderate abnormalities in left ventricular function or structure have been described, and they have been correlated to the COHb level and the duration of the CO exposure.\textsuperscript{34,35} Cardiac arrhythmias (either supraventricular or ventricular) have also been described and are likely secondary to CO-induced changes in cardiac conduction, cardiac ischemia, or myocardial cell hypoxia. In contrast to ventricular dysfunction, however, no correlation has been noted between COHb levels and electrocardiographic alterations.\textsuperscript{18,34,36}

CO intoxication during pregnancy deserves particular attention because adverse fetal outcomes following accidental CO exposure have been reported.\textsuperscript{37} Fetal tissues are more susceptible to hypoxia; furthermore, CO binds more tightly to fetal Hb and the elimination of CO by the fetus lags behind that of the mother.\textsuperscript{9,38} As a consequence, low-level exposure, which may be inconsequential for the mother, can present greater risk for the fetus. Thus, prolonged oxygen therapy is necessary and HBO should be considered.

Rhabdomyolysis and renal failure,\textsuperscript{39–41} noncardiogenic pulmonary edema,\textsuperscript{42} and cutaneous blisters\textsuperscript{43,44} have also been described following an acute exposure to CO. On the other hand, the “cherry red” skin color classically attributed to CO poisoning is uncommon in clinical practice.\textsuperscript{9,42}

\textbf{DIAGNOSIS}

Timely diagnosis of CO poisoning is critical, albeit challenging, because the clinical presentation is nonspecific and can mimic that of influenza or other viral illnesses. A high index of suspicion and consideration of the circumstances and environmental factors suggestive of exposure are therefore of paramount importance.\textsuperscript{2,9,20,21} Source identification is important in cases of nonintentional poisoning to limit the risk to others. In the absence of exposure history, CO poisoning must be considered when 2 or more patients are similarly or simultaneously sick. Concomitant cyanide toxicity should be considered in patients with CO poisoning after smoke inhalation.

COHb levels should be promptly obtained in patients suspected of CO exposure. COHb levels depend on the magnitude of the exposure (ambient CO concentration and the duration of the exposure), alveolar ventilation, blood volume, and metabolic activity.\textsuperscript{45} A COHb level greater than 3\% in nonsmokers and greater than 10\% in smokers confirms CO exposure; however, levels correlate poorly with the clinical picture.\textsuperscript{20,46,47} COHb can be interchangeably monitored with use of arterial or venous blood samples.\textsuperscript{48} Nonetheless, measurements should be performed with spectrophotometric CO-oximetry (a multi-wavelength spectrophotometric method capable of separately quantifying COHb, oxyhemoglobin, and reduced Hb).\textsuperscript{49,50} Unfortunately, COHb measurements are not always readily available (only half of acute care hospitals in a 4-state area were found to have the capability to measure COHb levels), and delays in treatment may occur.\textsuperscript{51}

Pulse oximetry is unreliable in assessing oxygenation in CO-exposed patients because dual-wavelength spectrophotometry, the method used in most pulse oximeters, cannot distinguish between oxyhemoglobin and COHb. Pulse oximetry,
therefore, overestimates arterial oxygenation in patients with severe CO poisoning. On the other hand, the difference in arterial saturation observed with pulse oximetry versus an in vitro assessment of oxyhemoglobin saturation (pulse oximetry gap) correlates with the COHb level and may be a cue to raise the suspicion of CO intoxication.52–54 Newly available multiwavelength pulse CO-oximeters have not been reliable for quantifying COHb.49,50

As described, CO lowers the threshold for cardiac ischemia and predisposes to myocardial dysfunction and cardiac arrhythmias18,34,36; therefore, cardiac function must be closely monitored with the use of electrocardiography, echocardiography, and cardiac biomarkers. If results are abnormal, cardiology consultation is recommended.

Plasma biomarkers have not been found to be useful in correlating the severity of the exposure, the clinical course, or the development of late complications.55 Conversely, a high blood lactate level on presentation was more frequently associated with altered mental status and high COHb levels and was independently associated with serious complications and the need for intensive care unit admission.56

Neuropsychological testing has been proposed to assess and quantify the degree of neurologic injury following CO exposure and the need for HBO57,58; however, this has limitations and is not widely used.59 Neuroimaging, on the other hand, has been more broadly studied. Structural changes of the brain delineated by computed tomography, particularly bilateral globus pallidus low-density lesions and symmetric and diffuse hypodensity in the cerebral white matter, have been well described.60–62 These lesions may appear several days after the CO exposure and may resolve with time. The clinical prognosis seems mostly associated with the severity of the cerebral white matter changes but not the size of the low-density abnormalities of the globus pallidus.61 Nevertheless, patients with any kind of abnormal neuroimaging findings are more likely to have poorer long-term neurologic outcomes. Magnetic resonance imaging and functional (single-photon emission computed tomography) imaging are also used to assess CO-induced neurologic injuries but are less widely available.9,30

TREATMENT

Field treatment of the CO-poisoned patient consists of removal of the patient from the source of exposure, immediate administration of 100% high-flow supplemental oxygen, and transport to a hospital, where aggressive supportive measures, including airway and cardiovascular support, can be provided.9,20,21 The administration of oxygen speeds the elimination of CO from the body. Without oxygen therapy, the elimination half-life of CO is 4 to 5 hours.47,63 Supplementation with 100% oxygen via a tight-fitting mask at normal atmospheric pressure (NBO) decreases the half-life by approximately half,47,64 whereas the use of hyperbaric oxygen (HBO) at 2.5 atm decreases it to less than 30 minutes.47 NBO should be administered before laboratory confirmation when CO poisoning is suspected. Once the diagnosis is confirmed, oxygen therapy and observation must continue long enough to prevent delayed sequelae as COHb unloads.65 Although there are no guidelines indicating the recommended duration of the NBO treatment, up to 24 hours for patients with minor neurologic symptoms and up to 72 hours for those with major neurologic symptoms have been proposed.66

HBO has been used for severe CO poisoning for decades; however, its indication remains controversial.59,67–70 Proposed mechanisms by which HBO reduces tissue hypoxia are decreasing the elimination half-life of COHb, increasing the fraction of oxygen dissolved in plasma, preventing leukocyte-mediated inflammatory changes,
improving mitochondrial oxidative processes, and decreasing cerebral edema by inducing vasoconstriction. Despite the controversy, a significant number of patients receive HBO for CO poisoning in the United States. Proponents of HBO recommend its use in patients presenting with severe neurologic or cardiovascular symptoms and very high COHb levels (>25%), citing reversal of neurologic injury or decreased incidence of DNS as a beneficial effect. However, several randomized trials have failed to show any favorable effects.

A recent clinical policy statement by the American College of Emergency Physicians concluded that HBO is a therapeutic option for CO-poisoned patients; however, its use could not be mandated. Furthermore, the American College of Emergency Physicians subcommittee failed to identify clinical variables, including COHb levels, that could identify a subgroup of poisoned patients for whom HBO would provide benefit or harm. After recently evaluating 6 randomized controlled trials, authors of a Cochrane review concluded that existing evidence does not establish whether the administration of HBO for CO poisoning reduces the incidence of adverse neurologic outcomes. Unfortunately, there is considerable heterogeneity among the trials reviewed; thus, the conclusions have to be carefully interpreted. The most apparent differences among these studies that may explain the contrasts in the observed outcomes after the use of HBO have been the duration of the CO exposure, the type of CO exposure (accidental or suicidal), the time interval between the exposure and the initiation of HBO therapy, the severity of the clinical presentation, the number and duration of treatments, the level of atmosphere absolute used, follow-up duration, and neurologic outcomes tracking.

If a decision is made to provide HBO treatment, comatose patients with acute non-suicidal CO poisoning and COHb greater than 25% may be the most suitable candidates. One HBO session at 2 atmosphere absolute initiated within 12 hours after the end of CO exposure may be the best approach. The use of HBO in pregnant women deserves special mention. Pregnancy was an exclusion criterion in most of the randomized trials comparing HBO to NBO; thus, existing data are limited to small case reports. Nevertheless, because of the potential benefit to the mother and the fetus and the difficulty of assessing intrauterine hypoxia, HBO should be considered when treating CO-poisoned pregnant women.

No data exist on children younger than 15 years supporting the use of HBO in this population. Side effects of HBO include painful barotrauma (ears and sinuses) and, less commonly, oxygen toxicity, seizures, pulmonary edema, and decompression sickness.

**DISPOSITION/PREVENTION**

No definitive guideline exists on how to triage patients with CO poisoning, although most patients can be managed in the ED because most symptoms improve with NBO. As a general approach, patients with minor symptoms should receive NBO in the ED until their COHb levels decrease to less than 10% and symptoms resolve. Patients with more severe or nonresolving symptoms, higher COHb levels, and major comorbidities should be hospitalized. Because many hospitals lack the ability to measure COHb, clinicians practicing in such hospitals should consider the transfer of patients with severe intoxication to high-complexity medical centers with COHb-monitoring capabilities and access to HBO if needed.

CO poisoning can be entirely preventable by the correct installation, maintenance, and operation of combustion devices that may emit CO, combined with the appropriate use of home CO monitors, which are inexpensive and widely available.
Prevention strategies aimed at the general public are available from the US Environmental Protection Agency and the Centers for Disease Control and Prevention.\textsuperscript{8,78}

**SUMMARY**

CO poisoning is common, potentially fatal, and frequently underdiagnosed because of its nonspecific clinical presentation. Immediate NBO with the highest possible fraction of inspired oxygen should be administered to patients with suspected poisoning, and aggressive supportive treatment should be promptly instituted. Diagnosis of CO exposure should be made by COHb measurement using multiwavelength spectrophotometry (CO-oximetry). The use of HBO is controversial and, if used, should be relegated for those patients presenting with severe symptoms, high COHb levels, or pregnancy. The source of CO should be identified and corrected.

**REFERENCES**
