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EM - REVIEW

Clinical chameleons: an emergency medicine focused review of carbon monoxide poisoning

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Abstract
Carbon monoxide (CO) is a colorless, odorless gas that is found in the environment, in the home, and in the human body as a normal part of mammalian metabolism. Poisoning from CO, a common exposure, is associated with significant morbidity and mortality if not recognized and treated in a timely manner. This review evaluates the signs and symptoms of CO poisoning, conditions that present similar to CO poisoning, and an approach to the recognition and management for CO poisoning. CO poisoning accounts for thousands of emergency department visits annually. If not promptly recognized and treated, it leads to significant morbidity and mortality. CO poisoning poses a challenge to the emergency physician because it classically presents with non-specific symptoms such as headache, dizziness, nausea, and vomiting. Due to nonspecific presentations, it is easily mistaken for other, more benign diagnoses such as viral infection. The use of specific historical clues such as exposure to non-conventional heat sources or suicide attempts in garages, as well as the use of targeted diagnostic testing with CO-oximetry, can confirm the diagnosis of CO poisoning. Once diagnosed, treatment options range from observation to the use of hyperbaric oxygen. CO poisoning is an elusive diagnosis. This review evaluates the signs and symptoms CO poisoning, common chameleons or mimics, and an approach to management of CO poisoning.

Keywords Carbon monoxide · Headache · Chameleon · Vomiting · Hyperbaric oxygen

Introduction

Carbon monoxide (CO) is a colorless, odorless gas produced by the burning of fuels and organic material [1, 2]. It is also produced in low amounts as a byproduct of normal human metabolism. According to the CDC's *Clinical Guidance for Carbon Monoxide (CO) Poisoning After a Disaster* online resource, a normal carboxyhemoglobin (COHb) concentration in the body is less than 2% [3]. This number can increase up to 9–15% in heavy smokers; however, this upper limit in smokers is not well established [1]. CO is also produced by the burning of fuels. Exposures to high levels of CO can occur in building fires, in industrial plants; in garages with vehicle engines running, from charcoal briquettes, from boat propulsion engines; or in the home from malfunctioning gas stoves, heating appliances, or generators. Other sources include forklifts, zambonis, indoor tractor pulls, and concrete saws powered by gas [2–4].

CO poisoning is an important condition in emergency medicine, as it is a common exposure that leads to significant morbidity and mortality [5]. According to the Centers for Disease Control and Prevention (CDC), more than 20,000 emergency department (ED) visits per year are related to CO poisoning, which occurs more commonly in a patient's residence rather than workplace [6]. CO poisoning is caused by intentional and accidental exposure, and is a leading cause of death [7, 8]. To guide emergency medical treatment of CO poisoning, the American College of

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Emergency Physicians (ACEP) in 2017 published a clinical policy for CO poisoning [9]. The authors of the ACEP policy performed a systematic review to answer three critical clinical questions, demonstrated in Table 1.

This review discusses this clinical policy and evaluates the literature about CO poisoning. CO poisoning can be an elusive diagnosis, and several dangerous conditions may mimic CO poisoning. This review investigates these mimics, and explores the evidence concerning normobaric oxygen (NBO) and hyperbaric oxygen (HBO) therapy in CO poisoning.

Discussion

How does carbon monoxide cause toxicity?

CO interferes with oxygen transport and delivery to cells. It has greater affinity for hemoglobin when compared to oxygen (approximately 230–270 times), thus impairing oxygen transport and delivery in the bloodstream leading to cellular hypoxia [10, 11]. COHb is formed when CO binds to hemoglobin. As the concentration of COHb increases, physiologically it causes a leftward shift of the oxyhemoglobin dissociation curve resulting in decreased oxygen delivery to cells. Thus, even with high partial pressures of oxygen, hemoglobin is unable to effectively deliver oxygen to the cells resulting in an intracellular hypoxia. Additionally, CO increases nitric oxide formation that causes vasodilatation as well as microvascular damage that may partially account for the long-term morbidity. CO binding to myoglobin also causes further myocardial impairment. The toxin can also directly damage cells through intracellular protein binding, lipid peroxidation, mitochondrial oxidation, apoptosis, and inflammation [12–18]. Morbidity initially involves systems with high oxygen requirements, most commonly the cardiovascular and neurological systems [13–18]. More specifically, CO poisoning can lead to deadly dysrhythmias and permanent neurological sequelae if not promptly recognized and managed [13, 19].

How does a patient exposed to carbon monoxide present?

Patients with CO poisoning may present with a variety of non-specific symptoms, with headache being one of the most commonly reported (Table 2) [11–15]. Other symptoms such as nausea, vomiting, dizziness, weakness, or confusion are also commonly reported [12–35]. Less common presentations include syncope, chest pain, dysrhythmias, neurological deficits that can present similar to stroke, dysrhythmia and dyspnea, as well as fatigue [12–35]. Skin findings such as pallor and cherry red color have been reported [30, 31]. Ernst et al. describe the frequency of presenting symptoms in patients with CO poisoning [8]. In their study, the most common symptoms in descending order are headache, dizziness and weakness. Neurologic findings including faltering concentration, disturbance of memory, emotional changes, stupor, coma, gait difficulty, and movement disorders have also been reported [20–28]. The symptoms are often non-specific, and at times can be mistaken for other conditions.

Table 2 Frequency of presenting symptoms in patients with elevated COHb concentrations [10]

Presenting symptom	Patients presenting with elevated COHb levels ($n = 106$) (%)
Headache	35
Dizziness	30
Nausea	30
Vomiting	24
Altered mentation	21
Chest pain	12
Fatigue	7
Syncope	6

Table 1 ACEP clinical policy recommendations for the evaluation and management of CO poisoning in adults [9]

Management question	Patient management recommendation
In ED patients with suspected acute CO poisoning, can noninvasive COHb measurement be used to accurately diagnose CO toxicity?	Do not use noninvasive COHb measurement (pulse CO oximetry) to diagnose CO toxicity in patients with suspected acute CO poisoning (Level B)
In ED patients diagnosed with acute CO poisoning, does HBO therapy as compared with normobaric oxygen therapy improve long-term neurocognitive outcomes?	Emergency physicians should use HBO or high-flow normobaric therapy for acute CO-poisoned patients. It remains unclear whether HBO therapy is superior to normobaric oxygen therapy for improving long-term neurocognitive outcomes (Level B)
In ED patients diagnosed with acute CO poisoning, can cardiac testing be used to predict morbidity or mortality?	In ED patients with moderate to severe CO poisoning, obtain an ECG and cardiac biomarker levels to identify acute myocardial injury which can predict poor outcome (Level B)

How is carbon monoxide poisoning diagnosed?

Initial suspicion of CO poisoning is obtained via the history and physical examination [20–28]. A history of exposure to CO, such as through a fire, a home heater during the winter, or an enclosed space such as garage should help the emergency physician move CO poisoning/exposure higher in the differential when patients present with non-specific symptoms such as headache, fatigue, nausea, and vomiting. Historical evidence of other people and pets in the household having similar symptoms (e.g. birds or dogs suddenly passing out) at the same time suggest CO exposure [20–28]. However, there are numerous diagnoses that may present similar to CO poisoning. The physician must be aware of these potential clinical chameleons to narrow the differential in cases of potential CO poisoning and direct their diagnostic testing. For example, influenza is a common infection that can present with headache, dizziness, and weakness, which are common symptoms reported in CO poisoning. Some potential historical clues that can help distinguish the diagnosis are specific testing (influenza, co-oximetry) and some signs such as rhinorrhea or cough that are not classically seen with CO poisoning [24]. The differential for other causes of headache, dizziness, and weakness is broad, and includes tick borne illnesses and intracranial infections like abscess, encephalitis, and meningitis [31, 36–75]. Other conditions that may have similar presentations to CO poisoning include vascular pathologies [36, 37, 76, 77]. Endocrinological pathologies such as hypoglycemia and diabetic ketoacidosis may also present similarly. Pregnancy-related disorders including posterior reversible encephalopathy syndrome and eclampsia are also part of this differential. Furthermore, hemoglobinopathies such as sulfhemoglobinemia and methemoglobinemia and exposures to different occupational and environmental gases can present with nonspecific symptoms such as malaise and fatigue, just like CO poisoning [31–35]. Exposures to different chemicals such as hydrocarbons, cyanide, and hydrogen sulfide can also have a presentation similar to CO poisoning as they can also poison the mitochondria [32–35, 78, 79]. In many of these processes, nonspecific symptoms such as headache, dizziness and weakness can characterize the presentation. Fortunately, a careful history, physical examination and laboratory workup can assist the provider in distinguishing CO poisoning from many of these mimics.

The diagnosis of CO poisoning is confirmed by an elevated COHb concentration as measured by a CO-Oximeter [23]. A CO-Oximeter is a device that takes advantage of the unique absorptive properties of various forms of hemoglobin including oxyhemoglobin, deoxyhemoglobin, methemoglobin, and COHb [23]. The specific formulas and algorithms used by each CO-Oximeter differ depending on the manufacturer [22]. Generally, two wavelengths, 660 and 930 nm, are registered by conventional pulse oximetry. The wavelength of oxyhemoglobin and CO are similar enough that the standard pulse oximeter cannot tell the difference between the two, and therefore, is not reliable to exclude the diagnosis [22, 80]. Newer devices can use other wavelengths in addition to the 660 and 930 nm to help determine the proportion of oxyhemoglobin vs deoxyhemoglobin vs methemoglobin vs COHb; however, some of these devices produce variable results when compared to gold standard measurements [81]. As such, the gold standard remains conventional co-oximetry [80]. With level B evidence, the ACEP clinical policy does not recommend the use of non-invasive COHb measurement to diagnose CO toxicity [9].

A COHb concentration > 2% can be abnormal. However, as mentioned previously, other factors, such as smoking can cause an elevation of baseline COHb concentrations [82]. The COHb concentration must be interpreted in the context of a patient's clinical presentation to help determine if a patient requires specific therapy. There is a wide range of reported baseline COHb concentrations in smokers. Some reports suggest that 5–8% is normal in individuals who smoke regularly, while other reports describe concentrations up to 15% as being expected in patients who smoke regularly [82, 83]. Furthermore, even higher baseline concentrations of COHb have been reported in patients who smoke products other than traditional filtered cigarettes (e.g., hookah, unfiltered products, foreign cigarettes, etc.) [82, 83].

Other diagnostics include an electrocardiogram to assess for dysrhythmias as well as a troponin and creatine kinase to assess for possible cardiac ischemia and rhabdomyolysis, respectively [13]. If certain exposures or medical history suggests involvement of a potential ingestion, one can consider adding acetaminophen and salicylate concentrations. Additionally, chest X-ray study and head computed tomography (CT) may be considered especially in patients with severe CO toxicity due to the potential for severe end organ damage [16–18]. Chest X-ray study may display a variety of findings including ground-glass appearance, perihilar haze, peribronchial cuffing, and edema. A head CT may demonstrate abnormal findings in up to 53% of the patients admitted for CO poisoning [15–18]. Cerebral edema and focal lesions involving the basal ganglia may be found [16]. A pregnancy test should be obtained in females, as a positive result may ultimately change management in a patient poisoned with CO [29]. With Level B recommendations, the 2017 ACEP clinical policy recommends obtaining an ECG and cardiac biomarker levels in ED patients with moderate to severe CO poisoning to identify acute myocardial injury [9].

Once diagnosed, how is carbon monoxide poisoning treated?

The mainstays of treatment include removal from CO source, and administration of 100% normobaric oxygen or

hyperbaric oxygen [17–20, 23–26]. The elimination half-life of CO varies with the amount of dissolved oxygen in a patient's bloodstream as oxygen and CO competitively bind hemoglobin (Table 3). Some studies suggest HBO should be considered in the patient exhibiting signs of acute, severe CO poisoning (e.g. evidence of major end-organ damage including but not limited to myocardial infarction, altered mental status, neurological deficit, or syncope), CO concentration > 25% or if age > 55 years [1, 74]. In these patients, some suggest that hyperbaric oxygen treatment can reduce rates of delayed neurological sequelae (DNS), which has been measured via scores on various tests including but not limited to digit span, trail making, and story recall [5]. DNS are neurologic deficits that occur following CO poisoning. While the deficits can improve with time, they can also be permanent. Thom et al. report data on a prospective, randomized study in patients with mild to moderate CO poisoning. Patients were treated with NBO or HBO, and neurological sequelae were compared based on treatment group [82]. HBO treatment decreased the incidence of delayed neurological sequelae after CO poisoning in this study population [82]. In contrast, Scheinkestel et al. in 1999 find that HBO therapy does not improve outcomes in their randomized controlled trial assessing neurological sequelae in patients with CO poisoning treated with HBO or NBO. They excluded pregnant patients, children, burn victims, or those patients who refused consent [84]. Annane et al. studied a group of 385 patients with acute CO poisoning and syncope. They report that HBO therapy is not superior to NBO therapy [85]. Hampson et al. report on the effects of HBO therapy vs NBO therapy in the treatment of CO-induced headaches. They find no significant difference in the outcomes of the two treatment groups [86]. As seen, there are conflicting data on the efficacy of HBO therapy in the management of CO poisoning, and this area of management remains controversial.

The 2017 ACEP Clinical Policy on CO Poisoning provides Level B recommendations that HBO therapy or high-flow normobaric therapy should be used for acute CO-poisoned patients, though the effects of HBO versus normobaric therapy on long-term neurocognitive outcomes remain unclear [9]. Consultation with a poison center, expert in hyperbarics or medical toxicologist can assist the provider in determining if HBO is an appropriate treatment.

Alternatively, induced hypothermia has been explored as part of the treatment strategy for severe acute CO poisoning. Oh et al. perform a retrospective review of 227 patients who were diagnosed with severe CO poisoning [30]. This was defined as a patient who had a history of CO exposure and any of the following: GCS < 9, carboxyhemoglobin concentration > 25%, or S100B protein level > 0.165 μg/L. S100B is a protein that has been reported to be used as a biochemical marker for brain injury in CO poisoning. Fifteen patients were included in their case study. These patients received two HBO treatments and then were cooled to 33 °C. The S100B protein concentrations were measured before and after hypothermia was induced. The investigators report a decrease in the S100B protein concentrations after hypothermia is induced, and patients receiving hypothermia also had good recovery [30]. Hypothermia in CO poisoning has not been extensively studied, nor has it been directly compared to monotherapy with HBO. Thus, any definitive conclusions comparing the efficacy of these two treatment modalities in isolation or in combination cannot be made at this time.

Another important factor to consider is ensuring that the source of the exposure is managed properly. Local authorities can help with this. The approach to addressing potential CO sources in homes varies from department to department. The local health department should be contacted.

Table 3 Elimination half-life of CO [9]

Treatment	Elimination half-life (min)
Room air	240–300
100% normobaric oxygen	60–90
Hyperbaric oxygen	20–30

Conclusions

Carbon monoxide poisoning is an elusive diagnosis. Due to the non-specific signs and symptoms which include headache, nausea, fatigue, and chest pain, CO poisoning can be mistaken for other pathologies. A detailed yet targeted history and examination, as well as specific testing with a carboxyhemoglobin level, can assist the emergency physician in making the correct diagnosis. Treatments such as oxygen therapy and hyperbaric oxygen therapy can reduce the elimination half-life of CO in the body and possibly prevent delayed neurologic sequelae.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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