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FROM THE HBO_2 INDICATIONS MANUAL:
CHAPTER 3

Carbon monoxide poisoning

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ABSTRACT

Despite established exposure limits and safety standards as well as the availability of carbon monoxide (CO) alarms, each year 50,000 people in the United States visit emergency departments for CO poisoning. Carbon monoxide poisoning can occur from brief exposures to high levels of CO or from longer exposures to lower levels. Common symptoms can include headaches, nausea and vomiting, dizziness, general malaise, and altered mental status. Some patients may have chest pain, shortness of breath, and myocardial ischemia, and may require mechanical ventilation and treatment of shock. Individuals poisoned by CO often develop brain injury manifested by neurological problems, including cognitive sequelae, anxiety and depression, persistent headaches, dizziness, sleep problems, motor weakness, vestibular and balance problems, gaze abnormalities, peripheral neuropathies, hearing loss, tinnitus, Parkinsonian-like syndrome, and other problems. In addition, some will have cardiac issues or other ailments.

While breathing oxygen hastens the removal of carboxyhemoglobin (COHb), hyperbaric oxygen (HBO_2) hastens COHb elimination and favorably modulates inflammatory processes instigated by CO poisoning, an effect not observed with breathing normobaric oxygen. Hyperbaric oxygen improves mitochondrial function, inhibits lipid peroxidation transiently, impairs leukocyte adhesion to injured microvasculature, and reduces brain inflammation caused by the CO-induced adduct formation of myelin basic protein.

Based upon three supportive randomized clinical trials in humans and considerable evidence from animal studies, HBO_2 should be considered for all cases of acute symptomatic CO poisoning. Hyperbaric oxygen is indicated for CO poisoning complicated by cyanide poisoning, often concomitantly with smoke inhalation. ∎

RATIONALE

Introduction and definitions

While the human body produces a small amount of carbon monoxide (CO) endogenously from heme-protein breakdown for signaling and neurotransmitter functions, exogenous CO can be toxic. Common sources of CO include gasoline engines in motor vehicles, small engines, and boats, carbon-fueled appliances such as furnaces, water heaters, and boilers, charcoal and propane heating and cooking sources, and methylene chloride [1,2]. The operation of any carbonaceous fuel-burning engine or appliance without proper ventilation, including outdoors [3-6], can result in CO poisoning. A flame is not required for CO production (e.g., smoldering charcoal briquettes) [7,8].

Carbon monoxide poisoning occurs when sufficient CO is inhaled to cause symptoms. Common symptoms of CO poisoning include headache, nausea, vomiting, lethargy, dizziness, slowed thinking, shortness of breath, and chest pain but can include many others [9-11]. Specific symptoms do not correlate with carboxyhemoglobin (COHb) levels, but at higher levels loss of consciousness occurs and can be rapidly followed by death. Because of their smaller size and more rapid ventilation, children take up CO faster than adults but eliminate it more quickly for these same reasons. Additional perspectives on CO poisoning are available in three recent review articles [11-13].

The World Health Organization (WHO) has recommended that 24-hour exposure not exceed 6.1 parts per million (ppm) [14], while the U.S. Environmental Protection Agency, under the Clean Air Act, recommends that ambient air not exceed 9 ppm [15]. These recommendations take into consideration the effects of CO on sensitive populations such as the elderly, infants and children, pregnant women, and individuals with heart

KEYWORDS: carbon monoxide poisoning; carboxyhemoglobin; hyperbaric oxygen

TABLE 1. CO exposure guidelines

standards organization	setting	exposure limit
World Health Organization [14]	indoor	Modeled to maintain COHb ≤2% 15 minutes: 86 ppm; excursions to this level should not occur more than once per day; light exercise 1 hour: 30 ppm; excursions to this level should not occur more than once per day; light exercise 8 hours: 9 ppm; light to moderate exercise 24 hours: 6 ppm; awake and alert but not exercising
Environmental Protection Agency [15]	outdoor	8-hour average: 9 ppm 1-hour average: 35 ppm Not to be exceeded more than once per year
U.S. National Institute for Occupational Safety and Health (NIOSH) [18]	occupational	8-hour time weighted average (TWA): 35 ppm
Occupational Safety and Health Administration (OSHA) [19,20]	occupational	Final rule (vacated by court order) TWA: 35 ppm [20] Enforced TWA: 50 ppm [19]
American Conference of Governmental Industrial Hygienists (ACGIH) [21]	occupational	TWA: 25 ppm
National Research Council of the National Academies (NRC) [22]	occupational (submarine)	Navy standard (2007) TWA: 20 ppm NRC TWA: 9 ppm

disease. The WHO and various United States standards organizations have established limits for human exposure, summarized in Table 1. Most occupational limits aim to maintain blood carboxyhemoglobin (COHb) levels below 5% in non-smoking healthy adults during an eight-hour work shift; however, occupational limits are not appropriate for non-occupational circumstances. All of these recommended threshold levels presume sea level exposure. The hypoxic effects of CO will be increased at altitude [16]. For example, the U.S. National Institute for Occupational Safety and Health (NIOSH) proposed that forest fire fighters working at increased altitude not be exposed to CO levels greater than 23 ppm at 5,000 feet and 17 ppm at 10,000 feet during an eight-hour shift [17].

Carbon monoxide alarms can protect against CO poisoning [23]. Although CO is 3% lighter than air, its movement through any space is governed by diffusion and CO alarms can be effective at any vertical location within a room [24]. Carbon monoxide moves readily through drywall [25], and even residences without a CO-producing appliance are well advised to have CO alarms. The current CO alarm standard requires alarm activation based on mathematical modeling of a 10% COHb level (Table 2) [26]. These alarm thresholds may be inadequate to protect populations vulnerable to damage from CO, such as those with heart disease [14,20], pulmonary or vascular disease or anemia [14] or pregnant women [14], for whom an alarm with a lower threshold might be appropriate. In addition, repetitive exposures to CO at levels that do not reach alarm thresholds (Table 2) may cause harm.

Exposures to high levels of CO (e.g., greater than 10,000 to 20,000 ppm) may rapidly result in death, possibly without symptoms, as loss of consciousness can occur before symptom onset [27]. Carbon monoxide exposure for several hours to concentrations of 500 to 1000 ppm can be lethal to humans. At lower ambient levels of CO exposure (less than 500 ppm), common symptoms are headaches, nausea and vomiting, dizziness, general malaise, and altered mental status [9,11,12]. Some patients may have chest pain, shortness of breath, and myocardial ischemia and may require mechanical ventilation and treatment for shock [9].

Poisoning can occur from brief exposures to high levels of CO or from longer exposures to lower levels. Some patients with occult CO poisoning have manifested

TABLE 2. Response time requirements for CO alarms [26]

CO concentration (ppm)	response time
30 ± 3	Not sooner than 30 days
70 ± 5	60–240 minutes
150 ± 5	10–50 minutes
400 ± 10	4–15 minutes

symptoms for weeks, months or even years [28]. Symptoms are similar to those with acute poisoning, although those with chronic CO poisoning often have more fatigue, affective problems, and neurological abnormalities [29,30]. Often the poisoning etiology is discovered when a heating appliance or water heater is identified as faulty. Some patients have an acute episode of poisoning that draws attention to prior unrecognized CO exposure [11]. Any patient with CO poisoning can develop permanent sequelae regardless of the exposure duration [14,29,31].

Carbon monoxide poisoning is a clinical diagnosis based upon the presence of symptoms and the CO exposure conditions (i.e., history of inhalation of CO or elevated ambient CO levels). Exposure can be confirmed by an elevated COHb. However, the half-life of COHb is relatively short, particularly when breathing supplemental oxygen, and some CO-poisoned patients will have normal COHb levels at the time of evaluation [32-34]. A COHb level of at least 3%-4% in non-smokers or 10% in smokers indicates likely exogenous CO exposure [35].

Carboxyhemoglobin can be measured by blood gas oximeter (spectrophotometer) from arterial or venous blood [36]. Traditional non-invasive pulse oximeters cannot discriminate COHb from oxyhemoglobin (HbO_2) [37], but a newer multi-wavelength pulse oximeter can do so [38,39]. In a prospective study conducted in the emergency department setting the false positive rate for carboxyhemoglobin saturation (SpCO) by this monitor was 9%, and the false negative rate was 18% [40]. Those authors recommend the results from this monitor could broaden the differential diagnosis to consider CO exposure, but the monitor should not be used to rule out CO poisoning [40]. In the correct clinical setting, SpCO results can confirm the diagnosis of CO poisoning.

CO pathophysiology and HBO_2

The injuries caused by CO traditionally have been viewed as due to a hypoxic stress brought on by an elevated COHb level and leftward shift of the oxyhemoglobin curve [41]. Carbon monoxide preferentially binds to hemoglobin in place of oxygen, and CO in the blood distributes via diffusion through the extravascular tissues. There, CO binds to heme proteins responsible for the production of adenosine triphosphate and interrupts cellular metabolism. However, perivascular and neuronal injuries arise by mechanisms other than hypoxia [42,43]. Neuropathology is due to a complex cascade of biochemical events involving several immunological and inflammatory pathophysiologic processes [11,44-50], many independent of pure hypoxic stress [51-53], that can evolve over weeks of time [54]. Endothelial-derived microparticles may be the initial stimulus for a subsequent cascade of immunological effects [55]. Some biochemical changes are independent of poisoning severity [56].

The two organ systems most susceptible to injury from CO are the cardiovascular and central nervous systems. The COHb level is not predictive as a risk factor for CO-mediated morbidity or mortality [57-65]. In some animal models CO-mediated hypoxia plus a decrease in perfusion due to an associated cardiovascular insult are required to precipitate CNS pathology [43,44,66-68], yet loss of consciousness is not required for cognitive sequelae [64,69,70]. Exposure to relatively low levels of CO (50-90 ppm for 60 minutes) causes vascular oxidative stress in animal studies [42,71,72].

Human and animal data indicate that major cardiac injury at the time of poisoning is due primarily to CO-induced hypoxic stress [66,73,74]. Carbon monoxide may increase the risk for cardiovascular-related death in patients with initial CO-induced cardiac injury over the 10 years following injury [75], although another study suggests that increased mortality due to psychosocial factors and accidents is more likely [76]. As with brain injury from other causes, many neurological problems can follow CO poisoning, including cognitive sequelae, anxiety and depression, persistent headaches, dizziness, sleep problems, motor weakness, vestibular and balance problems, gaze abnormalities, peripheral neuropathies, hearing loss, tinnitus, somatic complaints, and Parkinsonian-like syndrome. Neuropsychological sequelae following CO poisoning are common [10,31,77-79]. The incidence of anxiety and depression is high following acute CO poisoning and may not be favorably influenced by HBO_2 [80].

Breathing oxygen hastens the removal of COHb. The half-life of COHb in adults breathing air at sea level is approximately five to six hours [32], but reduced alveolar ventilation would lengthen the half-life. With ad-

ministration of normobaric oxygen, the COHb half-life in adults is 74 ± 25 minutes (mean ±1 SD) [33]. Hyperbaric oxygen accelerates COHb dissociation compared to breathing pure oxygen at sea-level pressure [32,34, 81-83]. Additionally, HBO_2, but not ambient pressure oxygen, has several actions that are beneficial in ameliorating CNS injuries. These include an improvement in mitochondrial function [67,84], inhibition of lipid peroxidation [85], impairment of leukocyte adhesion to injured microvasculature [86] and reduction in brain inflammation caused by the CO-induced adduct formation of myelin basic protein [87]. Animals poisoned with CO and treated with HBO_2 have a more rapid improvement in cardiovascular status [81], lower mortality [88], and lower incidence of neurological sequelae [87-89]. Table 3 describes the pathophysiology of CO poisoning and the mechanisms of action by which HBO_2 can favorably influence this pathophysiology.

Patient selection criteria

Patients manifesting signs of serious CO poisoning (e.g., transient or prolonged unconsciousness, neurologic signs, cardiovascular dysfunction, or severe acidosis) should be referred for HBO_2 therapy regardless of the COHb level. Epidemiologic studies suggest that prognosis is poorer for patients who have underlying cardiovascular disease, are older than 60 years of age, have suffered any interval of unconsciousness due to CO poisoning, or demonstrate severe acidosis [58,59].

Despite many texts and articles claiming the contrary, the COHb level does not correlate with signs and symptoms [9], nor with the development of neurological or cognitive sequelae after poisoning [31,57-59,64,158]. Nevertheless, referral of patients with COHb ≥25% for HBO_2 is reasonable [159]. A majority of hyperbaric physicians use HBO_2 for patients with less severe symptoms when COHb levels are elevated to the range of 25%-30% or when neuropsychological testing is abnormal [160], even though the role of neuropsychological tests in patient selection for HBO_2 therapy is not clear [10,79,161-165].

One study's univariate analysis of patients not treated with HBO_2 which inspected potential risk factors for six-week cognitive sequelae revealed that age ≥36 years, loss of consciousness, COHb levels ≥25%, or with CO exposure intervals ≥24 hours were at increased risk for cognitive sequelae without HBO_2. However, the multivariable logistic regression, which included patients receiving HBO_2, revealed that patients ≥36 years old treated with HBO_2 had reduced six-week cognitive sequelae rates. Although the multivariable logistic regression showed that longer CO exposure duration was associated with increased cognitive sequelae rates, the sample size was underpowered regarding an HBO_2 effect [31]. However, of five patients with CO exposure duration >24 hours, none treated with HBO_2 had cognitive sequelae. Cerebellar dysfunction (e.g., abnormal finger-to-nose, rapid alternating movements, or heel-shin testing) at the time of evaluation may also indicate increased risk for cognitive sequelae [10]. In this regard, it is important to recognize that HBO_2 can reduce six-week cognitive sequelae in patients without initial cerebellar dysfunction (p=0.05) [10,166]. When other risk factors are present the absence of cerebellar abnormalities should not dissuade a physician from using HBO_2.

No risk factor is fully predictive of long-term outcome. In another study, individuals with no loss of consciousness and COHb ≤15% shared the same risk for cognitive sequelae as those with more severe poisoning [64]. Even mildly poisoned patients demonstrate many biochemical changes in blood [56]. Research suggests that patients who do not carry the apolipoprotein E4 allele, a genetic marker associated with worse outcome after brain injury [167,168] may respond much more favorably to HBO_2 following CO poisoning than E4 carriers [169]. However, only 14%-25% of humans carry the E4 allele [170], and genetic information is not available at the time of acute evaluation. Based on all the above factors, it is recommended that HBO_2 be considered for all cases of acute symptomatic CO poisoning [10,12,31].

Clinical management

Administration of supplemental oxygen is recommended to treat CO poisoning although there are no clinical trials demonstrating improved outcomes using oxygen therapy administered at atmospheric pressure. Nevertheless, supplemental oxygen inhalation will hasten dissociation of CO from hemoglobin and provide enhanced tissue oxygenation [33].

The optimal HBO_2 dosing (pressure, duration and frequency) is not known, but the optimal benefit from HBO_2 occurs in those treated with the least delay after exposure [61]. The majority of HBO_2 facilities offer a single HBO_2 session to CO-poisoned patients [171]. However, in selected patients repeated treatments may yield a better outcome than a single treatment [77]. Randomized trials demonstrating improved outcomes have offered two protocols:

TABLE 3. CO Pathophysiology and Effects of HBO_2

CO Pathophysiology	Effect of HBO_2
Formation of COHb [90,91]	Rapid clearance of CO from blood and tissues [34]
Increased Hb affinity for oxygen and leftward shift of oxyhemoglobin dissociation curve [41,91]	Sufficient dissolved oxygen in blood that O_2Hb is unnecessary [92-96]
Tissue hypoxia [97-100]	Normalization of tissue oxygenation [101]
Binding to cellular proteins (i.e., cytochromes, myoglobin) and increased steady-state concentration of nitric oxide [102-113]	Reversal of cytochrome binding [67,114]
Inhibition of cellular metabolism [104,115-117]	Preservation of adenosine triphosphate production [84,118-120]
Oxidative stress (i.e., due to mitochondrial production of reactive oxygen species and free radical production from heme degradation) [43,44,46,105,110,113,121,122]	Adaptive/protective oxidative stress response through increased heme oxygenase-1 [123,124] Upregulation and modulation of various antioxidant enzymes [125-131] Induction of heat shock protein, which protects against oxidative stress [132-133]
Dopamine/catecholamine hyperexcitability via gene upregulation [134], hypothesized to damage the globus pallidus/ deep white matter [135]	Favorable modulation of gene expression to regulate dopamine [134]
Impaired astrocyte neurotrophic function [136-137]	Preservation of astrocyte ability to synthesize and secrete neurotrophins [136,137]
Elevation of microparticles [55]	
Activation of platelet adhesion molecules and platelet-neutrophil aggregation, resulting in neutrophil degranulation, release of myeloperoxidase, and endothelial cell oxidative stress [42,48,51,71,112,113]	Reduced myeloperoxidase activity [127,138,139]
Neutrophil adherence to vasculature, leukocyte immune response, and conversion of xanthine dehydrogenase (XD) to xanthine oxidase (XO) [47,51,86,111,140,141]	Reduced leukocyte adhesion [142,143] Inhibition of immune response [86,144] Blocking XD conversion to XO [86]
Lipid peroxidation [46,141]	Prevention of brain lipid peroxidation [85]
Alteration in the structure of myelin basic protein and subsequent lymphocyte proliferation [52]	Muted adduct formation and blocked inflammatory response to altered myelin basic protein [51,87]
Excitatory neurotransmitter toxicity [45,68,145-148]	
Activation of hypoxia-inducible factor-1alpha [149,150] Neuronal necrosis and apoptosis [49,154]	Decrease in hypoxia-inducible factor-1 expression [151-153] Reduction of necrosis and protection against accelerated apoptosis [119,153,155-157]

1. Initial compression to 3 atmospheres absolute (ATA) (303.98 kPa), then 2 ATA (202.65 kPa) for 140 minutes, followed by two HBO_2 sessions at 2 ATA (202.65 kPa) for 90 minutes (five-minute air-breathing periods were used periodically to reduce oxygen toxicity) in six-hour to 12-hour intervals [10].
2. Initial compression to 2.8 ATA (283.71 kPa), then 2 ATA (202.65 kPa) for 120 minutes, without further HBO_2 [79].

A blinded randomized trial testing the first protocol compared neuropsychological outcomes in patients who received only the first HBO_2 session to outcomes in patients who received all three sessions in 24 hours. This trial found no difference between groups in cognitive sequelae rates at six weeks and six months (available in abstract form) [172].

Two review papers have offered guidance for medical management beyond HBO_2 [11,12]. Of note, poisoned

patients should have an electrocardiogram and serial measurement of cardiac enzymes such as the creatinine kinase MB fraction and troponin I. If there is evidence of cardiac injury, further cardiac evaluation and follow-up is advisable [75,173].

Although the frequency is reduced by HBO_2 [10,11,31, 79], some patients will develop cognitive or other adverse sequelae. As clinical investigations involving neuroimaging and neuropsychiatric assessment become more sophisticated, they seem to demonstrate that some cognitive and cerebral vascular abnormalities from CO persist despite aggressive therapy [10,80,160,174-176], although the incidence is lower with HBO_2 treatment [10,31,79, 177]. Follow-up of poisoned patients and referral of those with sequelae to the appropriate resource is important.

Children with CO poisoning may be safely treated with HBO_2 [178]. Children can have an uneventful recovery following poisoning or can have long-term problems [179, 180]. A recent small prospective study found that all enrolled children had neuropsychological test results in the average range at six weeks and six months after poisoning, although many had symptoms suggesting CO-related problems. Additionally, most had vestibular and balance abnormalities consistent with brain injury [181,182].

In contrast, CO can be teratogenic and toxic to the developing fetus, particularly in cases of serious poisoning [183-185]. Based upon mathematical modeling derived from animal experiments, the half-life of fetal COHb is 1.5 times the half-life of adult COHb [186]. One prospective study concluded that mild exposures are likely to result in normal fetal outcome, but severe CO poisoning carries serious risk to the fetus in terms of viability and development and that HBO_2 may decrease fetal hypoxia and improve outcome [183]. Pregnant women can be safely treated with HBO_2 for acute CO poisoning without fetal harm [187,188]. If there is evidence of fetal distress, HBO_2 may be considered even if the mother is asymptomatic.

Although not approved for human use, a novel human-engineered human neuroglobin – which displaces CO from COHb, then is excreted by the kidneys – may hold promise as an antidote for acute CO poisoning [189]. In vitro this agent reduced COHb half-life from >500 minutes to 25 seconds, while in mice, COHb elimination was 35% faster than breathing 100% oxygen. It has not been tested in humans and may not reduce the immune-mediated aspects of CO poisoning. Clinical trials are necessary to determine whether this potential antidote is safe and effective in humans [190].

Patients with CO poisoning should be followed after discharge. Even with HBO_2 treatment, they may have persistent problems after CO poisoning [10] or even develop new problems weeks to months later [191,192]. Common complaints in patients with these problems are headaches, dizziness, imbalance, fatigue, sleep disturbance, and neuropsychological and affective symptoms [193], similar to those reported in post-concussive syndrome [194]. Treatment is supportive. Some patients have cardiac problems after CO poisoning that require intervention [195].

Studies that have followed CO-poisoned patients to a year and beyond have documented long-term adverse effects on cognitive function, quality of life, and general health [10,31,80,196-199]. From three-year follow-up of 84 accidental and intentional CO-poisoned patients, Smith and Brandon [196] reported that 11% had "gross neuropsychiatric sequelae" directly attributable to the poisoning, while 30%-40% had memory, personality or affective changes. In long-term follow-up of 52 CO-poisoned patients (mean six years from poisoning, range 3.4-10.8 years), 13%-19% had cognitive impairments in memory, attention and executive function, and 38% had neurological deficits [197,198]. In another study that followed poisoned patients for 30 years after a mass casualty mining accident, investigators found cognitive dysfunction in 69% of survivors. In the subgroup of 129 who had brain MRI, 83% had structural neuroimaging abnormalities [199]. From the Taiwan National Insurance database, patients with CO poisoning appear to have a higher risk for developing dementia, Parkinson's disease, diabetes mellitus, and cardiovascular disease [200-203]. Those treated with HBO_2 had reduced short-term and long-term mortality [204]. From the University of Pittsburg a retrospective analysis of 1099 CO-poisoned patients showed a reduction of inpatient and one-year mortality with HBO_2 [65].

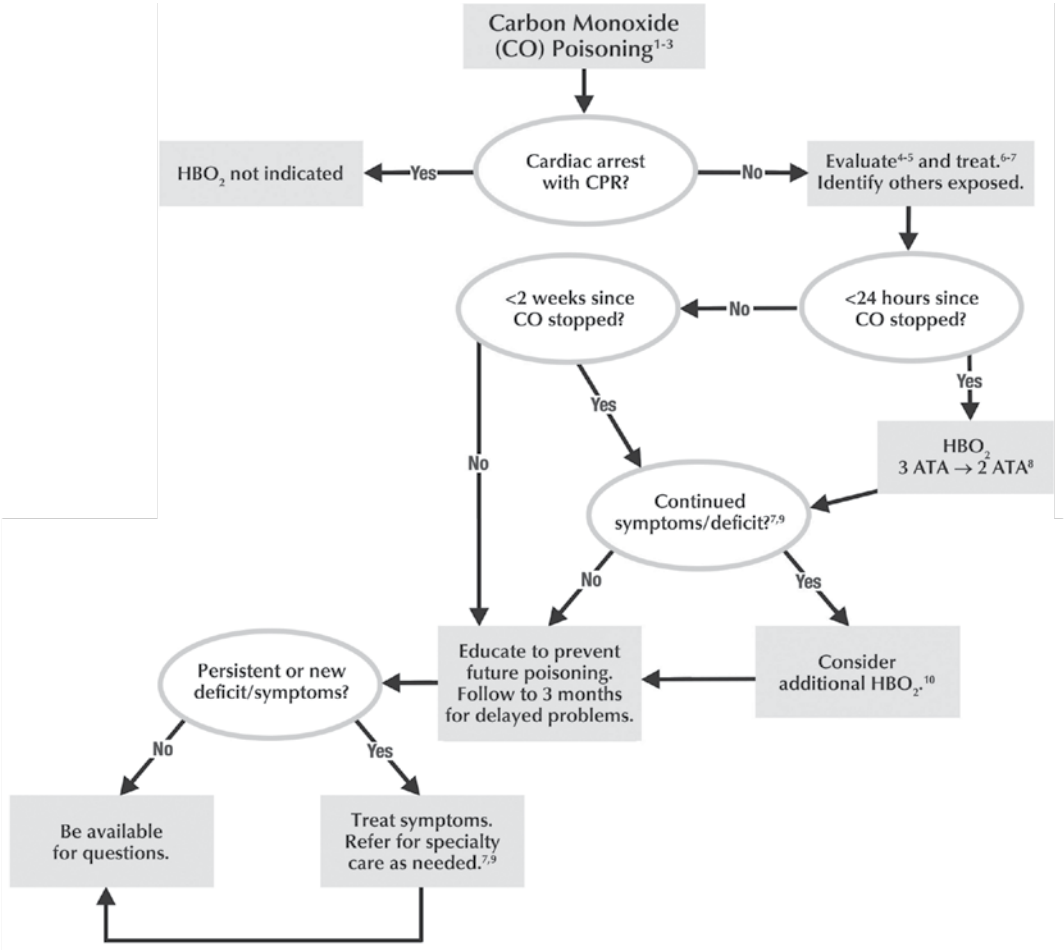
Some case reports and series report benefit with HBO_2 administration weeks, months, or even years after poisoning [205-212], but this has not been studied in randomized, controlled trials. In this circumstance, HBO_2 is used to treat brain injury from CO poisoning, which is likely analogous to other types of brain injury [213,214].

Evidence-based review

More than 16,000 CO-poisoned patients were treated in North American hyperbaric chambers from 1992-2002 [171]. However, researchers estimate more than

FIGURE 1. Flowchart for Carbon Monoxide Poisoning Treatment

Details of management are described in the text.



NOTES

[1] CO Poisoning = CO Exposure + Symptoms.

[2] May be acute or chronic (>24 hours exposure, typically intermittent).

[3] COHb and SpCO may be elevated or normal due to time from poisoning and oxygen administration

[4] Neurological evaluation: rapid alternating movements, finger-to-nose, heel/shin; if able to stand, tandem gait, Sharpened Romberg test.

[5] Laboratory evaluation: COHb, pregnancy test, troponin I, electrocardiogram. As indicated, CBC, lactate, CMP, CK, drug screen, liver function tests, chest radiograph, echocardiogram. Do not delay HBO_2.

[6] Non-rebreather facemask oxygen, high-flow nasal cannula oxygen (heated, humidified oxygen at up to 60 liters per minute), or 100% oxygen by endotracheal tube if indicated. If smoke inhalation, consider cyanide antidote, rapid intubation, and treatment of thermal injuries.

[7] For shortness of breath, palpitations, chest pain, or fatigue, refer for cardiac evaluation.

[8] This protocol has been shown to reduce sequelae (Weaver LK, et al. N Engl J Med. 2002;347:1057-1067): 3.0 ATA for 60 minutes with two five-minute air-breathing periods, then 2.0 ATA for 60 minutes with one five-minute air-breathing period. Other treatment schedules at 2.5-3.0 ATA may be similarly effective.

[9] For cognitive, affective, somatic, or neurological complaints, refer for neurological, neuropsychological, or psychological evaluation as indicated.

[10] Some advocate daily HBO_2 to a clinical plateau.

50,000 CO-poisoned patients are evaluated in emergency departments annually in the United States [215]. Among patients treated with HBO_2, both mortality and neurocognitive morbidity are improved beyond that expected with ambient pressure supplemental oxygen therapy [10-12,31,60-62,77,79,216-218].

There are six published randomized clinical trials in acute CO poisoning with conflicting results [10,79,161,162, 219,220]. In the study by Raphael, et al., no statistically significant benefit was observed when HBO_2 was compared with normobaric oxygen therapy [161]. However, the lack of benefit with HBO_2 may be attributed to nearly half of the study group being treated more than six hours after exposure and use of HBO_2 at only 2 ATA (202.65 kPa) [221]. Conclusions from this study are further compromised by lack of neuropsychological outcome measures and because only mildly poisoned patients were used in the comparative trial (no patients had loss of consciousness).

In follow-up to this clinical trial, the study group conducted a similar study that enrolled 385 CO-poisoned patients over 11 years [220]. Patients without loss of consciousness were randomized to six hours of normobaric oxygen or four hours of normobaric oxygen plus one HBO_2 session (Trial A). Patients with loss of consciousness were randomized to four hours of normobaric oxygen plus one HBO_2 session versus four hours of normobaric oxygen plus two HBO_2 sessions (Trial B). Patients who received HBO_2 were compressed to 2 ATA (202.65 kPa) at 100% oxygen over 30 minutes, remained at 2 ATA (202.65 kPa) for 60 minutes, then decompressed over 30 minutes to atmospheric pressure. All HBO_2 patients received 10 mg intramuscular diazepam prior to compression. In patients without loss of consciousness, recovery rates were similar between groups (58% vs. 61%). In patients with loss of consciousness, recovery was lower in those receiving two HBO_2 sessions compared to one HBO_2 session (47% vs. 68%).

These trials have been criticized for under-dosing HBO_2 [221-222]. In mechanistic terms, the lower 2 ATA (202.65 kPa) treatment pressure may not have promoted recovery of mitochondrial metabolism [84]. A partial pressure of oxygen greater than 2 ATA (202.65 kPa) is necessary to achieve maximum inhibition of adhesion molecules in human polymorphonuclear leukocytes [223]. The latter mechanism is an important HBO_2-related beneficial property modulating CO-mediated oxidative injury (Table 3 [86].

The studies by Ducasse, et al. and Thom, et al. were both prospective, randomized clinical trials involving treatment at 2.5–2.8 ATA (253.32–283.71 kPa) within six hours of poisoning, and both studies found significantly better outcomes with HBO_2 versus normobaric pressure oxygen treatment [79,162]. The lack of blinding potentially limits the strength of inferences one can draw from these two studies.

A blinded, randomized clinical trial from Australia demonstrated that HBO_2 therapy did not improve outcome at hospital discharge (approximately three days after poisoning) as compared to three to six days of O_2 via high-flow mask (or endotracheal tube) [219]. This trial has several important methodological issues that limit confidence in the conclusions including:

1. One-month cognitive outcomes were not reported. Rather, only cognitive outcomes after a few days after poisoning were reported.
2. Poor one-month follow-up. Only 46% of enrolled patients returned for one-month evaluation.
3. Patients in the control group were treated unconventionally (all were admitted to the hospital and received three to six days of high concentrations of supplemental normobaric O_2).
4. Cluster randomization was employed, which might have biased the results.
5. No intention-to-treat analysis was performed, although with a low follow-up rate the results probably would be similar.
6. The neuropsychological testing instrument could not discern depression from cognitive dysfunction [163]. Over half the patients had attempted suicide, raising a major question about the true incidence of neurological sequelae in this trial.

A double-blind randomized clinical trial [10] meeting all elements of the CONSORT statement for reporting clinical trials [166,224] demonstrated a significant reduction in six-week neuropsychological sequelae rates in patients treated with HBO_2 (25% vs. 46%; p=0.007). In this study, patients randomized to HBO_2 received three sessions: an initial session of 150 minutes, with 60 minutes at 3 ATA (303.98 kPa), followed by two sessions of 120 minutes at 2 ATA (202.65 kPa) in a 24-hour period. Pre-chamber cerebellar dysfunction was strongly associated with cognitive sequelae, but even after correction for pre-chamber cerebellar dysfunction and stratification variables (age, loss of consciousness, time to chamber) HBO_2 remained the more effective therapy. The favorable influence of HBO_2 was maintained through 12-month follow-up.

Based on the American Heart Association (AHA) recommendation classification system [225] HBO_2 is recommended for patients with acute CO poisoning (Class I – Strong). This recommendation is made based upon Level B-R evidence, supported by one high-quality randomized trial, two moderate-quality randomized trials, a supportive meta-analysis [226] and significant animal research.

Some advocate treating CO-poisoned patients who have continued symptoms with HBO_2 daily until a clinical plateau is achieved (personal communication), analogous to HBO_2 recommendations in patients with decompression illness [227]. Case series may support this recommendation [205-212].

Utilization review

Determination of the optimal pressure and number of hyperbaric oxygen treatments will require additional study, as will the time following poisoning after which therapy is no longer effective. Based on favorable evidence from randomized trials, dosing between 2.5 and 3 ATA (253.32–303.98 kPa) is recommended [10,79,162,221]. While the majority of hyperbaric centers treat with a single HBO_2 session, the best evidence for reduced cognitive sequelae after CO poisoning is for three HBO_2 treatments within 24 hours [10], and some practitioners follow this recommendation [171]. Preliminary results from a blinded, randomized trial of one versus three HBO_2 sessions revealed that three sessions did not confer advantage over one session in preventing neuropsychological sequelae. Enrollment in this study was limited to non-intubated, English-speaking patients with accidental CO poisoning at a single institution.

Currently, there is no clear consensus among hyperbaric practitioners as to the length of delay from poisoning beyond which there is little chance for benefit from HBO_2 [171,228]. One animal study found the optimal time to HBO_2 treatment was five hours from CO exposure [155]. In the randomized trial by Weaver, et al. more than 60% of enrolled patients were treated with HBO_2 in less than six hours following poisoning, the remainder within six to 24 hours. Therefore, this trial was not powered to determine the role of HBO_2 after six hours [10]. Whether HBO_2 confers clinical improvement or a reduced rate of neurocognitive sequelae if administered beyond six hours from poisoning is unknown; however, because brain injury can follow CO poisoning, it is reasonable to treat CO-poisoned patients as soon as possible, up to 24 hours after poisoning. Most hyperbaric oxygen practitioners do not offer HBO_2 when the interval from CO poisoning to HBO_2 is more than 24 hours [171], though some have reported successful outcomes with this practice [205, 207, 209, 212, 229]. A CO treatment strategy is offered in Figure 1.

The Divers Alert Network can provide a referral to a hyperbaric chamber capable of caring for CO-poisoned patients (+1-919-684-9111). A list of accredited hyperbaric facilities can be found on the UHMS website (*www. uhms.org*).

Cost impact

The cost of HBO_2 as a primary therapy in CO poisoning is modest; however, prevention of morbidity from neurologic and cognitive sequelae represents a substantial cost savings to the health care system and society.

CO poisoning complicated by cyanide poisoning

Rationale

Individuals with CO poisoning from fires may also have been exposed to cyanide [230] from the burning of synthetic hydrocarbon products. In combination these two agents may exhibit synergistic toxicity [231-233]. Severe cyanide poisoning is rapidly fatal; symptoms of mild or moderate cyanide exposure can be similar to that of CO poisoning and include headache, nausea, confusion, altered mental status, and cardiac problems [230,234]. While CO poisoning can be rapidly diagnosed by carboxyhemoglobin (COHb) via co-oximetry, currently laboratory testing for cyanide cannot be performed quickly enough to confirm diagnosis before initiating treatment [230]. Carbon monoxide poisoning complicated by cyanide should be considered in patients presenting from fires who manifest altered mental status and those patients with soot in the mouth or mucous membranes [235].

Once in the body, cyanide binds to the enzyme cytochrome c oxidase and blocks production of adenosine triphosphate (ATP). The result is cellular hypoxia and metabolic acidosis [236]. Patients with cyanide poisoning often require life support measures such as assisted ventilation, supplemental oxygen, and blood pressure support [230,235].

After supportive care has been established, a cyanide antidote can be administered. A number of antidotes exist but vary in their regional availability [237]. If available, hydroxocobalamin with or without sodium thiosulfate is considered the antidote of choice [230,237-239], as these agents appear to be effective and have a lower risk of serious side effects than other pharmacotherapies [240]. Amyl nitrite and sodium nitrite induce methemoglobinemia to bind cyanide to methemoglobin, facilitating the binding of cyanide, forming cyanomethemoglobin. However, methemoglobinemia potentially impairs the oxygen-carrying capacity of hemoglobin, and those treatments are now considered contraindicated in the setting of concomitant CO poisoning [235-241]. Caregivers should be aware that administration of hydroxocobalamin before COHb measurement may yield unreliable co-oximetry results [242-244].

Clinical reports involving the use of HBO_2 in pure cyanide poisoning are infrequent; however, some reports suggest a benefit [245-247]. There are no controlled clinical trials examining HBO_2 for pure cyanide poisoning or CO poisoning complicated by cyanide. A clinical trial evaluating hydroxocobalamin also treated patients with HBO_2, and no adverse interactions were reported [248].

Theoretically, HBO_2 may be of benefit in cyanide poisoning, as it is known to preserve ATP production [67]. However, the interplay of CO, cyanide, and nitric oxide regarding cytochrome c oxidase is complicated [249], and the role of HBO_2 is not known. Early animal work examining HBO_2 for pure cyanide poisoning found that animals receiving HBO_2 immediately after potassium cyanide injection had improved survival [250,251]. Hyperbaric oxygen also restored brain electrical activity in mice [250] and protected mitochondrial function in rabbits [252]. However, in another murine experiment HBO_2 was not better than atmospheric oxygen in enhancing the effect of the cyanide antidotes sodium nitrite and sodium thiosulfate [253].

More recent animal work has shown that in rats with elevated interstitial brain lactate and glucose concentration after cyanide poisoning, HBO_2 and hydroxocobalamin comparably reduced these markers [254]. In this experiment, HBO_2 conferred the added benefits of increased cerebral tissue oxygen partial pressure and reduced respiratory distress and cyanosis [254]. Hydroxocobalamin is predominantly active in the extracellular space [255], and in a rat model HBO_2 increased the concentration of cyanide in circulating blood when administered both immediately and five hours after cyanide exposure [256]. The mechanism of action for this process is not fully understood [256], and this effect has not been reliably observed in humans with cyanide poisoning [257], perhaps due to variability in patient management and presentation.

Evidence-based review of HBO_2 for cyanide poisoning

See the section on carbon monoxide poisoning above. At this time, the evidence does not support HBO_2 for pure cyanide poisoning, but HBO_2 is indicated for acute CO poisoning including mixed poisoning. Clinically, HBO_2 has been widely applied for CO poisoning complicated by cyanide [235,248,258].

Utilization review of HBO_2 for cyanide poisoning

The treatment protocol is the same as for CO poisoning.

Cost impact of HBO_2 for cyanide poisoning

Since most patients with CO poisoning complicated by cyanide poisoning will receive a few treatments, the cost of HBO_2 for this condition is justifiable. In this serious condition, a reduction in mortality and possibly morbidity reduces health care cost.

Smoke inhalation

Based on anecdotal clinical reports and controlled animal trials [259-262], HBO_2 is of possible benefit for the pulmonary injury related to smoke inhalation. However, there is currently insufficient evidence to support HBO_2 for smoke inhalation unless the patient has concomitant CO poisoning. Smoke inhalation patients are often critically ill, and only hyperbaric medicine centers with critical care expertise can treat them [263].

■

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