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Practice Recommendations in the Diagnosis, Management and Prevention of Carbon Monoxide Poisoning

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At a Glance Commentary: Four experts in the field of carbon monoxide (CO) poisoning provide evidence-based practice recommendations about some of the most common clinical questions with regard to the diagnosis and management of CO poisoning.

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Abstract

Carbon monoxide (CO) poisoning is common in modern society, resulting in significant morbidity and mortality in the United States annually. Over the past two decades, sufficient information has been published about carbon monoxide poisoning in the medical literature to draw firm conclusions about many aspects of the pathophysiology, diagnosis and clinical management of the syndrome, along with evidence-based recommendations for optimal clinical practice. This article provides clinical practice guidance to the pulmonary and critical care community with regard to the diagnosis, management and prevention of acute CO poisoning. The paper represents the consensus opinion of four recognized content experts in the field. Supporting data were drawn from the published, peer-reviewed literature on CO poisoning, placing emphasis on selecting studies that most closely mirror clinical practice.

Key Words: Carbon monoxide poisoning, diagnosis, treatment, prevention

Introduction

Carbon monoxide (CO) poisoning results in an estimated 50,000 emergency department visits in the US annually (1) and is one of the leading causes of poisoning death. The last two decades have witnessed an enormous expansion of knowledge about clinical CO poisoning, much of it published in the peer-reviewed medical literature. That body of information is sufficient to draw firm conclusions about many aspects of the pathophysiology, diagnosis and clinical management of the syndrome, along with construction of evidence-based recommendations for best clinical practice related to CO poisoning.

The four authors have published over 100 papers on CO mechanisms, and the diagnosis and management of CO poisoning. In this manuscript, they have collaborated to synthesize a state-of-the-art clinical practice approach to the CO-poisoned patient. This manuscript represents a consensus of expert opinion. It is an evidence-based summary and not a meta-analysis or a comprehensive review of CO poisoning, but rather addresses the clinical issues that most frequently arise with regard to CO poisoning.

In 1857, the physiologist Claude Bernard described the fact that CO produces hypoxia by binding with hemoglobin, reducing the oxygen carrying capacity of the blood and producing hypoxia in the tissues (2). CO also shifts the oxyhemoglobin curve to the left, which further reduces tissue PaO2. This hemoglobin mechanism is reversible because the binding of the CO molecule at the oxygen carrying heme sites on hemoglobin is competitive with oxygen. The formation of carboxyhemoglobin (COHb) and the attendant tissue hypoxia was considered until fairly recently to be the major mechanism of CO toxicity. A number of scientific and clinical observations have indicated that additional mechanisms must be involved. For instance, the clinical presentation of the CO-poisoned patient has repeatedly been noted not to correlate with the blood COHb level (3,4) and clinical improvement in the patient's condition does not correlate with clearance of the blood COHb level. Moreover, in canine studies, the toxicity of CO is greater when CO is administered by inhalation than by transfusion of CO-exposed red blood cells to the same COHb level (5), suggesting the importance of cellular toxicity caused by the cumulative effects of CO diffusing into the tissues, particularly during long exposures. Indeed, a low tissue PO2 promotes cellular CO accumulation and CO binding to heme proteins.

It is now known that carbon monoxide poisoning causes both tissue hypoxia and direct cellular changes involving immunological or inflammatory damage by a variety of mechanisms (6-16). Some of these have been demonstrated only in animal models to date, while others have been confirmed in human studies. These mechanisms include:

- Binding to intracellular proteins (myoglobin, cytochrome a,a_3)
- NO generation -> peroxynitrIte production
- Lipid peroxidation by neutrophils
- Mitochondrial oxidative stress
- Apoptosis (programmed cell death)
- Immune-mediated injury
- Delayed inflammation

Indeed, some of these effects are related to interference with the normal signaling functions of endogenous CO, which is a physiological gas produced by enzymatic heme degradation (17) and is even being tested in preclinical and phase I studies as potential therapy in specific diseases (18). Most of the toxic mechanisms identified have been demonstrated to be modulated more favorably by hyperbaric than by normobaric oxygen. The contribution of each of these mechanisms of toxicity to clinical CO poisoning and in humans has not yet been determined. While the use of CO as a therapeutic molecule is an exciting area, it is not the topic of this discussion of CO poisoning and its management. The interested reader is referred to the excellent review of the therapeutic CO field by Motterlini and Otterbein (18).

I. Diagnosis

The diagnosis of CO poisoning is a clinical one: the common definition requires a history of recent CO exposure, the presence of symptoms consistent with CO poisoning, and demonstration of an elevated carboxyhemoglobin level.

Symptoms are required for diagnosis, but no single symptom is either sensitive or specific in CO poisoning. The most common symptoms in one series of 1,323 patients referred for treatment of CO poisoning in the US included headache, dizziness, nausea/vomiting, confusion, fatigue, chest pain, shortness of breath, and loss of consciousness (19). A high index of suspicion is warranted, particularly during cold weather, in patients with acute coronary syndrome and arrhythmias. Failure to diagnose CO poisoning can have disastrous consequences for the patient and other members of an affected household. Despite the fact that some authors have long maintained that certain symptoms correlate closely with COHb levels, this is incorrect (19). There is no combination of symptoms that either confirms or excludes a diagnosis of CO poisoning. Although headache is the most common symptom, there is no characteristic headache pattern typical of CO poisoning (20).

For decades physicians have been taught to look for "cherry-red" skin coloring in patients with CO poisoning, but this is rare (21,22). The concept is that the color of blood changes when it is loaded with CO, as described by Hoppe in 1857 (23). Because carboxyhemoglobin is a brighter shade of red than oxyhemoglobin and the color of capillary blood contributes to skin color, it would seem reasonable that a poisoned patient's appearance might change with sufficient amounts of circulating COHb. However, a lethal carboxyhemoglobin level is required for a human's skin and mucous membranes to appear "cherry-red." Even when reflectance spectrophotometry is used to measure skin color of individuals dying of CO poisoning, less than one-half have "cherry-red" skin (24).

The clinical diagnosis of acute CO poisoning should be confirmed by demonstrating an elevated carboxyhemoglobin level. COHb levels ≥ 3-4% in nonsmokers and ≥ 10% in smokers can be considered outside the expected physiological range (25). The COHb level in smokers is generally in the 3-5% range (25). In the Second National Health and Nutrition Survey (NHANES II), one pack per day smokers had COHb levels up to 5.6% (26). As a general rule, for each pack of cigarettes smoked per day, the COHb rises approximately 2.5% (27). Very rarely the COHb level in selected heavy smokers, especially those with underlying lung pathology, can be > 10% (28). COHb can be measured by laboratory spectrophotometry on blood obtained at the scene and transported with the patient to the hospital (29) or obtained at the time of emergency department evaluation. Laboratory spectrophotometry uses an instrument called a CO-oximeter (or spectrophotometer) to measure the concentrations of the various hemoglobin species. This is done by transilluminating a specimen of blood with multiple wavelengths of light, measuring differential absorbance at the various wavelengths, then calculating concentrations from the known absorption spectrum of each form of hemoglobin. Either arterial or venous blood may be used, as the COHb levels are similar (30,31), provided the CO body stores are in near-equilibrium with the CO partial pressure in the lungs. Under non-steady state conditions, venous COHb may be slightly above or below arterial COHb due to CO uptake or egress from tissues.

Confusion regarding arterial oxygenation and the presence of COHb may arise in two areas. First, many newer blood gas machines incorporate CO-oximeters and perform spectrophotometry on injected blood, directly measuring the concentrations of oxy-, deoxy- carboxy-, and methemoglobin. The SaO2 (oxygen saturation) reported with the blood gas results represents the amount of oxyhemoglobin present relative to the sum of all four hemoglobin species. This has not always been the case. Older blood gas machines contained algorithms for the calculation of oxygen saturation based upon the oxyhemoglobin dissociation curve and effect of pH. An arterial blood specimen with pHa 7.40, PaO2 100 mm Hg, and PaCO2 40 mm Hg would be calculated from PaO2 and pHa to have an SaO2 of 97-98%. That result would be reported, irrespective of the amount of carboxyhemoglobin present. Thus, a patient with 40% COHb and PaO2 100 mm Hg would be reported to have an arterial oxygen saturation of 97-98%, when in reality 40% of the hemoglobin is bound with CO and the true fraction carrying oxygen would be 60% at maximum. This may remain an issue at a facility using a blood gas machine without a CO-oximeter.

A second area of potential confusion relates to the fact that standard pulse oximeters using two-wavelengths (660 nm and 990 nm) cannot differentiate carboxyhemoglobin (32). COHb and HbO2 have similar absorbances (extinction coefficients) at 660 nm. This results in pulse oximeters measuring COHb very similarly to HbO2. This was demonstrated in one series of 30 CO-poisoned patients with COHb $\geq$ 25% measured by CO-oximeter and simultaneous SpO2 (pulse oximeter oxygen saturation) > 90% in all (32). Because of differing extinction coefficients at 990 nm, COHb and HBO2 are measured similarly but not identically. This only becomes apparent when COHb > 40%. In a patient with COHb 50%, the SaO2 calculated from blood gas values is approximately 5% higher than the SpO2 value from a pulse oximeter (32).

Carboxyhemoglobin can also be measured at the scene with fingertip pulse CO-oximetry (33,34), a technology commercially available since 2005. The accuracy and reliability of the available pulse CO-oximeter in the clinical setting has been questioned (35,36) and also supported (37,38). As such, if pulse CO-oximetry is the basis for diagnosis, we recommend laboratory-based measurements by spectrophotometry for confirmation upon arrival in the emergency department for patients being considered for hyperbaric oxygen therapy until more experience has been gained with this technique. Since most hospitals do not have hyperbaric chambers, hyperbaric oxygen administration requires transfer, inconvenience, cost and a small risk. As such, it would seem reasonable to confirm the pulse CO-oximeter measurement with laboratory CO-oximetry in that group. It is not necessary to document an elevated COHb level in symptomatic persons who were in the same environment and simultaneously exposed as someone with a documented COHb elevation. Since the COHb level only serves to confirm the diagnosis and does not predict either symptoms or outcome, measuring it in the simultaneously exposed, symptomatic individual does not change clinical management. In patients referred for suspected exposures to elevated environmental CO levels, COHb should be measured to document the exposure.

CO poisoned patients are often discovered or present to the hospital emergency department with confusion or altered mental status. Whether or not there is a reliable exposure history, 100% normobaric oxygen should be administered to any person suspected of having CO poisoning while waiting for confirmation of the diagnosis with the measurement of the COHb level (16).

In addition to considering a diagnosis based upon the presenting symptoms and potentially an elevated COHb level, which could be low, or normal due to the interval from CO exposure to COHb measurement and oxygen treatment, information about poisoning environment is important. Sometimes emergency or ambulance personnel measure ambient CO levels. These levels may be lower than at the time of actual CO exposure because of open doors or windows, but elevated ambient levels can confirm CO poisoning. It is important to discover the CO exposure source before discharging the patient, and for the source to be eliminated to prevent re-exposure.

II. Management

In all cases of CO poisoning, high flow oxygen by mask or endotracheal tube is the front-line treatment (16). Oxygen accelerates the elimination of COHb and alleviates tissue hypoxia compared to air. It should be recognized, however, that no clinical trials have demonstrated superior efficacy of normobaric 100% oxygen over air (16). Increasing alveolar ventilation by adding CO_2 to O_2 for spontaneously breathing individuals was advocated to hasten COHb removal based on observations dating to the 1920's (39). There are, however, marked individual differences in ventilatory responses thus making use of fixed CO_2-O_2 mixtures unreliable and also risky because use may exacerbate acidosis in patients who are retaining CO_2 due to ventilatory depression from either severe CO poisoning or ingested drugs (40). Newer apparatus to increase ventilation while maintaining normocapnea has been described, but because CO pathophysiology is more complex than merely COHb-mediated hypoxia, applying such interventions may add complexity with limited benefits (41)

When hyperbaric oxygen is not available, it is reasonable to recommend the administration of 100% normobaric oxygen in the emergency department until COHb is normal (≤ 3%) and the patient's presenting symptoms of CO poisoning have resolved, usually for about 6 hours. The COHb is influenced by the fractional concentration of inhaled oxygen (FiO2) and falls more quickly as the FiO2 increases.

One hundred percent normobaric oxygen accelerates the dissolution of COHb with an elimination half-life of approximately 74 minutes (42) compared to 320 minutes while breathing room air (43). For example, a poisoned patient with an initial COHb of 30% could have a relatively modest COHb level less than 10% if he breathed 100% normobaric oxygen for 2 hours. The FiO2, the duration of oxygen inhalation and the interval from when the CO exposure stopped to when the COHb level was measured is therefore important. If the patient has been compliant with high flow oxygen breathing for that approximately 6 hours and feels well, repeating the COHb level is not necessary.

Due to the relative inconvenience and cost of hyperbaric oxygen, a number of studies published in the past 15 years have tried to compare the efficacy of hyperbaric and normobaric oxygen in the treatment of CO poisoning (25,44-50) (Table 1). Most of these studies have had significant methodological limitations that make drawing inferences about the efficacy of hyperbaric oxygen difficult (51-54). Problems have included such things as insignificant differences in the oxygen dose in the treatment arms (52), randomization to lengthy or impractical durations of normobaric oxygen administration (48), low rates of short-term follow-up (4-6 weeks after poisoning and treatment) (48), clinically irrelevant outcome measures (42), and absence of any long-term follow-up (44-48,50). The latter is especially important since it has been demonstrated that even individuals with significant structural brain injury on neuroimaging from CO poisoning can show long-term improvement in cognitive functioning impairment for 3 months to 12 months post-poisoning (55).

Some authors have used a statistical meta-analysis from different trials and attempted to assign value to each study and then sum their discordant results for guidance. The American College of Emergency Medicine (ACEP) (53) and the Cochrane Review (54) both used this approach to the analysis of CO poisoning treatment and each concluded that additional, properly conducted trials would be desirable. Until such studies are available, patients must be treated on the basis of the information available. It is arguably as appropriate to select the existing study with the best design that most closely addresses the actual practical handing of these patients and use its findings to guide clinical practice. We feel that this study is that of Weaver and colleagues, published in 2002 (49), with supplemental information published in 2004 (56). In that study, CO-poisoned patients who received three hyperbaric oxygen treatments within 24 hours following presentation manifest approximately one-half the rate of cognitive sequelae at 6 weeks, 6 months and 12 months following treatment as those who were treated with normobaric oxygen.

Hyperbaric oxygen should at least be considered in all cases of serious acute CO poisoning and normobaric 100% oxygen continued until the time of hyperbaric oxygen administration. While risk factors for long-term cognitive impairment in patients not treated with hyperbaric oxygen have been identified, including age $\geq$ 36 years, exposure $\geq$ 24 hours, loss of consciousness, and COHb $\geq$ 25%, no criterion is 100% predictive (3). In young patients in otherwise good health who have been experimentally exposed to CO for a short period of time, usually two hours or less, and with COHb levels less than 20%, acute measurable neurobehavioral effects of are rarely manifest (57). However, a similar incidence of residual cognitive sequelae 6 weeks following CO poisoning has been reported in one group of patients with apparently milder poisoning compared to those with more severe poisoning (58). Thus, treatment decisions in the mildly poisoned patient are difficult and the subject of controversy, even among experts in the field. Pediatric CO poisoning can pose special challenges as inability to communicate can limit historical accounts, but in large series there appear to be no marked differences in manifestations versus those reported in adult populations (59-62).

Apolipoprotein E (APOE) is a 299-amino acid lipid-binding protein with three human isoforms., ε2, ε3 and ε4. The ε4 allele occurs in 14-25% of the population (63). APOE is involved in the distribution of cholesterol in the brain and neuritic growth and repair (64). APOE is upregulated after neural injury (65). The presence of the ε4 allele is associated with worse outcome after brain injury (66-68). Since the APOE genotype is associated with the degree of damage in various brain injury disorders, researchers characterized the APOE alleles in patients with CO poisoning treated with HBO2 of normobaric oxygen in a randomized trial (49). They discovered an interaction between APOE genotype and the response to hyperbaric oxygen treatment in patients with acute CO poisoning (69). Those possessing the ε4 allele may not derive benefit of treatment with hyperbaric oxygen, whereas those who do not have the ε4 allele appear to have a reduction in the incidence of cognitive sequelae following hyperbaric oxygen therapy. Since most individuals in the general population do not carry the ε4 allele, some recommend hyperbaric oxygen for all patients with acute CO poisoning, including those with milder poisoning (69).

Hyperbaric oxygen treatment may be precluded by such things as patient condition (70), logistical problems, and social issues, among others. For example, patients with significant body burns in addition to CO poisoning from a fire may be at greater risk for mortality from their burns than CO poisoning. They should be managed in a specialized burn unit and cared for by a qualified burn surgeon. The decision regarding use of HBO_2 should be deferred to an experienced burn surgeon.

Other special populations, such as pregnant women and young children are at risk for permanent sequelae of CO poisoning, and adult treatment criteria are generally applied to these patients. In pregnancy, fetal distress and fetal death are special concerns in CO poisoning, and HBO2 has been administered safely to pregnant women, but there are no prospective studies of efficacy.

Since only about 3% of CO-poisoned patients who come to hospital-based medical management die and no study to date has clearly shown a reduction in mortality with hyperbaric vs. normobaric oxygen therapy (71), the goal of hyperbaric treatment is the prevention of long-term and permanent neurocognitive dysfunction, not enhancement of short term survival rates. Hyperbaric oxygen should not be withheld because a CO-poisoned individual is doing well clinically and appears not likely to die from the event (16).

The optimal dose and frequency of hyperbaric oxygen treatments for acute carbon monoxide poisoning remains unknown (51). As such, the protocol used and number of treatments administered is left to the discretion of the managing hyperbaric physician. In the Weaver study noted above, patients were treated at 3.0 atm abs during their first hyperbaric oxygen treatment (49). Of 1,165 patients treated from 2008-2011 and reported to a national surveillance system, 804 (69%) were also treated at 3.0 atm abs (72). It is reasonable to retreat persistently symptomatic patients to a maximum of three treatments, the number used for all patients in the 2002 Weaver study (49). Information for further guidance on treatment practices is available in the form of survey data gathered from US hyperbaric treatment facilities (73).

If the CO exposure is believed to be intentional, toxicology screening should be considered to assess for toxic co-ingestions. In one study of 426 patients referred for treatment of intentional poisoning, 44% reported co-ingestion of other drugs or ethanol (74). Among patients with co-ingestions, 66% ingested ethanol. If a patient with intentional CO poisoning has mental status changes that seem disproportionate to his reported CO exposure, co-ingestion should be ruled out with measurement of a blood alcohol level, at a minimum.

Severe metabolic acidosis correlates with a high short-term mortality rate in CO-poisoned patients and, if the CO source was a housefire, is likely due to concomitant cyanide poisoning (71). That study demonstrated short-term mortality of 30-50% in CO-poisoned patients with initial pHa $\leq$ 7.20, regardless of COHb levels. If arterial blood gas analysis demonstrates severe metabolic acidosis with pH $<$ 7.20 (71) or plasma lactate level $\geq$ 10 mmol/L (75) and the source of CO was a house fire, we feel that consideration should be given to empiric treatment for cyanide poisoning. A specific antidote is hydroxocobalamin, which has few side effects in individuals with smoke inhalation (75,76). Smoke is heterogeneous mixture of particulates, respiratory irritants and systemic toxins. Each of these agents, along with heat, contributes to the pathological insult and treatment recommendations are beyond the scope of this article. Current treatment is based on supportive care and – not surprisingly – concomitant smoke inhalation with CO poisoning compounds health risks (77,78).

All patients treated for acute accidental CO poisoning should be seen in clinical follow-up one to two months after the event. Although uncommon, late or evolving cognitive impairments including such things as memory disturbance, depression, anxiety, inability to calculate, vestibular problems, and motor dysfunction can develop (16,49,79-82). These adverse sequelae can occur even after acute treatment of CO poisoning. If possible, a family member should accompany the patient to the follow-up appointment to provide their observations. Any person not felt to have recovered to baseline functioning by that time should be referred for formal neuropsychological evaluation, as well as symptom-directed evaluation and treatment. Individuals surviving an episode of accidental CO poisoning have an increased long-term mortality rate, as compared to the normal population (83). Causes of excess death (falls from heights, motor vehicle accidents, accidental drug overdose, etc.) suggest that residual brain injury may play a role. Patients with evidence of cardiac damage following poisoning should be referred for appropriate cardiology evaluation.

Persons surviving an episode of intentional CO poisoning are at extreme risk for premature death due to subsequent completion of suicide (83). All patients treated for intentional CO poisoning should have mandatory psychiatric follow-up. Family members should be made aware of this and recruited to assist in insuring compliance.

III. Prevention

It is thought that public education programs designed to increase awareness of CO poisoning risks and the placement of warning labels on fuels or devices that emit large amounts of CO are effective at reducing the incidence of poisoning. When it was recognized in the early 1990's that many of those poisoned through indoor use of charcoal briquettes did not speak English (84), a nonverbal pictogram warning against indoor use was mandated on bags of charcoal briquettes starting in 1998 by the US Consumer Product Safety Commission (CPSC). CPSC data show that from 1981-1997 there were approximately 25 CO deaths in the US annually due to charcoal briquettes. From 1998-2007, that number was reduced to approximately 10 deaths per year.

Planning effective educational programs and warning labels requires accurate knowledge of CO poisoning epidemiology. From 2008-2011, the US Centers for Disease Control and Prevention teamed with the Undersea and Hyperbaric Medical Society (Durham, North Carolina) to collect unidentified demographic and epidemiologic data on 1,912 CO-poisoned patients treated in the US (85,86). It is hoped that the insights gained will lead to enhanced effectiveness for public education programs and poisoning prevention.

As an example, CO poisoning has been shown to be especially common during storm-related power outages when people turn to the indoor use of charcoal briquettes for cooking and heating, improper use of gasoline-powered electrical generators to provide electricity, and indoor use of gasoline-powered pressure washers to clean up (87). Sufficient data are available to predict the predominant sources of CO depending upon geography and type of storm, as well as the window of opportunity for intervention after the storm strikes. Broadcasting public service warnings, multilingual in some cases, offers the potential for significant poisoning prevention.

Significant opportunities exist to prevent CO poisoning through the use of CO alarms (88,89). The US Centers for Disease Control and Prevention recommends a CO alarm in every residence (90). They should be installed in the hallway outside sleeping areas (91). Even though CO is slightly lighter than the mixture of nitrogen and oxygen comprising air, CO alarms can be installed at any height because the gas diffuses rapidly throughout an enclosed space (92).

Legislation mandating the installation of residential CO alarms, in addition to smoke alarms already present, has recently been enacted by numerous states and is currently being considered by many others (93). The state laws differ mainly with regard to whether homes without fuel-burning appliances or attached garages are exempted from required CO alarm installation. It is our opinion that they should not be exempted because a large proportion of patients treated for severe CO poisoning in the US are exposed from CO-emitting devices (e.g. charcoal grills, gasoline powered electrical generators) that are brought indoors or otherwise improperly operated (73).

A recent publication emphasized that proper operation of residential CO alarms themselves is equally important (94). Among a sampling of 30 CO alarms in current residential use, 12 (40%) were older than 10 years. Of these, 8 (75%) malfunctioned when tested. Depending upon the make and model, CO alarms require replacement at either 5 or 7 years following installation. Many newer models alert the consumer when replacement is necessary.

IV. Conclusions

An enormous body of information about carbon monoxide poisoning has been developed in the past two decades. Most accidental CO poisoning should be preventable. However, when it is not prevented, these guidelines offer clear recommendations with regard to the optimal clinical practice based on current information in the diagnosis and management of patients with CO poisoning.

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Table 1. Summary of studies comparing normobaric to hyperbaric 100% oxygen for treatment of CO poisoning.

Study	**Year**	**Design**	**Intervention**	Result	N
Raphael	1989	Randomized; If LOC, HBO_2 used.	HBO_2 (2.0 ATA) v. 6 hr. mask O_2 if no LOC; 1 HBO_2v. 2 HBO2 if LOC	No difference in symptoms between groups at one month	343
Ducasse	1995	Randomized, not blinded	HBO2 (2.5 ATA) v. mask O_2	HBO_2 improved cerebral blood flow reactivity to acetazolamide	26
Thom	1995	Randomized, not blinded, excluded LOC	HBO_2 (2.9 ATA) v. mask O_2	No sequelae in HBO_2 v. 23% for mask O_2; NNT=4.3	65
Scheinkestel	1999	Double blind RCT; cluster randomization ; included LOC	3 to 6 HBO2 (2.8 ATA) sessions v. 3 days of mask O2	Very high number lost to 1 month follow-up (54%), limiting any conclusion	191
Mathieu	1996	Randomized, not blinded, excluded LOC	HBO_2 v. mask O_2	Abstract only – HBO_2 reduced sequelae at 1 and 3 months; none at 1 year	575
Weaver	2002	Double blind randomized, included LOC	3 HBO_2 (3 ATA for initial) in 24 hours v. 100% O_2 + 2 sham chamber sessions	Reduced 6 wk cognitive sequelae (25 v 46%) at 6 wks (OR 0.39; 95% CI 0.2-0.78; p=0.007; NNT=4.8; with significant differences persisting to 12 months	152
Annane	2010	Randomized, not blinded	Trial 1 - HBO2 session (2.0 ATA) + 4 hours mask O2 v. 6 hours mask O2 if transient LOC. Trial 2 - 2 HBO2 + 4 hours mask O2 v. 1 HBO2 + 4 hours mask O2 if initial coma.	Outcomes measured by symptom questionnaire and physical exam at 1 month. Trial 1 – no difference in outcome as measured. Trial 2 – “Complete recovery” rate 47% with 2 HBO2 v. 68% with 1 HBO2.	385

LOC, loss of consciousness; HBO_2, hyperbaric oxygen; NNT, number needed to treat; ATA, atmosphere absolute

Table 2. Key Messages on Carbon Monoxide Poisoning

I. Basic Pathophysiology – Several mechanisms of CO toxicity exist, in addition to hypoxemia from carboxyhemoglobin (COHb) formation.

II. Diagnosis
   a. Symptoms – Nonspecific. Most common are headache, dizziness, nausea/vomiting, confusion, fatigue, chest pain, shortness of breath, and loss of consciousness.
   b. Signs – Cherry red discoloration is rare.
   c. Role of carboxyhemoglobin level – Confirms clinical diagnosis. Correlates poorly with symptoms or prognosis.
   d. Pre-diagnosis management – Administer 100% oxygen while waiting for COHb level.

III. Management
   a. Normobaric oxygen therapy – If chosen for treatment, 100% oxygen by nonrebreather facemask or endotracheal tube until COHb normal (<3%) and patient asymptomatic (typically 6 hours)
   b. Selection for hyperbaric oxygen (HBO_2) therapy - Currently not completely clarified. Poisoned patients with loss of consciousness, ischemic cardiac changes, neurological deficits, significant metabolic acidosis, or COHb > 25% warrant HBO_2. More mildly poisoned patients may be treated at the discretion of the managing physician (see text).
   c. Goals of HBO_2 therapy - Prevent neurocognitive sequelae
   d. Optimal HBO_2 protocol – Unknown. Recommend retreatment of persistently symptomatic patients to a maximum of 3 treatments.
   e. Intentional poisonings – Coingestion of other toxins commons. Consider toxicologic screening.
   f. Concomitant cyanide poisoning – Suspect if CO source is house fire. Consider empiric treatment if pHa < 7.20 or plasma lactate > 20 mmol/L

IV. Patient Follow-up
   a. Accidental poisoning – Follow-up in 4-6 weeks to screen for cognitive sequelae
   b. Intentional poisoning – Psychiatric follow- up mandatory in light of high rate of subsequent completed suicide

V. Prevention
   a. Public education – Educate about proper generator use and risk from combustion of fuels indoors
   b. CO alarms - Encourage minimum of 1 per home, located near sleeping area. Replace alarms every 5-7 years, as per manufacturer's instructions.

Figure 1. Triad required for diagnosis of acute carbon monoxide poisoning.