Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department with Acute Carbon Monoxide Poisoning

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ABSTRACT

This clinical policy focuses on critical issues concerning the management of adult patients presenting to the emergency department (ED) with acute symptomatic carbon monoxide (CO) poisoning. The subcommittee reviewed the medical literature relevant to the questions posed. The critical questions are:

Should hyperbaric oxygen (HBO_2) therapy be used for the treatment of patients with acute CO poisoning; and

Can clinical or laboratory criteria identify CO-poisoned patients who are most or least likely to benefit from this therapy?

Recommendations are provided on the basis of the strength of evidence of the literature. Level A recommendations represent patient management principles that reflect a high degree of clinical certainty; Level B recommendations represent patient management principles that reflect moderate clinical certainty; and Level C recommendations represent other patient management strategies that are based on preliminary, inconclusive, or conflicting evidence, or based on committee consensus. This clinical policy is intended for physicians working in hospital-based EDs.

INTRODUCTION

Carbon monoxide (CO) poisoning is the third leading cause of unintentional poisoning death in the United States.[1] Although death rates have declined by 80% since the introduction of the catalytic converter in 1957, CO poisoning still caused 491 accidental and 1,747 suicidal deaths in 1998.[2] Estimates of diagnosed nonfatal poisoning cases vary widely, from 15,000 to 40,000 events per year.[3,4] However, because misdiagnosis of CO poisoning is common, the true numbers are likely much higher.[5,6]

The mechanisms of toxicity of CO poisoning are not completely understood. CO binds hemoglobin with an affinity approximately 220 times that of oxygen, impairing delivery of oxygen to tissues. CO also binds to myoglobin, worsening the hypoxia in cardiac muscle, and mitochondrial cytochrome oxidase, impairing adenosine triphosphatase production. CO poisoning causes platelet and neutrophil activation, free radical formation, and lipid peroxidation in brain and other tissues, likely through an immunologic mechanism.[7] Acutely, this injures tissue in the brain, heart, and other organs. In addition, a condition of neurologic sequelae has been reported in survivors of acute severe poisoning. Although there are no established diagnostic criteria for this disorder, neurologic sequelae are typified by memory loss, impairments of concentration or language, affective changes such as depression, and parkinsonism.[8,9] Signs of injury may persist from the time of poisoning ("persistent neurologic sequelae") or occur after a latent period of 2 to 21 days ("delayed neurologic sequelae"). The reported incidence of neurologic sequelae varies widely, from 12% to 68% in published clinical trials,[10-16] with spontaneous recovery being reported anywhere from 75% to 100%.[14,16,17]

Administration of oxygen speeds the elimination of CO from the body. Without therapy, the elimination half-life of CO is 4 to 5 hours.[18] Administration of 100% oxygen by tight-fitting face mask at normal atmospheric pressure decreases this half-life to approximately 1 hour.[19] The elimination half-life is further decreased to 20 minutes in a hyperbaric oxygen (HBO_2) chamber at 2.5 atmospheres absolute pressure.[20] Based in part on the rationale that HBO_2 therapy improves CO elimination, restores tissue oxygenation, improves mitochondrial function, and alters inflammatory response induced by CO, it has been advocated as a therapy for CO poisoning for more than 40 years.[21,22]

Generally, US textbooks, review articles, journal editorials, and commentaries endorse the use of HBO_2 in treating severe CO poisoning.[8,9,23-37] However, the ability of HBO_2 therapy to reduce the incidence and severity of neurologic sequelae has been questioned in other studies.[38-44]

Published CO poisoning treatment algorithms commonly attempt to risk-stratify patients, with the goal of providing HBO_2 therapy only to those patients deemed most likely to benefit.[8,9,25-28,32-37] Recommended indications for the use of HBO_2 vary considerably. Patients with transient loss of consciousness or ongoing altered mental status are generally deemed to be candidates for HBO_2 therapy.[8,9,25-28,32-37] Additionally, metabolic acidosis, hypotension, ataxia, and evidence of myocardial injury are often but variably cited as appropriate treatment indications. Although the ability of carboxyhemoglobin levels to predict mortality, morbidity, or response to therapy is universally considered poor, various treatment algorithms still recommend that HBO_2 therapy be administered, regardless of signs or symptoms of poisoning, if carboxyhemoglobin levels exceed 15%, 20%, 25%, or 40%.[8-10,12-14,25,26,28,36,37] One particularly difficult situation involves pregnant women with apparently mild CO poisoning. CO poisoning can cause fetal demise, limb and vertebral abnormalities, and brain injury.[45-47] Because it is impossible to conduct a detailed neurologic assessment on a fetus, some treatment algorithms recommend HBO_2 treatment for all pregnant women with significant CO exposure on the theory that one is treating the fetus, who may be more severely poisoned than the mother. In this situation, maternal carboxyhemoglobin levels of 15%, 20%, or 25% have been proposed as the threshold for empiric therapy with HBO_2.[9,26,28,33,34,36,37] Many also point out that HBO_2 therapy is generally safe. The most common complications were anxiety and middle ear barotraumas, reported in 0% to 8% of HBO_2 treatment subjects.[10,12-14] Although older studies report the incidence of seizures to be as high as 5%, only 1 of the 1,037 CO poisoning patients who received HBO_2 in the 4 included trials and a large, consecutive patient case series seized or developed other major complications (0.10%; 95% confidence interval [CI] 0.01% to 0.48%).[10,12-14,48]

Faced with these conflicting recommendations, many emergency physicians are left wondering which patients, if any, require HBO_2 therapy for CO poisoning. Most hospitals in the United States do not have 24-hour HBO_2 chamber availability. Safety and logistical issues involved in procuring HBO_2 therapy vary widely from case to case.

This clinical policy uses an evidence-based approach to evaluate the literature and make recommendations about the management of CO poisoning. The critical questions were generated by the subcommittee, with input from the American College of Emergency Physicians (ACEP) Sections of Toxicology and Hyperbaric Medicine, because they are believed

to be important for emergency physicians initially providing care in the emergency department (ED).

This policy evolved from the 1999 ACEP "Clinical Policy for the Initial Approach to Patients Presenting with Acute Toxic Ingestion or Dermal or Inhalation Exposure."[49]

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. MEDLINE searches for articles published between January 1980 and January 2006 were performed using a combination of key words and their variations, including "carbon monoxide poisoning," and "hyperbaric oxygen." Searches were limited to English-language sources. Additional articles were reviewed from the bibliography of articles cited and from published textbooks and review articles. Subcommittee members also supplied articles from their own files.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.[50] This policy is a product of the ACEP clinical policy development process and is based on the existing literature; where literature was not available, consensus of emergency physicians, toxicologists, and physicians with hyperbaric medicine expertise was used. Expert review comments were received from individual physicians with topic expertise and from individual members of the American Academy of Clinical Toxicology, American College of Medical Toxicology, Divers Alert Network, and Undersea and Hyperbaric Medical Society. Expert review comments were also received from members of ACEP's Toxicology Section and Hyperbaric Medicine Section. Their responses were used to further refine and enhance this policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

All articles used in the formulation of this clinical policy were graded by at least 2 subcommittee members for strength of evidence and classified by the subcommittee members into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest evidence and design 3 representing the weakest evidence for therapeutic, diagnostic, and prognostic clinical reports, respectively (Appendix A). Articles were then graded on 6 dimensions thought to be most relevant to the development of a clinical guideline: blinded versus nonblinded outcome assessment, blinded or randomized allocation, direct or indirect outcome measures (reliability and validity), biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size. Articles received a final grade (Class I, II, III) on the basis of a predetermined formula taking into account design and quality of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in formulating recommendations in this policy. Evidence grading was done with respect to the specific data being extracted, and the specific critical question being reviewed. Thus, the level of evidence for any one study may vary according to the question, and it is possible for a single article to receive different levels of grading as different critical questions are answered. Question-specific level of evidence grading may be found in the Evidentiary Table included at the end of this policy.

Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on strength of evidence Class I or overwhelming evidence from strength of evidence Class II studies that directly address all of the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on strength of evidence Class II studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of strength of evidence Class III studies).

Level C recommendations. Other strategies for patient management that are based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain enough quality information to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. ACEP clearly recognizes the importance of the individual physician's judgment. Rather, this clinical policy defines for the physician those strategies for which medical literature exists to provide support for answers to the crucial questions addressed in this policy.

Scope of Application. This clinical policy is intended for physicians working in hospital-based EDs in a location at which HBO_2 therapy is an available treatment option (whether on site or by reasonably practical patient transfer).

Inclusion Criteria. This clinical policy is intended for adult patients presenting to the ED with acute CO poisoning.

Exclusion Criteria. This clinical policy is not intended for application to a pediatric population, for fetal exposures, for patients with chronic CO poisoning, or patients with delayed

presentations (greater than 24 hours after cessation of exposure) of CO poisoning.

CRITICAL QUESTIONS

Should HBO_2 therapy be used for the treatment of patients with acute CO poisoning; and

Can clinical or laboratory criteria identify CO-poisoned patients who are most or least likely to benefit from this therapy?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations.

1. HBO_2 is a therapeutic option for CO-poisoned patients; however, its use cannot be mandated.
2. No clinical variables, including carboxyhemoglobin levels, identify a subgroup of CO-poisoned patients for whom HBO_2 is most likely to provide benefit or cause harm.

Review of the available medical literature found 6 published studies[10,12-14,51,52] and 2 abstracts[16,53] related to this critical question in which treatment outcomes with and without HBO_2 were compared in groups of CO-poisoned patients with similar severity. After structured analysis, the 2 abstracts were automatically assigned a class of X, and 2 articles were downgraded to a class of X and therefore excluded from further analysis.[16,51-53] All identified studies evaluated the effect of HBO_2 on the outcome of neurologic function; none evaluated the effect of HBO_2 on other forms of morbidity or on mortality. Of the 4 remaining studies, 2 supported the use of HBO_2 (1 Class II[10] and 1 Class III[14]) and 2 did not (1 Class II[13] and 1 Class III[12]). These studies have generated great debate over the ideal methodology, variables, and outcomes for studying HBO_2 therapy in CO poisoning.[40,54-60]

In a Class II study, Weaver et al[10] reported a randomized, double-blinded, placebo-controlled, human clinical trial involving 152 patients. All enrolled patients received treatment with either 3 sessions of HBO_2 therapy or normobaric oxygen with sham HBO_2 therapy to maintain blinding. Critically ill patients were included, with half of enrolled patients having lost consciousness and 8% requiring intubation. The follow-up rate was excellent (95%), with assessments performed by trained examiners and compared with age, sex, and education-controlled norms. The definition of neurologic sequelae was fulfilled in self-reported symptomatic patients by an aggregate performance on 6 neuropsychological tests that was at least 1 SD below predicted or by an aggregate score of 2 or more SDs below expected in asymptomatic individuals. Six weeks after poisoning, HBO_2 was associated with a 21.1% (95% CI 6% to 34%) absolute reduction in the rate of neurologic sequelae (46.1% versus 25.0%), with an unadjusted (odds ratio [OR] of 0.39; 95% CI 0.20 to 0.78) favoring treatment with HBO_2. Twelve months after poisoning, the amount of benefit diminished to an absolute reduction in rate of 14.5% (95% CI 1% to 28%) but remained statistically significant (unadjusted OR 0.46; 95% CI 0.22 to 0.98). Although the incidence of the primary outcome varied markedly between treatment groups, 6 weeks after poisoning no differences were found in several secondary outcomes: group mean neuropsychological test scores and measurements of various aspects of physical and emotional health were the same in both the HBO_2 and normobaric oxygen groups, and no patient reported CO-related interference with activities of daily living.

Weaver et al[61] analyzed the above clinical trial data with the clinical data from another 91 patients who were eligible but were not enrolled in the study. This Class III study demonstrated that age 36 or older and CO exposure duration of 24 hours or greater were risk factors associated with 6-week cognitive sequelae. Symptoms such as lethargy, dizziness, nausea/vomiting, and loss of consciousness, as well as the initial CoHb level were not independent risk factors associated with 6-week cognitive sequelae. Weaver did not relate any of these clinical factors to sequelae at 6 or 12 months after the CO exposure.

Thom et al[14] also reported a benefit to HBO_2. In this Class III study, 65 CO-poisoned patients were randomized to a single HBO_2 treatment session or mask oxygen. Blinding was not used, and patients with loss of consciousness were excluded. The primary outcome measure, self-reported symptoms of neurologic sequelae combined with deterioration in at least 1 of 6 neuropsychological tests occurring at any time after treatment, was found in 0% (95% CI 0% to 12%) of the HBO_2-treated patients and 23% (95% CI 10% to 42%) of the patients treated with ambient pressure oxygen. All patients with reported neurologic sequelae had resolution by 77 days. Of the remaining asymptomatic patients, those treated with ambient pressure performed slightly worse on 1 of 6 neuropsychological tests (trail making) at 4 weeks than those treated with HBO_2 therapy.

One Class II[13] and 1 Class III[12] study reported no difference in outcomes in patients treated with HBO_2, compared with those receiving normobaric oxygen. In the Class II randomized controlled trial by Scheinkestel et al,[13] 191 patients were treated with continuous oxygen by face mask for 3 days after CO poisoning, with daily trips to the HBO_2 chamber. Patients with severe poisoning were included; more than half were comatose. To maintain blinding, patients randomized to the non-HBO_2 group received "sham" HBO_2 treatments that simulated actual HBO_2 therapy. Additional treatments (up to 6 daily sessions total) were performed in patients without neurologic recovery. This study had a high rate of adverse neurologic outcomes in all patients, regardless of treatment assignment, 74% in HBO_2-treated patients and 68% in controls (reported OR 1.7; 95% CI 0.8 to 4.0; $P=0.19$, NS). This is potentially due to the fact that 73% of all patients enrolled were considered to have "severe CO poisoning," as defined by 1 of 13 criteria. Assessment included 7 neuropsychological tests, with an abnormal score being considered 1 SD below the mean and 2 or more abnormal scores being considered a poor outcome. Endpoints were measured at the completion of therapy and at 1-month follow-

up. At the completion of treatment, the only statistically significant difference between the groups was a favor toward normobaric oxygen therapy in one of the 7 neuropsychological tests (verbal learning). With 54% of subjects lost to follow-up, data on 1-month follow-up were not reported but said to show no difference. Multiple statistical comparisons were reported without apparent planning or statistical correction. Both treatment arms received continuous supplemental mask oxygen for 3 days between their dives or "sham" dives, resulting in greater overall oxygen doses than conventional therapy. As such, comparison of this normobaric oxygen cohort with a more typical normobaric oxygen group receiving ambient air may be speculative.

The second study to report no difference in outcomes is a Class III study by Raphael et al.[12] In this unblinded study, 343 CO-poisoning patients without loss of consciousness were randomized to 1 HBO_2 treatment session or an equivalent duration of mask oxygen. The primary outcome measure was a symptom questionnaire, supplemented by physical and neurologic examination, in an unspecified number of patients. One month after treatment, 32.1% of patients who received HBO_2 therapy and 33.8% of control patients reported neurologic symptoms ($P=0.75$, NS, χ^2), and 97% of patients in each group had resumed their previous occupation. Data from this study were republished, with additional subgroup analysis showing no change in outcome.[62]

Unfortunately, none of the identified clinical trials prospectively designated subgroups of patients for separate analysis, weakening the reliability of conclusions based on subgroup analysis. Subject matter experts most commonly identify loss of consciousness, persistent mental status alteration, pregnancy, and high carboxyhemoglobin levels as indications for HBO_2 therapy.

Loss of Consciousness

Two studies randomized patients both with and without loss of consciousness from CO poisoning to HBO_2 and non-HBO_2 treatment groups.[10,13]

Weaver et al[10] did not present outcomes data on patients who lost consciousness separately from the aggregate.

Although Scheinkestel et al[13] did not separately report outcomes in patients with and without loss of consciousness, loss of consciousness is one of the 13 criteria used to define "severe CO poisoning" in their study. In this "severely CO-poisoned" subset (N=139; 73% of all subjects), HBO_2 was associated with a 20% absolute increase in poor neurologic outcomes at hospital discharge. Neurologic sequelae at hospital discharge were reported in 85% of HBO_2-treated and 65% of control patients with severe CO poisoning (reported OR 3.6; 95% CI 1.1 to 11.9; $P=0.03$). It is unclear from the article whether this subgroup analysis and the composite definition of "severe CO poisoning" were planned *a priori* or *post hoc*. If any multiple-measures statistical correction is used, this finding becomes no longer statistically significant, and outcomes at 1-month follow-up were the same in both treatment groups.

As noted above, the 2 Class III studies that enrolled only patients who did not lose consciousness produced conflicting results.[12,14]

In a separate arm of their study, Raphael et al[12] randomized patients who had loss of consciousness or coma (groups B1 and B2, n=286) to receive either 1 or 2 HBO_2 treatments. Although this does not inform the question of whether HBO_2 therapy is better than ambient oxygen treatment for these patients, this study arm did show that outcomes are worse in the more severe poisoning group, regardless of treatment group assignment.

Altered Mental Status or Coma

Apart from the above, no study reported separate data about whether HBO_2 therapy affected outcomes differently in patients with or without coma or abnormal mental status on hospital presentation or chamber entry.

Age

No study reported separate data about whether HBO_2 therapy affected outcomes differently in patients of advanced age. No child younger than 15 years was enrolled in any trial.

Carboxyhemoglobin Level

One Class II[13] and 2 Class III[12,14] studies reported no difference in outcomes, regardless of treatment modality, in patients with high or low carboxyhemoglobin levels.[12-14]

Pregnancy

All clinical trials excluded pregnant women. Although fetal outcomes in CO-exposed women have been described in several case series and 1 structured literature review, no study has compared pregnancy outcomes in women of similar poisoning severity treated with different therapeutic options.[45,63-69]

Cardiac Arrest

A Class III retrospective case series reported 18 consecutive patients who presented to a single institution after resuscitation from CO-associated cardiac arrest.[70] Despite prompt and aggressive treatment of all patients with HBO_2, none survived to hospital discharge (0%; 95% CI 0% to 18.5%). However, survival, albeit with devastating neurologic injury, has been reported in a survivor of CO-associated cardiac arrest treated with HBO_2.[71]

Future Areas of Research

Because of the conflicting results of previous clinical trials, an additional large, multicenter human clinical trial is needed. A future trial should include randomization, strict blinding of patients and evaluators to treatment group assignment, an objective assessment of outcome, and serial outcome measurements to evaluate the severity and duration of neurologic sequelae in study subjects. Outcome assessments should include validated instruments that allow

for rigorous quantification of the severity of any impairment. Pretreatment clinical data should be collected and analyzed by prospectively defined subgroups to determine which clinical features best predict response or nonresponse to therapy. In addition to neuropsychological measurements, a future trial should report in detail an assessment of patients' ability to work and perform other activities of daily living and a structured measurement of impact on quality of life. Sufficient data on the severity of impairment are necessary to permit a cost-benefit analysis, which will be particularly important if the number needed to treat is high. Detailed information about patient selection, including patients who declined to participate in the study, is needed to allow comparison between patients included in the study and all CO-poisoned patients treated in EDs. Such a clinical trial will take years to perform. In the interim, analysis of subgroup data from completed studies, using prospectively defined criteria compared across studies, may be useful to identify a group of patients who are either highly likely or highly unlikely to benefit from HBO_2 therapy. In addition, studies about the outcomes and therapy of CO poisoning in children and pregnant women, important patient populations who were excluded from all previous trials, are needed.

Relevant industry relationships for the following carbon monoxide poisoning subcommittee members are as follows: Dr. Lavonas was the Medical Director of Hyperbaric Medicine at Carolinas Medical Center, Charlotte, NC during the development of this clinical policy.

Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical question.

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Evidentiary Table.

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Weaver et al[10]	2002	Randomized controlled trial (Design 1); double-blinded; N=152; patients of all severity included	All patients received ≥3 h mask O_2; all patients received 3 sessions in HBO_2 chamber within 24 h; number of HBO_2 sessions in HBO_2 group: 3; maximum HBO_2 treatment pressure: 3.0 ATA first session, 2.0 ATA subsequent 2 sessions; control patients received sham HBO_2 to preserve blinding; block randomizations used	Primary outcome: neurologic sequelae at 6 wks defined as either symptoms+aggregate of 6 neuropsychological test scores ≥1 SD below predicted or no symptoms+aggregate of 6 neuropsychological test scores ≥2 SD below predicted; blinded assessment	Primary outcome: neurologic sequelae 6 wks after poisoning in 25.0% of HBO_2-treated patients and 46.1% of controls (OR 0.39; 95% CI 0.20-0.78; P=0.007); NNT=4.8; incidence of neurologic sequelae decreased but still statistically significant at 6 and 12 mo; no significant difference between HBO_2 and control groups in overall/mean neuropsychological test scores, depression, activities of daily living, or subscores of the 36 item short form general health survey	Lost to enrollment/declined to participate: 54%; lost to follow-up: 5%; suicidal patients: 31%; mean time to treatment: 5.6 h; Limitations: difference in baseline cerebellar dysfunction between the 2 groups; cerebellar dysfunction showed strong correlation to poor outcome; attempted control for cerebellar dysfunction with logistic regression was performed; control group with greater duration of CO exposure; high percentage (54%) of eligible patients "declined" contributing to selection bias; subjective component to primary outcome contributing to detection bias; study used block randomization	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Raphael et al[12]	1989	Randomized controlled trial (Design 1); N=343; (groups A0 and A1); patients with loss of consciousness excluded (7 mistakenly enrolled)	All patients received 6 h O_2; number of HBO_2 sessions in HBO_2 group: 1; maximum HBO_2 treatment pressure: 2.0 ATA; no use of sham HBO_2	Symptom questionnaire; physical examination in some patients; no formal neuropsychological instruments; primary outcome: any sign or symptom of CO poisoning at 1-mo follow-up	Neurologic sequelae in 32.1% of HBO_2-treated patients and 33.8% of controls (OR 0.93; 95% CI 0.56-1.53; *P*=0.84, NS); NNT=59	Lost to enrollment: 9%; lost to follow-up: 10%; suicidal: 0% (excluded); mean time to treatment: 6.2 h; separate arm of same trial randomized patients with loss of consciousness to 1 vs 2 HBO_2 treatments; parallel study (groups B1 and B2, N=286) of patients with loss of consciousness/coma not considered in analysis except as noted; Limitations: blinded assessment not stated; large subjective component to primary outcome contributing to detection bias; no sham therapy for the NBO group	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Scheinkestel et al[13]	1999	Randomized controlled trial (Design 1); Double blinded; N=191; patients of all severity included	All patients received ≥3 days of mask O_2; number of HBO_2 sessions in HBO_2 group: 3; up to 3 additional if symptoms persisted; maximum HBO_2 treatment pressure: 2.8 ATA each session; control patients received sham HBO_2 to preserve blinding	Primary outcome: persistent neurologic sequelae at the end of treatment defined as ≥2 of 7 neuropsychological test scores ≥1 SD below predicted; secondary outcome: delayed neurologic sequelae at 4 wks	Persistent neurologic sequelae in 74% of HBO_2-treated patients and 68% of controls (OR 1.7; 95% CI 0.8-4.0; *P*=0.19, NS); number needed to harm=16.7; delayed neurologic sequelae in 4.8% of HBO vs 0% NBO group; no significant difference between HBO_2 and control groups in 6 of 7 neuro-psychological test scores after 3 treatments; no difference between groups in any test found at 1 mo, but inadequate follow-up rate	Lost to enrollment: not stated; lost to follow-up: 54%; suicidal patients: 69%; mean time to treatment: 7.1 h; Limitations: poor follow-up at 1 mo; diminished generalizability because of high oxygen dose of control arm; study used cluster randomization	II (For persistent neurologic sequelae data) X (for delayed neurologic sequelae data)

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Thom et al[14]	1995	Randomized controlled trial (Design 1); N=65; patients with loss of consciousness excluded	All patients received O_2 until asymptomatic; number of HBO_2 sessions in HBO_2 group: 1; maximum HBO_2 treatment pressure: 2.8 ATA; no use of sham HBO_2	Primary outcome: development of a symptom+any amount of deterioration on ≥1 of 6 neuropsychological test scores at any time after poisoning; secondary outcome: neuropsychological testing in asymptomatic patients	Neurologic sequelae in 0% of HBO_2-treated patients (95% CI 0%-12%) and 23% of controls (95% CI 10%-42%); NNT=4.3; of asymptomatic patients, HBO_2 group performed better than control on 1 of 6 tests (trail making), but the statistical and clinical significances of this difference are uncertain	Lost to enrollment: 4%; lost to follow-up: 8%; suicidal patients: not stated; mean time to treatment: 2.0 h; primary outcome resolved in all patients by 77 days; Limitations: nonblinded enrollment; blinded assessment not stated; no sham therapy for NBO group; subjective component to primary outcome; unknown statistical significance of secondary outcome	III
Mathieu et al[16]	1996	Randomized controlled trial; not blinded; N=575	HBO_2 vs mask O_2; noncomatose	Not stated	Benefit from HBO_2 at 1 and 3 months (NNT=15.4); no benefit from HBO_2 at 1 y	Abstract only	X
Ducasse et al[51]	1995	Randomized controlled trial; not blinded; N=26	HBO_2 vs mask O_2	EEG, CBF at rest and with acetazolamide challenge	No benefit from HBO_2 on EEG and CBF tests; slight benefit from HBO_2 on CBF reactivity to acetazolamide (cannot calculate NNT)	No clinical outcome measurements	X
Gorman et al[52]	1992	Not randomized (practice pattern changed by dates); N=100	1 or 3 treatments of HBO_2 vs mask O_2	Unspecified neuropsychological tests	Benefit for 3 HBO_2 treatments vs 1 session; no benefit found for HBO_2 vs NBO	Because of small numbers in mask O_2 group (N=6), underpowered for this comparison	X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Raphael et al[53]	2004	Randomized controlled trial; not blinded; N=179	HBO_2 vs mask O_2; no loss of consciousness	Patient reported symptoms	No benefit from HBO_2	Abstract only	X
Weaver et al[61]	2007	Data from 1992 to 1999; not randomized; not blinded; included 147 patients from a previously published clinical trial and 91 patients who were eligible but were not enrolled in the study; 238 total patients included in analysis	75 patients received HBO_2 in the clinical trial; 163 patients did not receive HBO_2; 146 of the 163 received 100% O_2 for a mean time of 6.9 h; 17 of the 163 received no therapy after the CO exposure	Neuropsychiatric testing at 6 wks, 6 mo, and 12 mo; the primary outcome of the study was 6 wk cognitive sequelae, which was assumed to be related to the CO poisoning; in the patients who did not receive HBO_2, univariate and multivariable analysis were used to identify risk factors for cognitive sequelae at 6 wks	In all 238 patients 37% (87/238) had sequelae at 6 wks; in the 75 HBO_2 patients, the rate was 24% (18/75) sequelae at 6 wks; in the 146 O_2 therapy only patients the rate was 41% (60/146); and in the 17 no therapy patients, the rate was 53% (9/17) sequelae at 6 wks; risk factors for 6 wk cognitive sequelae: age ≥36 y and CO exposure duration ≥24 h; risk factor reduction with HBO_2 therapy in patients ≥36 y: OR 0.3 (0.2-0.6)	The mixing of clinical trial data with data from patients not enrolled in the clinical trial makes this a large case series only; the determination of risk factor reduction for cognitive sequelae with HBO_2 therapy using a larger control group outside of a clinical trial should not provide results that are any more reliable than those found within the context of the clinical trial itself, and should not be assumed to be more accurate or representative of the results that could be obtained in clinical practice	III (for 6 wk cognitive sequelae)

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Hampson and Zmaeff[69]	2001	Consecutive patient case series; N=18	HBO_2 after resuscitation from CO-associated cardiac arrest	Survival to hospital discharge	No benefit from HBO_2 (all patients died); (survival rate 0%; 95% CI 0%-18.5%)	Small sample size	III

ATA, atmosphere absolute; *CBF*, cerebral blood flow; *CI*, confidence interval; *CO*, carbon monoxide; *EEG*, electroencephalogram; *h*, hour; *HBO_2*, hyperbaric oxygen; *mo*, month; *NBO*, normobaric oxygen; *NNT*, number needed to treat; *NS*, not significant; *O_2*, oxygen; *OR*, odds ratio; *SD*, standard deviation; *vs*, versus; *wks*, weeks; *y*, year.

Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing ≥2 interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X