Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Carbon Monoxide Poisoning
This DRAFT is EMBARGOED – Not for Distribution

From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Carbon Monoxide Poisoning:

Richard D. Shih, MD (Writing Committee Chair)
Christian A. Tomaszewski, MD, MS, MBA
Amy Kaji, MD, MPH, PhD (Methodologist)
Deborah B. Diercks, MD, MSc (Committee Chair)

ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses a key issue in the evaluation and management of adult patients presenting to the emergency department with acute carbon monoxide poisoning. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical question: In emergency department patients diagnosed with acute carbon monoxide poisoning, does hyperbaric oxygen therapy as compared with normobaric (room pressure) oxygen therapy improve long-term neurocognitive outcomes? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Carbon monoxide (CO) is a clear odorless gas that is a product of incomplete combustion of carbonaceous material. Carbon monoxide is one of the leading causes of poisoning with over a million cases CO poisoning reported worldwide each year.[1] In the United States CO poisoning is a leading cause of non-suicidal poisoning deaths with nearly 50,000 emergency department (ED) visits annually.[2,3]

The CO molecule binds to hemoglobin with a higher affinity than oxygen and can cause problems related to hypoxia. Without treatment, CO has an elimination half-life of approximately 5 hours.[4] In the presence of oxygen, this is decreased to 85 minutes and 20 minutes, for high-flow non-rebreather mask and hyperbaric oxygen (HBO_2) therapy, respectively.[5]

In addition to the effects on hemoglobin, CO can cause a cascade of inflammatory and immunologic damage at the cellular level. Nitric oxide generation, free radical formation, lipid peroxidation, apoptosis and immune mediated injury can occur.[6,7] These effects can lead to damage in almost every organ system, however, the most consequential are cardiac and neurologic.

Acute toxicity can cause a wide range of clinical effects from mild headache or flu-like symptoms to chest pain, shortness of breath, myocardial infarction, dysrhythmia, confusion, altered mental status and coma. Flu-like symptoms in occult cases of CO poisoning, especially during colder weather, further confound diagnosis.[8,9]

After the initial CO exposure, patients can develop new neurologic findings 2 to 40 days later.[10,11] These central nervous system (CNS) abnormalities can range from problems in concentration and memory to seizures and

Parkinson's-like syndrome. Virtually any neuropsychologic abnormality can be seen including psychiatric ones like depression and psychosis. These late onset findings are called delayed neurological sequelae (DNS). Risk factors for DNS include older age (≥36 years), higher CO level (≥25%), longer CO exposure interval (≥24 hours), loss of consciousness due to CO poisoning, low Glasgow Coma Score, low Mini-Mental Status Examination score and positive findings on brain computed tomography scans (general swelling, white matter and/or globus pallidus).[12,13]

The previous ACEP clinical policy from 2017 addressed three critical questions: [14]

1. In ED patients with suspected acute CO poisoning, can noninvasive carboxyhemoglobin (COHb) measurement be used to accurately diagnose CO toxicity?
2. In ED patients diagnosed with acute CO poisoning, does HBO_2 therapy as compared with normobaric oxygen (NBO) therapy improve long-term neurocognitive outcomes?
3. In ED patients diagnosed with acute CO poisoning, can cardiac testing be used to predict morbidity or mortality?

As a part of the revision process for this Clinical Policy, after a thorough literature search and review process, it was determined that no new relevant studies were found regarding questions 1 and 3. The result was a reaffirmation of the recommendations for these questions.

The literature search for the HBO_2 versus NBO for DNS identified several new studies that met methodologic criteria. This question of whether HBO_2 therapy can improve DNS outcomes in CO poisoned patients has been debated for several decades and remains hotly contested.[15] In the 2017 ACEP clinical policy, 5 randomized controlled trials (RCTs) were identified that looked at this issue. Of the five, three[16-18] (one Class II and two Class III) reported no benefit from HBO_2 therapy, while the two others[11,19] (both Class II studies) found improved DNS outcomes.

In addition, there are over 700 HBO_2 treatment facilities in the United States, with some states having multiple locations and others without any.[20] Further, only a small proportion of these existing HBO_2 centers have the equipment and staff necessary to treat high acuity patients.[20] Transport over 50 miles for these patients may be needed from many areas of the United States with the additional risks accompanying travel and possible deterioration.[20-22]

Given the continued controversy for the use of HBO_2 to treat carbon monoxide poisoning, this clinical policy will revisit the issue, reviewing the eligible published literature since the recommendation made in the 2017 clinical policy.

METHODOLOGY

This ACEP clinical policy was developed by emergency physicians with input from medical librarians and a patient safety advocate; is based on a systematic review and critical, descriptive analysis of the medical literature; and is reported in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Search and Study Selection

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of PubMed, SCOPUS, Embase, Web of Science, and the Cochrane Database of Systematic Reviews were performed by a second librarian. Search terms and strategies were peer reviewed by a second librarian. All searches were limited to human studies published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

Using Covidence (Covidence, Melbourne, Australia), 2 subcommittee members independently reviewed the identified abstracts to assess for possible inclusion. Of those identified for potential inclusion, each full-length text was reviewed for eligibility. Those identified as eligible were subsequently abstracted and forwarded to the committee's methodology group (emergency physicians with specific research methodological expertise) for methodological grading using a Class of Evidence framework (Appendix E1).

Assessment of Risk of Bias and Determination of Classes of Evidence

Each study identified as eligible by the subcommittee was independently graded by 2 methodologists. Design 1 represents the strongest possible study design to answer the critical question, which relates to whether the

focus was therapeutic, diagnostic, or prognostic, or a meta-analysis. Subsequent design types (ie, Design 2 and Design 3) represent respectively weaker study designs. Articles are then graded on dimensions related to the study's methodological features and execution, including but not limited to randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and potential for conflicts of interest.

Using a predetermined process that combines the study's design, methodological quality, and applicability to the critical question, 2 methodologists independently assigned a preliminary Class of Evidence grade for each article. Articles with concordant grades from both methodologists received that grade as their final grade. Any discordance in the preliminary grades was adjudicated through discussion which involved at least 1 additional methodologist, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix E2). Studies identified with significant methodologic limitations and/or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of evidence. Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence for each critical question, the subcommittee drafted the recommendations and supporting text synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of scientific certainty (eg, based on evidence from one or more Class of Evidence I or multiple Class of Evidence II studies that demonstrate consistent effects or estimates).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate scientific certainty (eg, based on evidence from one or more Class of Evidence II studies, or multiple Class of Evidence III studies that demonstrate consistent effects or estimates).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

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 consistency of results, uncertainty of effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations. When possible, clinically-oriented statistics (e.g., likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient. This can assist the clinician in applying the recommendations to most patients but allow adjustment when applying to patients with extremes of risk (Appendix E3).

Evaluation and Review of Recommendations

Once drafted, the policy was distributed for internal review (by members of the entire committee) followed by external expert review and an open comment period for all ACEP membership. Comments were received during a 60-day open comment period with notices of the comment period sent electronically to ACEP members, published in *EM Today*, posted on the ACEP website, and sent to other pertinent physician organizations. The responses were used to further refine and enhance this clinical policy, although responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly.

Application of the Policy

This policy is not intended to be a complete manual on the evaluation and management of adult patients with carbon monoxide poisoning but rather a focused examination of critical questions that have particular relevance to the current practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within the critical question.

It is the goal of the Clinical Policies Committee to provide evidence-based recommendations when the scientific literature provides sufficient quality information to inform recommendations for the critical question. In accordance with ACEP Resolution 56(21), ACEP clinical policies do not use race-based calculators in the formulation of the recommendations. When the medical literature does not contain adequate empirical data to inform a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to inform the critical questions addressed in this policy. ACEP funded this clinical policy.

Scope of Application. This guideline is intended for physicians working in EDs.

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with suspected or diagnosed acute CO poisoning.

Exclusion Criteria. This guideline is not intended to be used for out-of-hospital emergency care patients, pediatric populations, pregnant patients and fetal exposures, those with chronic CO poisoning, or patients with delayed presentations (more than 24 hours after cessation of exposure) of CO poisoning.

CRITICAL QUESTION

1. In ED patients diagnosed with acute CO poisoning, does HBO_2 therapy as compared with normobaric oxygen therapy improve long-term neurocognitive outcomes?

Patient Management Recommendations

Level A recommendations. *None.*

Level B recommendations. *None.*

Level C recommendations. In symptomatic CO poisoning, selected patients may benefit from HBO_2 treatment, based on severity of symptoms and availability (distance and time).

Potential Benefit of Implementing the Recommendations:

- Improved neurologic outcomes.

Potential Harm of Implementing the Recommendations:

- Hyperbaric induced middle ear barotrauma.
- Oxygen toxicity (seizure).
- Risks and costs associated with transport to a hyperbaric chamber.
- Clinical deterioration during transport.
- Need for significant (>50 miles) travel to a hyperbaric chamber.
- Chamber induced claustrophobia.

Key words/phrases for literature searches: Carbon Monoxide Intoxication, Carbon Monoxide Poisoning, Hyperbaric Oxygen, Hyperbaric Oxygen Therapy, Hyperbaric Oxygenation, Hyperbaric Oxygenation, Normobaric Oxygen Therapy, and variations and combinations of keywords/phrases. Searches included January 2015 to search dates of August 26, 2022, and April 12, 2024 (Appendix E4).

Study Selection: Eight hundred fifty articles were identified in the searches. Three hundred eighty articles were selected from the search results as candidates for further review. After grading for methodological rigor, zero Class I studies, 0 Class II studies, and 4 Class III studies were included for this critical question (Appendix E5).

Since the publication of the 2017 ACEP CO clinical policy,[14] eight new studies were identified that addressed this critical question. Four of these studies were rated as Class III,[24-27] while the others were rated as Class X due to methodologic flaws or inability to directly attest to the question. Among the four manuscripts that met inclusion criteria, three were meta-analyses that included data that was predominantly made up of the five RCTs that were included in the 2017 clinical policy.[25-27] Because of this, we decided to include these earlier five pivotal RCTs in our current analysis.[11,16-19]

Of the five RCTs that were included in the 2017 clinical policy, three were graded as Class II[11,17,19] and two as Class III.[16,18] All of these studies randomized patients to either treatment with HBO_2 or NBO and their main outcome measure being neurologic sequalae at follow-up, the topic of this critical question. Two of the studies,[11,19] both Class II, showed improved long term neurologic outcome with HBO_2 and the other three, one Class II and two Class III, showed no significant effect.[16-18]

Although all five studies randomized CO exposed patients to HBO_2 and NBO, many other important variables differed.[11,16-19] Animal studies suggest that HBO_2 treatments are effective when started early with improved biochemical response as dose increases up to 3.0 atmospheres (ATA).[28] Multiple retrospective studies show that early HBO_2 (within several hours post exposure) versus late exposure led to better neurological outcomes.[29,30] Further, syncope is a strong predictor of poor neurologic outcome.[31] These five RCTs varied greatly

in all of these variables; inclusion when exposure occurred more than 6 hours, exclusion of comatose patients and utilization of many different HBO_2 treatment variables including pressures less than 2.5 ATA (see Table 1).[11,16-19] In addition, studies differed in blinding techniques. One study utilized sham HBO_2 treatments (graded Class II, HBO_2 beneficial) and other studies did not blind evaluators when assessing neurologic sequalae.

Table 1. Treatment Variables of Randomized Controlled Trials Informing 2017 Clinical Policy Recommendation.

Study	Time to HBO_2 Per Protocol (hrs)	Time to HBO_2 (mean)	Mean Age (yrs)	Number Of Subjects	Male	Initial HBO_2 Dose	Sham Control	Follow-up Assessment (blinded)	Suicide	Syncope	Outcome Favors HBO_2
Annane[18] (2011)	<12	<12 hrs	33.0	179	41%	2 ATA 2 hrs	NO	1 month (YES)	0%	97%	NO
Raphael[16] (1989)	<12	7.1 hrs	35.4	343	49%	2 ATA 2 hrs	NO	1 month (NO)	n/a	n/a	NO
Scheinkestel[17] (1999)	No Limit	7.1 hrs	36.3	191	81%	2.8 ATA 1 hr	NO	1 month (YES)	69%	53%	NO
Thom[11] (1995)	<6	2 hrs	37.0	65	52%	2.8 ATA 0.5 hr then 2.0 ATA 90 min	NO	4 weeks (NO)	n/a	n/a	YES
Weaver[19] (2002)	<24	5.6 hrs	35.5	152	71%	3 ATA 1 hr then 2 ATA 1 hr	YES	6 weeks, 6 months, 12 months (YES)	31%	53%	YES

Because of these many differences, all the RCTs have been criticized in the literature for not being designed properly to assess HBO_2's ability or inability to prevent DNS.[32-36] Because the findings of these RCTs have been equivocal with regards to HBO_2 efficacy, consensus has accordingly been difficult to reach.[14,32-34,37]

Of the four studies identified since the 2017 ACEP clinical policy,[24-27] only one is not a meta-analysis.[24] This study, the Nakajima et al, is a retrospective study that utilized data from a nationwide inpatient database in Japan.[24] The study included 2,034 patients, all CO poisoned and ill enough to require hospital admission. All patients received HBO_2 and were compared to a propensity matched control group that did not receive HBO_2. For hospital mortality, the HBO_2 group was unchanged, but earlier discharge, a lower proportion of depressed mental status (NNT 42; difference -3.2% 95% CI -4.9% to -1.5%) and improvement in activities of daily living (NNT 41;

difference -5.3% 95% CI -7.8% to -2.7%) were seen in the group receiving HBO_2 compared with the control group. Limitations included retrospective design, lack of long-term outcome beyond 7 days, and no standardization of HBO_2 therapy protocols, with some centers only using as little as 2.0 ATA of HBO_2 for as little as 60 minutes. With almost a quarter of subjects with some medical problem at discharge, primarily with activities of daily living, this study supports a modest benefit with HBO_2 treatment.

The other three studies, all Class III,[25-27] were meta-analyses of previously considered data (2017 ACEP CO Policy) (Table 2).[14] The first, Ho et al, was a network meta-analysis of 8 prior studies (N=1,785) looking at the effects of HBO_2 on mortality and neurological outcomes after CO poisoning.[25] However, 3 of the 8 RCTs (Annane 2001; Ducasse 1995; Hampson 2006) received X grades by ACEP Clinical Policies Committee methodologists.[38-40] Six studies specifically looked at the impact of NBO versus single HBO_2 treatment found no difference in any meaningful outcome: mortality (3 studies: Scheinkestel 1999; Annane 2011; Raphael 1989),[16-18] headache improvement (4 studies: Annane 2001; Ducasse 1995; Thom 1995; Raphael 1989)[11,16,38,39] and general fatigue (2 studies: Annane 2011; Raphael 1989).[16,18] The most important outcomes, factors potentially related to DNS, were provided by three studies (Annane 2011; Raphael 1989; Weaver 2002).[16,18,19] When pooled, there was no difference in relative risk of memory impairment or concentration impairment between the NBO and HBO_2 group. One criticism may be that not enough HBO_2 treatments were administered, but the included Annane (2011) study showed that additional treatments (up to three total) led to potentially worse outcomes in memory and concentration.[18] Further, only one of the eight included studies blinded investigators to the treatments.[19] The authors conclude that HBO_2 may not be an effective treatment for patients with CO poisoning.

Table 2. Summary of studies included in the three metanalyses (only listed studies that had an NBO control group for comparison).

STUDY	Lin[26] (2018)	Wang[27] (2019)	Ho[25] (2022)	ACEP[14] (2017) RATING	OUTCOME FAVORS HBO_2
Annane[39] (2001)	-	-	✓	X	NO
Annane[18] (2011)	✓	✓	✓	III	NO
Ducasse[38] (1995)	✓	✓	✓	X	YES
Mathieu[41] (1996)	-	✓	-	X	NO
Raphael[16] (1989)	✓	✓	✓	III	NO
Scheinkestel[17] (1999)	✓	✓	✓	II	NO
Thom[11] (1995)	✓	✓	✓	II	YES
Weaver[19] (2002)	✓	✓	✓	II	YES
Hampson[40] (2006)	-	-	✓	X	N/A

A second meta-analysis of six RCTs looked at the effect of NBO vs HBO_2 on neuropsychiatric outcome.[26] One (Ducasse 1995) of the 6 RCTs received Class X grade by the ACEP Clinical Policies Committee methodologists (see Table 1).[30] The effects included any or all of the following: headache, memory impairment, difficulty concentration, disturbed sleep, asthenia, or any other form of DNS. Compared with the NBO group, the HBO_2 patients had a lower percentage of almost all adverse neurological sequelae. Most importantly, the patients in the HBO_2 group had less DNS (25% versus 31.1%, risk ratio [RR] 0.35; 95% CI 0.02 to 5.97). Although the overall HBO_2 group had better outcomes, most of the 95% confidence intervals overlapped, suggesting any benefit may be random or modest. However, the HBO_2 group showed statistically significant benefit in memory impairment and difficulties in concentrating. As with the previous meta-analysis, all the studies except one lacked blinding. Overall, this study showed modest benefit from HBO_2 treatment.

The final Class III study added a seventh RCT study (Mathieu, 1996)[41] to the metanalysis.[27] Two of the seven included studies received Class X grades by the ACEP Clinical Policies Committee methodologists.[39,40] With a total of 2,023 patients diagnosed with CO poisoning, the authors concluded that HBO_2 compared to NBO was not associated with any improved outcomes regarding mortality, recovery, neurological sequalae, asthenia, or headache.

For one outcome, memory impairment, the data did show, with data available from only five cohorts, that HBO_2 was associated with a lower risk of memory impairment (RR 0.67; 95% CI 0.46 to 0.97). They also mentioned that two HBO_2 sessions, based on a single study (Anane, 2011), did not show additional benefit.[18] Potential limitations include that the outcome measures were within a short time frame and may not be sustained.

Summary

Since publication of the 2017 ACEP clinical policy on CO treatment with HBO_2,[14] only four new studies were identified that met methodological quality for inclusion in answering this critical question. Of these studies, only one had original data, but this was a retrospective propensity matched trial and showed only modest benefit.[24] The three meta-analyses included varying numbers of the same RCT studies that were graded and discussed in the previous ACEP clinical policy on addressing acute carbon monoxide poisoning.[14] In all but one of the RCTs (Weaver, 2002), patients were not blinded, but more importantly, the control NBO groups did not get standardized treatment to ensure 100% oxygen was continuously delivered.[19] Based on this review, the Clinical Policies Committee's conclusions are similar to those made in the 2017 clinical policy that HBO_2 may provide a modest benefit, especially in memory impairment.

Future Research

The efficacy of HBO_2 treatment to prevent DNS from CO poisoning remains controversial with studies having equivocal findings. These differences in results may be due to differences in methodology such as lack of blinding, poor follow-up, timing of HBO_2 treatment, differing inclusion criteria, HBO_2 dose, number of HBO_2 treatments, lack of critically ill patients and outcome measures (see Table 2). Future studies need to look at timing of HBO_2 initiation and perhaps targeting those CO poisoned patients most at risk for DNS.[12] As many of the past studies utilize different inclusion criteria, treatment, and outcomes, there is a need for interested researchers to meet and agree upon standard methodology for future RCTs.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.

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

REFERENCES

1. Mattiuzzi C, Lippi G. Worldwide epidemiology of carbon monoxide poisoning. *Hum Exp Toxicol*. 2020;39:387-392.

2. Sircar K, Clower J, Shin MK, et al. Carbon monoxide poisoning deaths in the United States, 1999 to 2012. *Am J Emerg Med*. 2015;33:1140-1145.

3. Shin M, Bronstein AC, Glidden E, et al. Morbidity and Mortality of Unintentional Carbon Monoxide Poisoning: United States 2005 to 2018. *Ann Emerg Med*. 2023;81:309-317.

4. Peterson JE, Stewart RD. Absorption and elimination of carbon monoxide by inactive young men. *Arch Environ Health*. 1970;21:165-171.

5. Weaver LK, Howe S, Hopkins R, et al. Carboxyhemoglobin half-life in carbon monoxide-poisoned patients treated with 100% oxygen at atmospheric pressure. *Chest*. 2000;117:801-808.

6. Thom SR. Carbon monoxide-mediated brain lipid peroxidation in the rat. *J Appl Physiol*. 1990;68:997-1003.

7. Hardy KR, Thom SR. Pathophysiology and treatment of carbon monoxide poisoning. *J Toxicol Clin Toxicol*. 1994;32:613-629.

8. Dolan MC, Haltom TL, Barrows GH, et al. Carboxyhemoglobin levels in patients with flu-like symptoms. *Ann Emerg Med*. 1987;16:782-786.

9. Ng PC, Long B, Koyfman A. Clinical chameleons: an emergency medicine focused review of carbon monoxide poisoning. *Intern Emerg Med*. 2018;13:223-229.

10. Choi IS. Delayed neurologic sequelae in carbon monoxide intoxication. *Arch Neurol*. 1983;40:433-435.

11. Thom SR, Taber RL, Mendiguren II, et al. Delayed neuropsychologic sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen. *Ann Emerg Med*. 1995;25:474-480.

12. Weaver LK, Valentine KJ, Hopkins RO. Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. *Am J Respir Crit Care Med*. 2007;176:491-497.

13. Ku HL, Yang KC, Lee YC, et al. Predictors of carbon monoxide poisoning-induced delayed neuropsychological sequelae. *Gen Hosp Psychiatry*. 2010;32:310-314.

14. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Carbon Monoxide Poisoning:; Wolf SJ, Maloney GE, Shih RD, Shy BD, Brown MD. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Carbon Monoxide Poisoning. *Ann Emerg Med*. 2017;69:98-107.

15. Seger D, Welch L. Carbon monoxide controversies: neuropsychologic testing, mechanism of toxicity, and hyperbaric oxygen. *Ann Emerg Med*. 1994;24:242-248.

16. Raphael JC, Elkharrat D, Jars-Guincestre MC, et al. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. *Lancet*. 1989;2:414-419.

17. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. *Med J Aust*. 1999;170:203-210.

18. Annane D, Chadda K, Gajdos P, et al. Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials. *Intensive Care Med*. 2011;37:486-492.

19. Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med*. 2002;347:1057-1067.

20. Chin W, Jacoby L, Simon O, et al. Hyperbaric programs in the United States: Locations and capabilities of treating decompression sickness, arterial gas embolisms, and acute carbon monoxide poisoning: survey results. *Undersea Hyperb Med*. 2016;43:29-43.

21. Sloan EP, Murphy DG, Hart R, et al. Complications and protocol considerations in carbon monoxide-poisoned patients who require hyperbaric oxygen therapy: report from a ten-year experience. *Ann Emerg Med*. 1989;18:629-634.

22. Bosco G, Garetto G, Rubini A, et al. Safety of transport and hyperbaric oxygen treatment in critically-ill patients from Padua hospitals into a centrally-located, stand-alone hyperbaric facility. *Diving Hyperb Med*. 2016;46:155-159.

23. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.

24. Nakajima M, Aso S, Matsui H, et al. Hyperbaric oxygen therapy and mortality from carbon monoxide poisoning: A nationwide observational study. *Am J Emerg Med*. 2020;38:225-230.

25. Ho YW, Chung PY, Hou SK, et al. Should We Use Hyperbaric Oxygen for Carbon Monoxide Poisoning Management? A Network Meta-Analysis of Randomized Controlled Trials. *Healthcare (Basel)*. 2022;10:1311.

26. Lin CH, Su WH, Chen YC, et al. Treatment with normobaric or hyperbaric oxygen and its effect on neuropsychometric dysfunction after carbon monoxide poisoning: A systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2018;97:e12456.

27. Wang W, Cheng J, Zhang J, Wang K. Effect of Hyperbaric Oxygen on Neurologic Sequelae and All-Cause Mortality in Patients with Carbon Monoxide Poisoning: A Meta-Analysis of Randomized Controlled Trials. *Med Sci Monit*. 2019;25:7684-7693.

28. Thom SR. Functional inhibition of leukocyte B2 integrins by hyperbaric oxygen in carbon monoxide-mediated brain injury in rats. *Toxicology and applied pharmacology*. 1993;123:248-256.

29. Lee Y, Cha YS, Kim SH, et al. Effect of Hyperbaric Oxygen Therapy Initiation Time in Acute Carbon Monoxide Poisoning. *Crit Care Med*. 2021;49:e910–e919.

30. Choi S, Nah S, Han S. Correlation between time to hyperbaric oxygen therapy and delayed neurological sequelae in acute carbon monoxide poisoning patients. *Diagnostics*. 2024;14:186.

31. Rose JJ, Zhang MS, Pan J, et al. Heart-Brain Score: the development and validation of a simple mortality prediction score for carbon monoxide poisoning utilizing deep learning. *Clin Toxicol (Phila)*. 2023;61:492-499.

32. Buckley NA, Juurlink DN, Isbister G, et al. Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev*. 2011;(13):CD002041.

33. Sethuraman K, Thom SR. Hyperbaric oxygen should be used for carbon monoxide poisoning. *Br J Clin Pharmacol.* 2023;89:939-941.

34. Juurlink DN. Hyperbaric oxygen should not be used routinely for carbon monoxide poisoning. *Br J Clin Pharmacol*. 2023;89:942-945.

35. Freytag DL, Schiefer JL, Beier JP, Grieb G. Hyperbaric oxygen treatment in carbon monoxide poisoning - Does it really matter? *Burns*. 2023;49:1783-1787.

36. Paganini M, Thom SR. Editorial: Carbon monoxide poisoning: updates on prevention, diagnosis, and treatment. *Front Med (Lausanne)*. 2024;11:1411547.

37. Chiew AL, Buckley NA. Carbon monoxide poisoning in the 21st century. *Crit Care*. 2014;221.

38. Ducasse JL, Celsis P, Marc-Vergnes JP. Non-comatose patients with acute carbon monoxide poisoning: Hyperbaric or normobaric oxygenation? *Undersea Hyperb. Med*. 1995;22:9-15.

39. Annane D, Chevret S, Jars-Guincestre C, et al. Prognostic factors in unintentional mild carbon monoxide poisoning. *Intensive Care Med*. 2001;27:1776-1781.

40. Hampson NB, Dunford RG, Ross, DE, et al. A prospective, randomized clinical trial comparing two hyperbaric treatment protocols for carbon monoxide poisoning. *Undersea Hyperb Med*. 2006;33:27-32.

41. Mathieu D, Wattel F, Mathieu-Nolf M, et al. Randomized prospective study comparing the effect of HBO versus 12 hours of NBO in non comatose CO poisoned patients: results of the interim analysis [abstract]. 1996. Undersea and Hyperbaric Medical Society Annual Meeting Abstracts. Available at: https://www.uhms.org/uhm-search/uhm-journal-volume-23/supplement-1996/supplement-1996.html. Accessed July 26, 2024.

Appendix E1. Literature classification schema.*

Design/ Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

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

Appendix E2. Approach to downgrading strength of evidence.

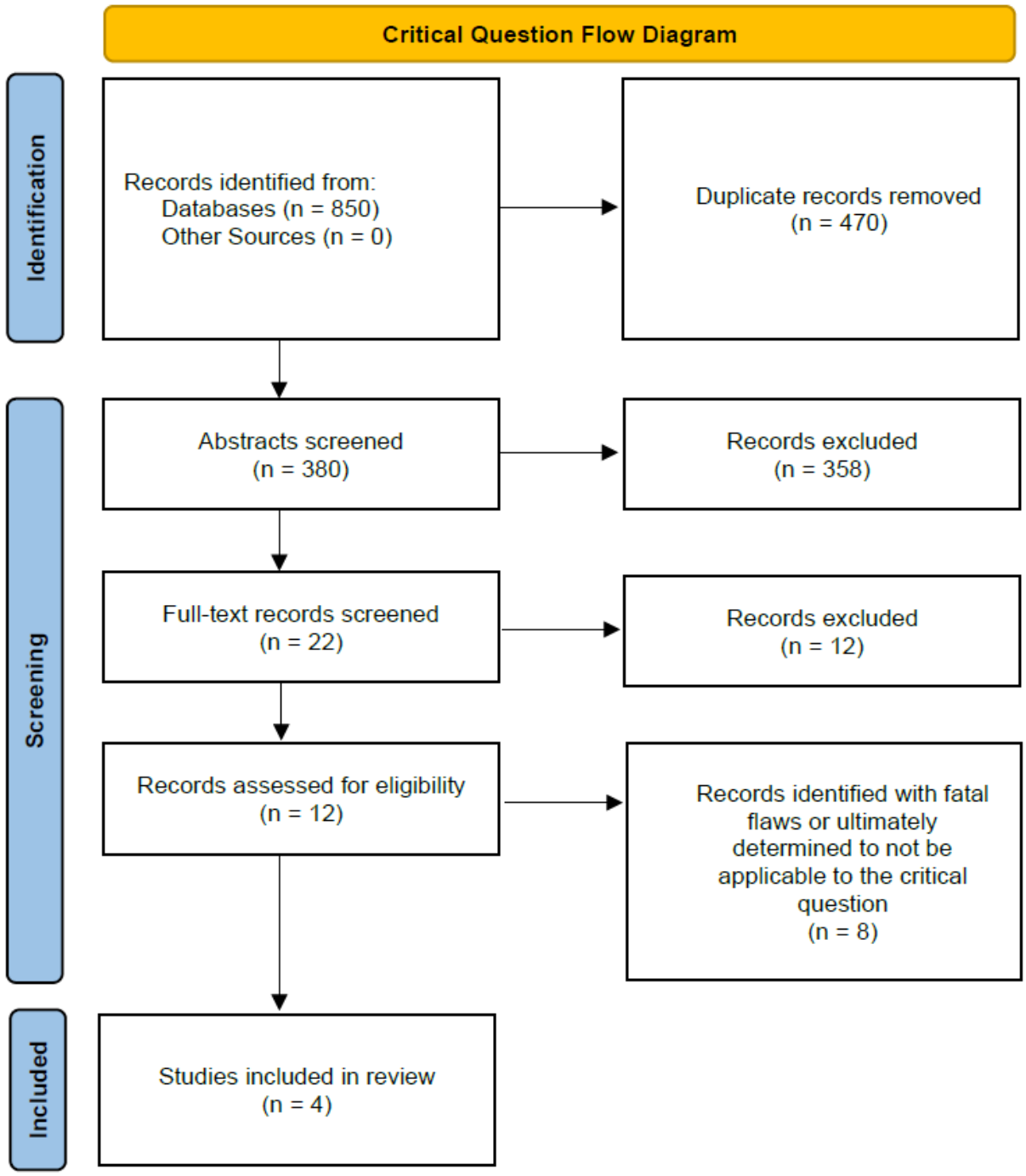
	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix E3. Likelihood ratios and number needed to treat.*

LR (+)	LR (–)	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Appendix E4. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagrams.[23]



Appendix E5. Literature Searches

Search Date	Database	Search Strings	Filters
8/26/2022 and 4/12/2024	PubMed	((carbon monoxide poisoning[tiab]) OR (carbon monoxide intoxication[tiab]) OR (Carbon Monoxide Poisoning[Mesh])) AND ((hyperbaric oxygenation[tiab]) OR (hyperbaric oxygen therap*) OR (Hyperbaric Oxygenation[Mesh]) OR (normobaric oxygen therap*[tiab]))	2015-Current
8/26/2022 and 4/12/2024	Scopus	TITLE-ABS-KEY ("carbon monoxide poisoning" OR "carbon monoxide intoxication") AND TITLE-ABS-KEY ("hyperbaric oxygen" OR "hyperbaric oxygen therap*" OR "normobaric oxygen therap*")	2015-Current
8/26/2022 and 4/12/2024	Embase	('carbon monoxide poisoning':ti,ab,kw OR 'carbon monoxide intoxication':de,ti,ab,kw) AND ('hyperbaric oxygenation':ti,ab,kw OR 'hyperbaric oxygen therap*':de,ti,ab,kw)	2015-Current
8/26/2022 and 4/12/2024	Web of Science	TS=("carbon monoxide poisoning" OR "carbon monoxide intoxication") AND TS=("hyperbaric oxygen" OR "hyperbaric oxygen therap*" OR "normobaric oxygen therap*")	2015-Current
8/26/2022 and 4/12/2024	Cochrane Library	("carbon monoxide poisoning":ti,ab,kw OR "carbon monoxide intoxication":ti,ab,kw) AND ("hyperbaric oxygenation":ti,ab,kw OR "hyperbaric oxygen therap*":ti,ab,kw)	2015-Current

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Nakajima et al[24] (2020)	III	Analysis of Japanese administrative database including data from >1,000 acute care hospitals and approximately 90% of all tertiary care emergency hospitals in the country; the database includes data on level of alertness and ADLs at discharge	Included patients had a main diagnosis of carbon monoxide poisoning and were discharged between April 2010 and March 2017; patients were excluded for cardiac arrest within 1 day of admission, discharge within 1 day of admission, those who were readmitted to the hospital, those with a high burn index ≥10, and use of intra-aortic balloon pump or extracorporeal life support; patients who received HBO_2 within 1 day of hospital admission were compared to those who did not; the relevant outcomes for this analysis were a depressed mental status at hospital discharge, as reported using the Japanese Coma Score, a 4 level instrument (alert, not fully alert but awake without stimuli, arousable with stimulation, and coma) and decreased ADLs, as measured using the Barthel Index; a propensity score analysis was used to compare those who did and did not receive hyperbaric oxygen	4,068 propensity score matched patients provided data on depressed mental status at discharge; depressed mental status was less likely among patients who received HBO_2 (between group difference -2.3%, 95% CI -3.8% to -0.9%, *P*=.002, NNT=42); 3,729 propensity score matched patients provided data on reduced ADLs at discharge; reduced ADLs at discharge was less likely among patients who received HBO_2 (between group difference -2.4%, 95% CI -4.7% to -0.2%, *P*=.035, NNT=41)	Starts as Design II for prognostic questions with one level downgrade for unblinded and unreliable measurement of outcomes; propensity score matching was used to create similar comparison groups (HBO_2 versus no HBO_2) though this tool only accounts for known and measured confounders; protocols for HBO_2 were not standardized

500 **Evidentiary Table.**

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Ho et al[25] (2022)	III	Network meta-analysis (registered PROSPERO) 8 studies contributed (7 to meta-analysis and 1 to qualitative synthesis) of RCTs comparing HBO_2 versus NBO and 1 session versus 2 sessions HBO_2	Inclusion criteria: RCTs of HBO_2; outcomes analyzed: mortality, headache recovery, fatigue, memory impairment, and difficulty with concentration; excluded non-RCTs and gray literature without details of trial design; funnel plot and Egger's regression intercept used to assess publication bias	N=1,785 patients; 8 studies reported no difference in HBO_2 versus NBO and noted that 2 session HBO_2 fared worse than 1 session HBO_2 for fatigue RR 1.80 (95% CI 1.01 to 3.19) and impaired concentration RR 1.85 (95% CI 1.19 to 2.89); 7 of 8 studies were at high risk for bias for participant and study personnel blinding, but 5 of 8 studies were at low risk for bias for sequence generation, allocation concealment, and selective reporting	Starts as Design I, but quality of individual studies not adequately described; 7 of 8 studies at high risk for bias due to participant and personnel blinding with no sensitivity analysis or regression analysis to account for it; though memory and concentration are measures of neurocognitive outcome, mortality and headache are not

501

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Lin et al[26] (2018)	III	Meta-analysis of RCT's comparing the effects of NBO to HBO_2 on neuropsychiatric outcomes	Inclusion criteria: RCTs of HBO_2; outcomes of headache recovery, fatigue, memory impairment, and difficulty with concentration; excluded non-RCT; funnel plot and Egger's regression intercept used to assess publication bias	Studies included were 6 RCTs published between 1989 and 2010; reported differences between HBO_2 and NBO for neuropsychiatric outcomes (16.2% versus 16.5%; RR 0.83; 95% CI 0.38 to 1.80), memory impairment (18.2% versus 23.8%; RR 0.80; 95% CI 0.43 to 1.49), difficulty concentrating (15.0% vs 18.4%; RR 0.86; 95% CI 0.55 to 1.34), and disturbed sleep (14.7% versus 16.2%, RR 0.91; 95% CI 0.59 to 1.39); for delayed sequelae delayed neurological sequelae (25% versus 31.1%; RR 0.35; 95% CI 0.02 to 5.97)	Starts as a Design 1; however, there was a high degree of heterogeneity and the studies demonstrated conflicting results; furthermore, the included studies have methodologic flaws; the primary methodologic flaw was lack of blinding; 3 studies it was unclear if there was any blinding at all; 3 studies were only single blinded; of the double blinded studies; 1 had a 38% loss to follow up; these issues are major methodologic limitations which reduced the quality assessment of the manuscript to a grade of III

504 **Evidentiary Table (continued).**

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Wang et al[27] (2019)	III	Meta-analysis of 7 RCTs comparing HBO_2 versus NBO and 1 session versus 2 session HBO_2; follow-up duration ranged from 21 days to 6 weeks; 26 to 575 patients were included in each trial (wide range); Jadad scale used to evaluate the quality, based on randomization, blinding, loss to follow-up, and the use of intention-to-treat analysis; heterogeneity - assessed using I^2 and Q statistics; publication bias assessed using funnel plots and Egger's regression intercept	Inclusion criteria: RCTs where outcomes were complete recovery, moderate sequelae, severe sequelae, all-cause death, asthenia, headache, memory impairment, disturbed sleep, difficulty in concentrating, visual disturbances, behavioral impairment, resumption of former activity, and neuropsychologic subset scores (including block design, trail making, digit span and digit symbol)	N=2,023 patients; 7 studies no significant difference between HBO2 versus NBO for: full recovery, moderate sequelae, severe sequelae, all-cause death, asthenia, headache memory impairment, disturbed sleep, difficulty in concentrating, visual disturbances, behavioral impairment, or resumption of former activity; neuropsychologic scores: block design weighted mean difference 3.95, 95% CI 2.99 to 4.9; trail making weighted mean difference 3.03, 95% CI 1.1 to 4.96, but no significant difference for digit span or digit symbol	Starts as Design I, large variation from 26 to 575 patients; outcomes were assessed in a relatively short timeframe (21 days to 6 weeks) when neurocognitive outcomes may not be apparent; normobaric group also includes high flow and oxygen mask, not just room air or simple nasal cannula; visual disturbance and behavioral impairment were too heterogeneous to combine (but they did); Jadad scale (0 to 5) is simplistic, may have inter-rater reliability issues and is based on blinding, randomization, and withdrawals/loss-to-follow-up, but not allocation concealment, which Cochrane views as critical to assess bias

ADL, activities of daily living; *CI*, confidence interval; *HBO_2*, hyperbaric oxygen; *NBO*, normobaric oxygen therapy; *NNT*, number needed to treat; *RCT*, randomized controlled trial; *RR*, risk ratio.