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

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ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses key issues 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 questions: 1) In emergency department patients with suspected acute carbon monoxide poisoning, can noninvasive carboxyhemoglobin measurement be used to accurately diagnose carbon monoxide toxicity? 2) In emergency department patients diagnosed with acute carbon monoxide poisoning, does hyperbaric oxygen therapy as compared with normobaric oxygen therapy improve long-term neurocognitive outcomes? 3) In emergency department patients diagnosed with acute carbon monoxide poisoning, can cardiac testing be used to predict morbidity or mortality? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

There are approximately 50,000 emergency department (ED) visits per year as a result of carbon monoxide (CO) poisoning.[1] Although many of these are nonfatal exposures with various degrees of toxicity, an estimated 1,000 to 2,000 patients a year die from severe toxicity.[1] However, given that CO is a colorless, odorless gas often with nonspecific toxicologic symptoms, these numbers are likely skewed by misdiagnosis. Thus, the true morbidity and mortality rates are probably considerably higher.[2,3]

As discussed in the 2008 published American College of Emergency Physicians (ACEP) clinical policy, "Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department with Acute Carbon Monoxide Poisoning,"[4] the mechanism of toxicity is known to be multifactorial, resulting from impaired oxygen delivery to highly metabolic tissues (eg, brain, heart), induced altered function of critical proteins (eg, myoglobin, mitochondrial cytochrome oxidase), toxic free radical formation, and other less well understood actions.[4,5]

Acute poisoning has an extremely varied presentation, from minimal symptomatology to unresponsiveness, hypotension, severe acidemia, or acute respiratory failure. Tissues with high metabolic needs are particularly at risk for dysfunction and injury. Classic presentations involve vague complaints of headache, dizziness, nausea, vomiting, shortness of breath, and/or chest pain.[6] Beyond acute toxicity, CO poisoning is known to be associated with longer-term morbidity and mortality. Neurologic sequelae (either persistent from the time of exposure or delayed in onset by 2 to 21 days) have been described in 12% to 68% of poisoned patients.[7-13] These sequelae tend to be typified by memory loss, impaired concentration or language, changes in affect such as depression, or parkinsonism and can spontaneously resolve or result in lifelong disability. However, virtually any neurologic abnormality can result from severe CO poisoning. Furthermore, poisoned patients have been shown to have up to a 3-fold increase in mortality compared with matched, unexposed individuals at a median follow-up of 7.6 years after their exposure.[14]

CO binds hemoglobin with an affinity approximately 220 times that of oxygen, which results in an elimination half-life in the body of 4 to 5 hours in the absence of therapy.[15] Oxygen therapy, whether administered normobarically by high-flow nonrebreathing face mask or hyperbarically by high-pressure chamber, has been shown to decrease the elimination half-life of CO to 85 minutes (range, 26 to 148 minutes)[16] and 20 minutes, respectively.[16,17] Considerable attention has been paid in the literature to the role of hyperbaric oxygen (HBO$_2$) over normobaric oxygen as a potentially beneficial therapeutic option for acute toxicity and as a means of reducing long-term sequelae; despite this, the role of HBO$_2$ remains controversial.[4,18]

The 2008 ACEP clinical policy[4] addressed critical questions about the role of HBO$_2$ therapy and concluded that although HBO$_2$ is a therapeutic option for CO-poisoned patients, its use cannot be mandated. Furthermore, at the time, no clinical variables seemed to identify poisoned patients for whom HBO$_2$ was most likely to provide benefit. Given the continued controversy surrounding this topic, this policy's revision will revisit the role of HBO$_2$, reviewing the literature published since our last recommendations. Additionally, this revision will address the role of noninvasive carboxyhemoglobin (COHb) measurement (pulse CO oximetry) to diagnose CO toxicity in patients with suspected acute CO poisoning and the role of cardiac testing to predict morbidity and mortality.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature and was based on a systematic review of the literature. Searches of MEDLINE, MEDLINE InProcess, Scopus, Web of Science, and the Cochrane Database were performed. All searches were

limited to English-language sources, human studies, and adults. 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.

This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; when literature was not available, consensus of emergency physicians was used. Expert review comments were received from emergency physicians, hyperbaric medicine specialists, medical toxicologists, the Council of Undersea and Hyperbaric Medicine Fellowship Directors, and the ACEP Undersea and Hyperbaric Medicine Section leadership. The draft was available for comments during a 60-day open-comment period, with notices of the comment period sent in e-mails, published in *EM Today*, and posted on the ACEP Web site. The responses were used to further refine and enhance this policy; however, the responses do not imply endorsement of this clinical policy. Clinical policies are scheduled for review and considered for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

Assessment of Classes of Evidence

All articles used in the formulation of this clinical policy were graded by at least 2 methodologists and assigned a Class of Evidence. Each article was assigned a design class, with design 1 representing the strongest study design and subsequent design classes (eg, design 2, design 3) representing respectively weaker study designs for therapeutic, diagnostic, or prognostic clinical reports, or meta-analyses (Appendix A). Articles were then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, and generalizability. Using a predetermined process related to the study's design, methodological quality, and applicability to the critical question, articles received a final Class of Evidence grade (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or that were ultimately not applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. Grading was done with respect to the specific critical questions; thus, the level of

evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive different Classes of Evidence as different critical questions were answered from the same study. Question-specific Classes of Evidence grading may be found in the Evidentiary Table (available online at www.annemergmed.com).

Translation of Classes of Evidence to Recommendation Levels

Strength of recommendations regarding each critical question were made by subcommittee members using results from strength of evidence grading, expert opinion, and consensus among subcommittee members according to the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (eg, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (eg, based on evidence from 1 or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of any 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 heterogeneity of results, uncertainty about effect magnitude and consequences, and publication bias, among others, might lead to such a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat [NNT]) are presented to help the reader better understand how the results may be applied to the individual patient. For a definition of these statistical concepts, see Appendix C.

This policy is not intended to be a complete manual on the evaluation and management of patients with suspected or diagnosed CO poisoning but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine.

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 adequate empirical data 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.

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 defines for the physician those strategies for which medical literature exists to provide support for answers to the critical questions addressed in this 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.

For potential benefits and harms of implementing the recommendations, see Appendix D.

CRITICAL QUESTIONS

1. **In ED patients with suspected acute CO poisoning, can noninvasive COHb measurement be used to accurately diagnose CO toxicity?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Do not use noninvasive COHb measurement (pulse CO oximetry) to diagnose CO toxicity in patients with suspected acute CO poisoning.

Level C recommendations. None specified.

Key words/phrases for literature searches: carbon monoxide poisoning, carboxyhemoglobin, blood gas analysis, troponin, oximetry, hospital emergency service, emergency room, emergency department, and variations and combinations of the key words/phrases. Searches included January 1, 1980, through the search date of July 21, 2015.

Study Selection: One hundred thirty-eight articles were identified in the search; 13 articles were selected from the search results for further review, with 5 studies included for this critical question.

In patients with suspected CO poisoning, CO exposure has traditionally been measured by co-oximeter analysis of venous or arterial blood for COHb levels. Nontoxic levels vary in the general population, but nonsmokers typically have a blood COHb level of 3% or less, whereas individuals who smoke tobacco have levels up to 10%. In 2005, the Food and Drug Administration first approved a noninvasive pulse CO-oximeter to measure CO saturation (analogous to a fingertip pulse oximeter commonly used for measuring and monitoring oxygen saturation).[19] A pulse CO-oximeter has several potential advantages over traditional blood COHb analysis: pulse CO oximetry is fast, is noninvasive, is capable of continuous measurement, and can assess multiple patients with little additional cost. However, because prompt treatment of CO can prevent disability, a diagnostic test without high sensitivity would not routinely be helpful. As a point of emphasis, the clinical question addressed here, the ability of noninvasive CO oximetry to accurately *diagnose* suspected CO exposure in ED patients, is a separate clinical question from the utility of noninvasive CO oximetry to *screen* for CO poisoning in undifferentiated populations of ED patients or in the out-of-hospital setting; for this latter use, a device with a lower sensitivity may still be of benefit. In reviewing the literature to determine the accuracy of noninvasive pulse CO oximetry, 1 Class II[20] and 4 Class III[19,21-23] studies were identified.

In the only Class II study included, Touger et al[20] enrolled 120 ED patients with suspected CO poisoning, each receiving concurrent conventional blood COHb testing and noninvasive COHb testing with a pulse CO-oximeter. Of these subjects, 23 met the authors' definition of CO toxicity (COHb level $\geq$15%) on blood testing. The mean difference between blood and noninvasive COHb values was 1.4% (95% confidence interval [CI] 0.2% to 2.6%); however, in 33.3% of patients, the agreement between the 2 tests exceeded the authors' predefined acceptable range ($\pm$5% COHb). The noninvasive test had a sensitivity of 48% (95% CI 27% to 69%) and a specificity of 99% (95% CI 94% to 100%), yielding a positive LR of 48 (95% CI 4.5 to undefined) and negative LR of 0.5 (95% CI 0.3 to 1.0) for detecting a COHb level greater than 15%. This study had several important limitations, including a low incidence of actual CO poisoning in the study population, unclear reporting of the exact timing of COHb testing, and no identification of smoking status, which can confound the diagnosis of CO poisoning.

Two Class III studies[19,21] were similarly designed to examine the diagnostic performance of CO oximetry. Sebbane et al[19] measured blood and noninvasive COHb levels in 93 patients in a single ED who had suspected CO toxicity. Although the mean difference in COHb between the 2 tests was small (-0.2% standard deviation [SD] 3.3; 95% limits of agreement -6.7, 6.3), the study had substantial limitations. Only 33% of patients received simultaneous testing, and noninvasive testing was performed before blood testing in 46% of the cohort (mean time difference=19 minutes) and after blood testing in the remaining 21% (mean time difference was not reported). Additionally, in the setting of asynchronous testing, the decision to perform the second test and thus enroll the patient in the study may have been influenced by the initial test result. In a smaller study, Coulange et al[21] included 12 patients with suspected CO poisoning and compared blood and noninvasive testing in each patient. The authors found a mean difference in COHb level of -1.5% (SD 2.5; 95% limits of agreement -6.4, 3.4). Together these 3 studies do not support the use of noninvasive testing to detect elevated COHb levels among patients with suspected CO poisoning.

Two additional Class III studies[22,23] explored noninvasive CO oximetry with convenience sampling of undifferentiated patients. A 2011 study by Roth et al[22] identified 1,578 patients with noninvasive CO oximetry screening tests who also had blood COHb testing within 60 minutes of the noninvasive measurement. Only 17 of 1,578 study patients received a diagnosis of CO poisoning (1.1%; 95% CI 0.6% to 1.7%), limiting the conclusions that can be drawn from this study. Noninvasive COHb readings in this cohort were 3% higher than blood COHb testing, and the limits of agreement between the 2 tests ranged from -3.6% to 9.5%. Finally, a Class III study by Weaver et al[23] measured simultaneous blood and noninvasive COHb levels in a convenience sample of 1,363 patients and identified CO poisoning in 4 patients (0.3%; 95% CI 0.1% to 0.7%). Although underpowered to provide meaningful data with respect to the accuracy of noninvasive testing for patients with suspected CO toxicity, the noninvasive testing underestimated COHb levels in each of the 4 patients identified as having CO poisoning. In 2 of these 4 cases, the affected patients had relatively lower blood COHb levels (8.7% and 8.4%), and noninvasive testing would not have supported the diagnosis of CO poisoning (noninvasive CO oximetry levels of 4% and 2%, respectively).

Future Research

First, if newer noninvasive devices are developed for the measurement of CO exposure, prospective ED-based studies should focus on patients with suspected acute CO poisoning and perform simultaneous comparison of these devices with conventional testing. Second, in the review of this literature, there were a number of clinical cases of occult CO poisoning identified with the use of noninvasive CO measurement. However, the clinical question addressed by our review involved the diagnostic accuracy of this device. Future studies, using either new data or a systematic review of previous data, should investigate the utility of noninvasive devices to screen for elevated COHb in undifferentiated cohorts of ED patients, especially in unsuspected poisoning.

2. **In ED patients diagnosed with acute CO poisoning, does HBO₂ therapy as compared with normobaric oxygen therapy improve long-term neurocognitive outcomes?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Emergency physicians should use HBO₂ therapy or high-flow normobaric therapy for acute CO-poisoned patients. It remains unclear whether HBO₂ therapy is superior to normobaric oxygen therapy for improving long-term neurocognitive outcomes.

Level C recommendations. None specified.

Key words/phrases for literature searches: carbon monoxide poisoning, hyperbaric oxygenation, normobaric oxygen therapy, treatment outcome, risk assessment, prognosis, neurologic sequelae, cognition disorders, neurotoxicity, and variations and combinations of the key words/phrases. Searches included January 1, 2006, through the search date of July 21, 2015.

Study Selection: Two hundred sixteen articles were identified in the search; 43 articles were selected from the search results for further review, with 7 studies included for this critical question.

Long-term neurocognitive deficits as a result of CO poisoning, generally referred to as neurologic sequelae, are some of the most feared clinical outcomes of acute CO toxicity. HBO₂ markedly reduces the half-life of COHb and has been postulated to improve neurologic outcomes after severe CO poisoning.[24] There are competing theories from a molecular physiology standpoint about the potential benefit of HBO₂ in reducing lipid peroxidation and the potential risk of cell death from oxygen free radical formation.[25] Despite a significant body of literature on the use of HBO₂ in prevention of neurologic sequelae, its benefits and use in acute CO poisoning remain controversial. For this critical question, all graded medical literature from the 2008 ACEP clinical policy was again reviewed. In addition, an updated literature search was performed. In total, 2 meta-analyses (1 Class II[26] and 1

Class III[27]) and 5 original research articles (3 Class II[7,10,11] and 2 Class III[28,29]) are used to support the recommendation for this critical question. Four of these studies[7,10,11,29] were extensively discussed in the previously published clinical policy.[4]

In 2011, a Class III Cochrane Database meta-analysis of 6 studies investigated the benefit of HBO_2 for the treatment of acute CO poisoning.[27] This review compared trials with an HBO_2 and normobaric arm, assessing neurologic sequelae as the primary outcome. In a total of 1,361 patients across all studies, the odds ratio (OR) for developing neurologic sequelae among patients receiving HBO_2 was 0.78 (95% CI 0.54 to 1.12). The authors noted significant statistical and methodological heterogeneity across the trials and identified biases that may have influenced results in trials with either positive or negative results. One of the positive-result trials did not adjust for multiple hypothesis testing[11] and another may have introduced bias during the trial by changing 1 of their primary endpoints.[7] Of the trials with negative results, 2 were limited by exclusion of severely poisoned patients[28,29] and 1 by a significant lost-to-follow-up rate.[10] These findings were nearly identical to a 2005 Class II meta-analysis[26] by the same lead author and have considerable overlap with respect to the included studies and data. In this earlier systematic review,[26] 6 studies were included, with a total of 1,479 randomized patients. The pooled OR for developing neurologic sequelae across groups was 0.77 (95% CI 0.51 to 1.14). The quality of the articles was carefully evaluated, and the statistical analyses were appropriate, using a random-effects model and sensitivity analysis. Both of these meta-analyses[26,27] included individual studies determined to have major methodological flaws by our Class of Evidence grading process (ie, Class X).[13,30] Both of these meta-analyses concluded that it is unclear whether the addition of HBO_2 improves long-term neurocognitive outcome over treatment with normobaric oxygen.

Each of the remaining clinical trials included in this review[7,10,11,28,29] was included in at least 1 of the above meta-analyses. Overall, these 5 original research studies[7,10,11,28,29] demonstrated inconsistent support for the use of HBO_2 for the treatment of acute CO poisoning. Three studies (1 Class II[10] and 2 Class III[28,29]) found no benefit, whereas 2 Class II studies[7,11] reported benefits of HBO_2 therapy for neurocognitive outcomes.

Studies Reporting No Benefit

In a Class II study, Scheinkestel et al[10] randomized 191 patients to HBO_2 or normobaric oxygen with sham treatment and found no statistical difference in neurologic sequelae at 1-month follow-up. A large number of patients (73%) had severe symptoms and many of the patients received multiple (>3) HBO_2 treatments. A significant limitation was the loss of 54% of subjects to follow-up. In addition, many of the patients had a delay to HBO_2 therapy in relation to CO exposure. All patients referred for CO poisoning were eligible regardless of when their CO exposure occurred (mean delay to the administration of HBO_2 therapy=7.1 hours).

Most recently, a 2011 Class III study, Annane et al[28] randomized 385 acutely poisoned CO patients into 2 trials (A and B) according to whether coma was present at the patient's initial presentation. The primary outcome for both trials was neurologic sequelae as determined by patient questionnaire and physical examination, not formal neuropsychiatric testing. The treatment intervention varied by trial. In trial A (n=179), patients without coma were randomized to either normobaric oxygen or normobaric oxygen plus 1 session of HBO_2. In trial B (n=206), patients with coma were randomized to either normobaric oxygen plus 1 HBO_2 session or normobaric oxygen plus 2 HBO_2 sessions. At interim analysis, trial A showed no benefit with HBO_2 therapy in terms of neurologic sequelae (58% versus 61%; unadjusted OR=0.90; 95% CI 0.47 to 1.71). Trial B showed a trend toward worse outcomes in the group randomized to receive 2 HBO_2 therapy sessions (47% versus 68%; unadjusted OR=0.42; 95% CI 0.23 to 0.79; number needed to harm=5). The study was stopped early, given the concerns for patient harm.

Last, an older Class III study by Raphael et al[29] randomized 629 acutely CO poisoned patients by presence or absence of coma. Noncomatose patients (n=343) were assigned to receive either HBO_2 or normobaric oxygen, whereas comatose patients (n=286) were randomized to 1 or 2 HBO_2 therapy sessions. In both study arms, the recovery rates were no different (arm A: 66% control versus 68% HBO_2 therapy; arm B: 52% control versus 54% HBO_2 therapy); however, the study may have been underpowered to detect a true difference (P=.75 for both arms).

Two additional methodological limitations exist for these studies showing no HBO_2 benefit.[10,28,29] First, all 3 studies included patients receiving therapy that was initiated up to 12 hours after their CO exposure. Research suggests the beneficial effects of HBO_2 therapy may diminish significantly with delay to therapy of more than 6 hours from time of exposure.[10,11,31,32] Second, the dose of HBO_2 therapy used in 2 of the studies may have been suboptimal.[28,29] The studies by Raphael et al[29] and Annane et al[28] used 2 atmospheres absolute (ATA) of pressure

during HBO$_2$ therapy, whereas studies demonstrating benefit have used 2.5 to 3 ATA. Concern has been raised that this dose difference may account for the variability in the point estimates for treatment effect.[33]

Studies Reporting Benefit:

In a 2002 Class II study, Weaver et al[7] reported improved outcomes in patients treated with HBO$_2$ in a blinded, single-center, randomized clinical trial. Patients in the treatment group were exposed to 3 HBO$_2$ sessions. The first session used 3 ATA for 1 hour followed by 2 ATA for 1 hour; the remaining sessions used 2 ATA. This study also included patients with HBO$_2$ therapy initiated up to 24 hours after CO exposure. At 6 weeks after poisoning, HBO$_2$ was associated with a 21% (95% CI 6% to 34%) absolute reduction in the rate of neurologic sequelae (46% versus 25%; unadjusted OR=0.39; 95% CI 0.20 to 0.78; NNT=5). Follow-up was excellent in each arm. The normobaric oxygen group received only 1 sham treatment, whereas the HBO$_2$ arm received 3 HBO$_2$ treatments. The major criticism of this study is that during enrollment, a disproportionate number of patients were randomized with cerebellar dysfunction to the control group (15% control versus 4% HBO$_2$ therapy).

The other study reporting benefit for HBO$_2$ was a Class II study by Thom et al.[11] This study was a smaller trial (n=60) of patients who received 1 session of HBO$_2$ versus 100% normobaric oxygen by face mask. The HBO$_2$ protocol was 2.8 ATA for 30 minutes followed by 2 ATA for 90 minutes. HBO$_2$ was associated with a 23% (95% CI 8% to 38%) absolute reduction in the rate of neurologic sequelae (23% versus 0%; unadjusted OR=0.06; 95% CI 0 to 1.03; NNT=4.3). This is the only study included in our systematic review in which all of the subjects presented within 6 hours of CO exposure. However, patients with loss of consciousness were excluded, so the cohort was both smaller and less severely poisoned compared with those in other trials. In addition, the outcome assessment for neurologic sequelae was made by nonblinded clinicians.

The current trials vary widely in their interpretation of the utility of HBO$_2$ for prevention of neurologic sequelae. The lack of standardization across trials (eg, severity of poisoning, timing of initial HBO$_2$ therapy delivery [<6 versus >6 hours], HBO$_2$ therapy dose [2 versus 2.5 to 3 ATA], definitions of neurologic outcomes, and follow-up windows) makes drawing any definitive conclusions about the benefit or harm of using HBO$_2$ therapy for the treatment of acute CO poisoning difficult. Although there are concerns of potential harm (eg, barotrauma, lack of access to immediate medical care while in the chamber,

long-distance transfers), it is difficult to determine from the existing data whether these harms outweigh the potential benefits of HBO$_2$.

Future Research:

Despite the existing literature on this topic, there are few well-designed clinical trials, and the results of these trials are not conclusive in regard to the efficacy of HBO$_2$ in preventing neurologic sequelae. An adequately powered multicenter randomized controlled trial with well-defined inclusion criteria, standardized treatment protocols, minimal delay in administration of HBO$_2$ therapy, and adequate retention for long-term follow-up is needed to definitively answer the question. Ideally, further research should include groups long thought to be at greater risk for neurologic sequelae, such as children and fetuses.

3. **In ED patients diagnosed with acute CO poisoning, can cardiac testing be used to predict morbidity or mortality?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In ED patients with moderate to severe CO poisoning, obtain an ECG and cardiac biomarker levels to identify acute myocardial injury, which can predict poor outcome.

Level C recommendations. None specified.

Key words/phrases for literature searches: carbon monoxide poisoning, acute carbon monoxide poisoning, heart function tests, diagnostic imaging, cardiac testing, echocardiography, radionuclide imaging, brain natriuretic peptide, creatine kinase, biological markers, myoglobin, troponin, tomography, survival or survival rate, prognosis, risk assessment, morbidity, mortality, and variations and combinations of the key words/phrases. Searches included January 1, 1980, through the search date of July 21, 2015.

Study Selection: Ninety-seven articles were identified in the search; 28 articles were selected from the search results for further review, with 2 studies included for this critical question.

CO is known to be cardiotoxic.[34] It is proposed that the gas binds to myoglobin and results in electrical, functional, and morphologic alterations of the heart, affecting patients with and without underlying cardiovascular disease. Toxicity likely occurs not only from direct tissue hypoxia but also because of changes and damage at a cellular level. Studies have shown that acute myocardial injury occurs in 37% to 53% of patients with acute CO poisoning.[14,35,36] Typically, this injury is determined by abnormal laboratory test results (eg, elevated creatine kinase or troponin level) or

ischemic electrocardiographic changes; some authors have specifically examined the T wave as an indicator.[37] It has been proposed that identifying cardiotoxicity might inform health care providers making treatment and follow-up decisions or considering an exposed patient's risk for morbidity and mortality; as such, authors have investigated whether cardiac testing can predict morbidity or mortality.[14,36,37]

In 2006, Henry et al (Class II)[14] published the only prospective study examining long-term mortality in patients poisoned with CO who demonstrated acute myocardial injury at the time of their exposure. In this study, 230 patients with moderate to severe poisoning were followed for a median of 7.6 years. Baseline data, including but not limited to the severity of presentation, hospital length of stay, ischemic changes on ECG, and presenting cardiac enzyme levels, were collected and compared with mortality rates to determine independent predictors of long-term mortality in CO-poisoned patients. Mortality rates were compared with those from matched national mortality data. Enrolled subjects had a mean age of 47 years and a low incidence of comorbidities. Despite a selection bias toward more severely poisoned patients (ie, 100% received HBO_2 therapy, 81% had transient or persistent loss of consciousness, 52% were intubated, 12% required lidocaine or nitroglycerine, and 6% required pharmacologic blood pressure support), only 5% (12 patients) experienced inhospital mortality; yet 24% died in the out-of-hospital setting during follow-up, which is 3 times the rate of matched national mortality data for unexposed patients. Among subjects with myocardial injury on enrollment, 38% died during follow-up compared with 15% of patients without myocardial injury. Equally notable was that the percentage of deaths from cardiac causes was significantly different (44% versus 18%). Multivariable analysis showed acute myocardial injury (adjusted hazard ratio=2.1; 95% CI 1.2 to 3.7) to be independently predictive of mortality even after a supplementary propensity score analysis (adjusted hazard ratio=1.90; 95% CI 1.02 to 3.37) controlled for baseline characteristics (eg, age, sex, diabetes, hypertension, tobacco use, previous cardiac disease). Thus, CO-poisoned patients with acute cardiac injury on presentation had significantly higher long-term mortality and were more likely to have their mortality attributed to a cardiac cause.

In 2015, Shen et al[36] (Class III) also found acute myocardial injury to be the only independent predictor of poor outcome (OR=2.8; 95% CI 1.2 to 6.5) in 148 intentionally poisoned patients with acute respiratory failure who underwent HBO_2 therapy. Poor outcome was defined as inhospital mortality or neurologic sequelae.

Other variables associated with poor outcome but not independently predictive included hypotension, WBC count, aspartate amino transferase levels, blood urea nitrogen level, and time from ED arrival to initiation of treatment.

Future Research

Future research addressing acute myocardial injury from CO poisoning should focus on the role of cardiac testing and subsequent intervention in a less severely poisoned population. Additionally, studies could investigate the role of more aggressive initial and long-term cardiac management in patients known to be at higher risk for morbidity and mortality after CO toxicity.

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 impact the specific aspect of disease addressed in the critical question.

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Appendix A. 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 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

Appendix C. 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 D. Potential benefits and harms of implementing the recommendations.

1. **In ED patients with suspected acute CO poisoning, can noninvasive COHb measurement be used to accurately diagnose CO toxicity?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Do not use noninvasive COHb measurement (pulse CO oximetry) to diagnose CO toxicity in patients with suspected acute CO poisoning.

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations: In patients with suspected CO poisoning, implementing this recommendation can help emergency physicians to reduce diagnostic error caused by relying on the use of noninvasive COHb testing.

Potential Harm of Implementing the Recommendations: The subcommittee identified no potential harms of implementing this recommendation.

2. **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 specified.

Level B recommendations. Emergency physicians should use HBO_2 therapy or high-flow normobaric therapy for acute CO-poisoned patients. It remains unclear whether HBO_2 therapy is superior to normobaric oxygen therapy for improving long-term neurocognitive outcomes.

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations: Given the inconclusiveness of the data (some trials showing benefit, some showing no benefit or harm), this recommendation may help provide support for emergency physicians who choose not to refer patients for HBO_2 therapy, especially when there are time, financial, or geographic constraints.

Potential Harm of Implementing the Recommendations: Based on review of the available research to date, the subcommittee identified no potential harms in implementing this recommendation.

3. **In ED patients diagnosed with acute CO poisoning, can cardiac testing be used to predict morbidity or mortality?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In ED patients with moderate to severe CO poisoning, obtain an ECG and cardiac biomarker levels to identify acute myocardial injury, which can predict poor outcome.

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations: The benefits of implementing this recommendation may include improved risk stratification and identification of CO-poisoned patients at significant risk for cardiac morbidity and mortality.

Potential Harm of Implementing the Recommendations: The identification of acute myocardial injury may result in unnecessary future cardiac testing and monitoring that may not improve patient-centered outcomes.

Evidentiary Table.

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Weaver et al[7] (2002)	II	Single referral center in Utah; randomized blinded controlled trial	All patients referred for CO poisoning; exclusions included pregnancy, children, delay (24 h or more) since exposure, moribund, or not consenting; block random allocation to HBO_2 (3 treatments with 6- to 12-h intervals) at 3, 2, and 2 atmospheres, respectively, vs NBO (sham treatment at 1 atmosphere); primary outcome: standardized neuropsychiatric testing at 6 wk	N=152 patients; 6-wk cognitive sequelae: 25% in HBO_2 vs 46% in NBO (P=.01); NNT=4.8; neurologic sequelae remained decreased in HBO_2 group during 12 mo; logistic regression adjusting for baseline cerebellar dysfunction difference maintained association between HBO_2 and outcome (OR=0.45; 95% CI 0.22 to 0.92; P=.03)	Lost to enrollment/declined to participate: 54%; lost to follow-up <10% in each arm; suicidal patients: 31%; mean time to treatment: 5.6 h; study used block randomization; imbalance in baseline characteristic of cerebellar function (15% in NBO vs 4% in HBO_2 groups); high percentage (54%) of eligible patients "declined" contributing to selection bias; control group with greater duration of CO exposure; subjective component to primary outcome contributing to detection bias; trial stopped early, after third interim analysis, for demonstrated efficacy
Scheinkestel et al[10] (1999)	II	Single quaternary care center in Austria; randomized unblinded controlled trial	All patients referred for CO poisoning; exclusions included pregnancy, children, burn victims, or not consenting; block random allocation to HBO_2 (3 treatments, once daily) vs NBO (sham treatment with 1 atmosphere); both groups with supplemental oxygen therapy between treatments; outcomes: standardized neuropsychiatric testing	N=191 patients (73% with severe CO poisoning); overall mortality=3%; prevalence of persistent neurologic sequelae=71% at discharge, 62% at follow-up; no significant differences from a battery of neuropsychiatric tests; subgroup analyses of patients with severe CO poisoning demonstrated possible poorer neuropsychiatric outcomes	Lost to enrollment: not stated; lost to follow-up: 54%; suicidal patients: 69%; mean time to treatment: 7.1 h; study used cluster randomization; reasonable balance in baseline characteristics between study groups, including severity of CO poisoning; a larger proportion of patients randomized to HBO_2 received >3 HBO_2 treatments (28% vs 15%); diminished generalizability because of high oxygen dose of control arm; treating clinicians were not blinded to allocation, which may have influenced overall care

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Thom et al[11] (1995)	II	Patients were referred from ED in their region; prospective randomized study, nonblinded without any allocation concealment	Inclusion criteria: history of acute exposure to combustion products, increased COHb, presence of symptoms consistent with CO poisoning; exclusion criteria: history of unconsciousness or cardiac compromise; patients randomly assigned to either HBO$_2$ at 2.8 ATA for 30 min and then 2.0 ATA for 90 min vs 100% NRB oxygen until all symptoms resolve; HBO$_2$ treatment started within 6 h of CO exposure; neurologic screening battery of 6 subtests (general orientation, digit span, trail making, digit symbol, aphasia screen, and block design) conducted after treatment on all and repeated after 3 to 4 wk if symptomatic; neither patients nor investigators blinded to treatment; outcome: DNS	N=60; 7/30 (23%) develop DNS after ambient pressure oxygen vs 0/30 in HBO$_2$ group; mean time to initiation of HBO$_2$=2+/-2 h; mean COHb=20 for normobaric oxygen vs 24 for HBO$_2$; DNS occurred mean 6 days +/-1 day after poisoning and persisted for 41 days +/- 8 days; 4 wk after poisoning, ambient oxygen group that had not sustained DNS exhibited worse mean scores in trail making when compared with age- and education-matched HBO$_2$ and control groups	Lost to enrollment: 4%, lost to follow-up: 8%, suicidal patients: not stated, mean time to treatment: 2 h, nonblinded and no allocation concealment; duration of exposure to CO may be a risk factor for DNS, and it is not clear if 1 group had a longer exposure (range 0 to more than 2 days); no sham therapy for NBO group; subjective component to primary outcome; unknown statistical significance of secondary outcome
Henry et al[14] (2006)	II	Academic medical center in Minnesota; prospective cohort study	Patients were included if they were >18 y and received hyperbaric oxygen therapy; patients were followed to determine whether they died after exposure to CO and whether there was a relationship between evidence of cardiac injury and death; propensity scoring was used to correct possible confounders for the probability of positive cardiac marker results; outcome: mortality	N=230 patients; inhospital mortality was 5% and out-of-hospital mortality was 24%; overall, among those with myocardial injury 38% died during follow-up compared with 15% of those without cardiac injury; on multivariable analysis myocardial injury was associated with subsequent death HR=2.1 (95% CI 1.2 to 3.7; P=.009) after adjustment with the propensity scoring myocardial injury remained predictive HR=1.90 (95% CI 1.02 to 3.37; P=.04)	There is a selection bias toward sicker patients because all of the patients in the study received hyperbaric oxygen; it is unclear what the proportions of patients with myocardial injury would be in those not treated or what the prognostic significance would be in that group

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Sebbane et al[19] (2013)	III	Single academic medical center; cross-sectional	Adult patients with suspected CO exposure; index test: SpCO; reference standard: COHb level	N=93; incidence of CO poisoning was 28%; median COHb was 5% (IQR 2,9), median SpCO was 4% (IQR 2.7,7.3); mean difference (COHb minus SpCO) was -0.2% (SD 3.3; 95% limits of agreement -6.7, 6.3)	Decision to obtain COHb may not have been independent of SpCO result because blood sampling in 46% of cases (tests performed simultaneously in 33%, COHb first in 21%); threshold values of SpCO to calculate sensitivity and specificity were determined post-hoc
Touger et al[20] (2010)	II	Urban Level I trauma and burn center with emergency hyperbaric oxygen chamber used for treatment of carbon monoxide poisoning; prospective cohort study	Adult and pediatric patients with suspected CO poisoning and who had arterial or venous blood COHb testing; measurement of RAD-57 Pulse CO-Oximeter was performed simultaneously with sampling of arterial or venous blood; Bland-Altman analysis used to assess bias; performance characteristic reported with CIs using COHb 15% as threshold for acute CO poisoning and ±5% as acceptable range; outcomes: percentage COHb level measured with RAD device and simultaneously sampled arterial or venous blood gas analysis	N=120, 23 with COHb ≥15%; mean difference between laboratory COHb values and RAD values was 1.4% (95% CI 0.2% to 2.6%); limits of agreement: -11.6% to 14.4% COHb; 33.3% of values exceeded ±5% range; performance characteristics: COHb 15% (95% CI); SN 48% (27% to 69%); SP 99% (94% to 100%); NPV 89% (81% to 94%); PPV 92% (62% to 100%)	Limited numbers of patients with CO poisoning at 15% COHb threshold for diagnosis; smokers were not identified; unclear reporting of the exact timing of COHb testing; not enough data to examine measurement differences in racial subgroups; no log transformation or normality assumption verification for Bland-Altman analysis
Coulange et al[21] (2008)	III	Single academic medical center; cross-sectional	Patients with suspected CO exposure; index test: SpCO; reference standard: COHb level	N=12; mean COHb was 13.9% (SD 8.3) and mean SpCO was 15% (SD 9); mean difference (COHb minus SpCO) was -1.5% (SD 2.5; 95% limits of agreement -6.4, 3.4)	Smokers excluded; study limited by small sample size

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Roth et al[22] (2011)	III	Urban academic medical center; Vienna, Austria; prospective cohort study	All patients who had either an arterial or venous blood gas test performed within 60 min of Masimo Radical 7 CO oximetry, which was used for pulse oximetry assessment for all patients during the study; Bland-Altman analysis used to assess bias—log-transformed, logistic regression for discrimination; outcomes: bias and precision of COHb oximetry compared with the criterion standard arterial or venous blood gas analysis	N=1,578, 17 (1.1%; 95% CI 0.6% to 1.7%) having CO poisoning; bias: 2.99% higher SpCO vs COHb, 1.50% smokers, 4.33% nonsmokers; limits of agreement: -3.55% to 9.53%, -4.30% to 7.30% smokers, -1.63% to 10.29% nonsmokers; performance characteristics: SpCO 6.6% (95% CI); SN 94 (71 to 100); SP 71 (75 to 79); PPV 4 (2 to 7); NPV 100 (98 to 100)	Limited numbers of patients with CO poisoning despite a generously low threshold for diagnosis; 31% of patients excluded because of VBG/ABG not tested or read after 60 min of initial reading
Weaver et al[23] (2013)	III	One Utah hospital ED; prospective convenience sample vs cross-sectional study performed in 2008	SpCO measured at same time as serum COHb; accuracy false positive defined by SpCO 3% greater than COHb; screening false positive defined by SpCO >6% with COHb ≤6% in a nonsmoker; accuracy false negative defined by SpCO 3% less than COHb; screening false negative defined by SpCO <6% with COHb ≥6% in a nonsmoker; outcome: false-positive rate in which blood COHb is criterion standard	N=1,363; primary outcome: only 4 had CO poisoning; 122 (9%) had accuracy false positive, 95 (7%) had screening false positive, whereas 247 (18%) had false negative; risk for false-positive SpCO=female and low perfusion index; methemoglobin, body temperature, smoking, and blood pressure influence SpCO accuracy; in the 4 patients with true CO poisoning, the SpCO underestimated COHb; when COHb was 35% and 27%, the SpCO was 31% and 17%; in 2 patients with COHb of 8.7% and 8.4%, the SpCO was 4% and 2% and would have missed the CO poisoning	Only 4 patients had CO poisoning; different monitors used; used statistical significance and forward stepwise regression for model selection; underpowered to detect false-negative range; too few subjects with elevated COHb to provide meaningful data for sensitivity and specificity
Buckley et al[26] (2005)	II	Meta-analysis of randomized controlled trials	Patients with acute CO poisoning; 2 arms: normobaric oxygen vs hyperbaric oxygen; outcome: neurologic sequelae at 1 mo	N=6 studies; a total of 242/761 (31.8%) patients in HBO₂ arms and 259/718 (36.1%) patients in NBO arms experienced the outcome; pooled OR for HBO₂ vs NBO was 0.77 (95% CI 0.51 to 1.14); I^2 test for heterogeneity was 59%	Adequate assessment of quality of included studies; appropriate statistical method (random-effects model) and sensitivity analysis

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Buckley et al[27] (2011)	III	Meta-analysis of randomized controlled trials	All randomized controlled trials of HBO_2 compared to NBO involving nonpregnant adults who are acutely poisoned with carbon monoxide; outcomes: presence of signs or symptoms possibly indicative of neurologic injury at follow-up (approximately 4 to 6 wk) after randomization	N=6 trials; 1,361 participants; HBO_2 OR for neurologic deficits 0.78, 95% CI 0.54 to 1.12	Studies exhibited significant methodological and statistical heterogeneity; all included trials were at considerable risk of bias; conclusions of 1 positive-result trial may have been influenced by failure to adjust for multiple hypothesis testing, whereas interpretation of the other positive-result trial is hampered by a high risk of bias introduced during the analysis, including an apparent change in the primary outcome; 3 negative trials had low power to detect a benefit of HBO_2 because of exclusion of severely poisoned patients in 2 and very poor follow-up in the other
Annane et al[28] (2011)	III	Single tertiary academic critical care unit in France; randomized, unblinded, controlled, parallel trials	Patients ≥15 y admitted for domestic CO poisoning within 12 h of exposure; trial A patients experienced only transient loss of consciousness and were treated with either 6 h of NBO or 4 h of NBO plus 1 HBO_2 session; trial B included patients with coma treated with either 4 h of NBO and 1 HBO_2 session or with 4 h of NBO and 2 HBO_2 sessions; outcome: complete recovery defined as absence of symptoms reported on a self-assessment questionnaire and a normal physical examination result	N=385 patients; in trial A (n=179) there was no difference in outcomes in the control (n=86) vs the intervention (n=93) (58% recovery vs 61% recovery; unadjusted OR=0.90; 95% CI 0.47 to 1.71); in trial B (n=206) there was no statistical difference in outcomes in the control (n=101) vs the intervention (n=105) (47% recovery vs 68% recovery; unadjusted OR=0.42; 95% CI 0.23 to 0.79)	Lost to enrollment: 48%, lost to follow-up: 16%, suicidal: 0% (excluded), mean time to randomization: 4-5 h; trial was terminated prematurely after an interim analysis; blinded assessment not stated; large subjective component to primary outcome contributing to detection bias, no sham therapy for the NBO group

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Raphael et al[29] (1989)	III	Single tertiary care center in France; randomized unblinded controlled trial	Patients ≥15 y admitted for domestic CO poisoning within 12 h of exposure; trial A patients experienced transient loss of consciousness and were treated with either 6 h of NBO or 4 h of NBO and 1 HBO_2 session; trial B was patients with coma who were treated with either 4 h of NBO and 1 HBO_2 session or with 4 h of NBO and 2 HBO_2 sessions; outcome: complete recovery, defined as absence of symptoms reported on a self-assessment questionnaire and a normal physical examination result	N=629 patients; in trial A (n=343) there was no difference in outcomes in the control (n=170) vs the intervention (n=173) (66% recovery vs 68% recovery; $P=.75$); in trial B (n=286) there was no difference in outcomes in the control (n=145) vs the intervention (n=141) (54% recovery vs 52% recovery; $P=.75$)	Lost to enrollment: 9%, lost to follow-up: 10% (excluded), mean time to treatment: 6.2 h; possibly inadequate sample size to detect a difference; blinded assessment not stated; large subjective component to primary outcome contributing to detection bias; no sham therapy for the NBO group
Shen et al[36] (2015)	III	Taiwanese university hospital ED that has HBO_2 center; retrospective cohort	Included patients with intentional exposure and acute respiratory failure; poor outcome defined by inhospital death, persistent neurologic sequelae, or delayed neurologic sequelae; myocardial injury defined by ECG changes (any ischemia) or troponin I level >0.05 ng/mL; CO-poisoned patients underwent at least 3 90-min HBO_2 sessions (3 ATA for the first treatment and then 2.5 ATA)	N=148; poor outcome=58 (39.2%); myocardial injury=77 (52%); predictors of poor outcome=hypotension (MAP <65), MI, delay to HBO_2, increased WBC, BUN, CK, and troponin levels; myocardial injury independently predicts poor outcome (OR=2.8, 95% CI 1.2 to 6.5)	Unclear whether groups had different durations of CO exposure or different CNS comorbidities (stroke, dementia, trauma); authors used statistical significance for model and predictor selection; unclear whether the outcome was measured without knowledge of the positive biomarker or abnormal ECG

ATA, atmospheres absolute; *BUN*, blood urea nitrogen; *CI*, confidence interval; *CK*, creatine kinase; *CNS*, central nervous system; *CO*, carbon monoxide; *COHb*, carboxyhemoglobin; *DNS*, delayed neurologic sequelae; *ECG*, electrocardiogram; *ED*, emergency department; *h*, hour; *HBO_2*, hyperbaric oxygen; *HR*, hazard ratio; *IQR*, interquartile range; *MAP*, mean arterial pressure; *MI*, myocardial infarction; *min*, minute; *mo*, month; *N*, number; *NBO*, normobaric oxygen; *NNT*, number needed to treat; *NPV*, negative predictive value; *NRB*, nonrebreather; *OR*, odds ratio; *PPV*, positive predictive value; *SD*, standard deviation; *SN*, sensitivity; *SP*, specificity; *SpCO*, pulse CO-oximetry; *VBG/ABG*, venous blood gas/arterial blood gas; *vs*, versus; *WBC*, white blood cell; *wk*, week(s); *y*, years.