Toxic Hemoglobinopathies In The Emergency Department

Abstract

Certain drugs and chemicals can disrupt the ability of hemoglobin to transport and deliver oxygen to peripheral tissues, leading to a toxic hemoglobinopathy. This issue reviews the 3 major hemoglobinopathies—carboxyhemoglobinemia, methemoglobinemia, and sulfhemoglobinemia—and looks at the current evidence for the diagnosis and treatment of each type. The kineticof these toxic exposures are examined, and the pathophysiology and clinical manifestations are reviewed. Carboxyhemoglobinemia, caused by carbon monoxide poisoning, is the most common toxic hemoglobinopathy, and it can lead to persistent and delayed morbidity and mortality. Evidence regarding the challenges of utilizing carboxyhemoglobin levels and other diagnostic tools to predict the symptoms and outcome of carbon monoxide poisoning are reviewed, and the critical elements of this clinical diagnosis are summarized. The conflicting evidence on using hyperbaric oxygen therapy is presented, as well as current guidelines and recommendations on its use. The etiology of methemoglobinemia is also reviewed, along with indications for treatment with methylene blue and/or transfusion. The causes, pathophysiology, and treatment indications for sulfhemoglobinemia are also discussed. Maintaining a high index of suspicion for these 3 conditions will facilitate early recognition and appropriate intervention.
Case Presentations

During a shift in your rural hospital ED, a local EMS agency calls on the radio: “We are en route with a 4-year-old girl who drank out of a bottle that she found in her older brother’s room. She is gray and appears anxious. Her oxygen saturation is 85%; she has good air movement and bilateral breath sounds…” The EMT breaks connection for a few seconds. He gets back on the radio and sounds much more concerned. “She has just lost consciousness, but has a pulse. ETA is 2 minutes.” The patient arrives obtunded and cyanotic but breathing. As the nurses gain additional IV access, apply the monitoring equipment, and obtain vital signs, you prepare your intubation equipment. The respiratory therapist utilizes BVM with 100% FiO2. You see that she has an adequate seal and good chest rise. You look at the monitor to see the following vital signs: pulse oximetry, 85% on room air; heart rate, 154 beats/min; blood pressure, 90/60 mm Hg; respiratory rate, 12 breaths/min; and temperature, 36.7°C. The patient’s oxygen saturation is not improving. As blood is drawn, the nurse shouts, “It looks like chocolate!”

As you survey the rest of the department, you see the wife of the patient in the next room trying to get your attention. Before your attention was directed to the child in front of you, you were in the middle of his history and workup. He is a pleasant 52-year-old man with a history of hypertension who was working on his car this evening in the garage. He states that he developed a headache and felt lightheaded. When he went outside to “get some air,” he thinks he passed out, but he does not remember for sure. After he recovered, he went back in to continue working but soon became unresponsive. He was found by his wife a few minutes later, and she called paramedics after dragging him outside onto the driveway. Upon EMS arrival, he was slightly confused and was placed on 100% oxygen via a nonrebreather mask. By the time he arrives in the ED, he is feeling well except for a slight headache. His cerebellar examination is significant for dysmetria and difficulty walking. You had ordered a carboxyhemoglobin measurement before you had to attend to the child. The nurse brings you the result; it is 34%. What are your next steps?

Introduction

Certain substances and chemicals can cause disruption of hemoglobin’s ability to transport and deliver oxygen, resulting in toxin-induced hemoglobinopathies. Carboxyhemoglobin (COHgb) results from the avid binding of carbon monoxide (CO) to the ferrous iron (Fe2+) in hemoglobin (Hgb). Methemoglobin (MetHgb) and sulfhemoglobin (SulfHgb) result from erythrocyte oxidant stress. MetHgb stems from the oxidation of Fe2+ to ferric iron (Fe3+) in the heme molecule, whereas SulfHgb develops from the oxidation of the porphyrin ring by sulfur. The disruption of oxygen delivery in critically ill patients mandates immediate recognition and treatment. This review provides a fundamental understanding of the pathophysiology of toxin-induced hemoglobinopathies and presents evidence-based recommendations to assist treating physicians in the management of the poisoned patient. For ease of discussion, this review is divided into the 3 major toxic hemoglobinopathies: carboxyhemoglobinemia, methemoglobinemia, and sulfhemoglobinemia.

Critical Appraisal Of The Literature

To identify primary relevant literature, the Cochrane Database of Systematic Reviews and Ovid MEDLINE® library were queried to identify germane studies. The following search terms were used: carbon monoxide, carbon monoxide poisoning, carboxyhemoglobin, delayed neurologic sequelae carbon monoxide, methemoglobin, methemoglobinemia, sulfhemoglobin, and sulfhemoglobinemia. Both high-yield clinical studies and review articles relevant to the current manuscript were identified. The references section of review articles1-7 and key toxicology textbooks8-11 were also reviewed to ensure that no pertinent literature had been overlooked. This search identified multiple clinically relevant trials, including 6 randomized controlled trials (RCTs) evaluating the efficacy of hyperbaric oxygen (HBO) therapy for CO poisoning. The literature addressing methemoglobinemia and sulfhemoglobinemia appears to be comprised of only observational studies and expert opinions; large placebo-controlled trials in humans are notably absent.

In considering the quality of the existing evidence, a major area of uncertainty is how to interpret the RCTs evaluating the effectiveness of HBO for CO poisoning. These RCTs differed by study location; subject characteristics; choice of placebo, type, and timing of treatment; and outcome measures. The conclusions of these trials are conflicting. A meta-analysis conducted by the Cochrane group concluded that existing trials “do not establish whether the administration of HBO to patients with CO poisoning reduces the incidence of adverse neurologic outcome.”

Additionally, this review is informed by national guidelines that comment on management of toxic hemoglobinopathies. Querying the National Guideline Clearinghouse (www.guideline.gov) yielded only 1 applicable entry, the American College of Emergency Physicians (ACEP) clinical policy.8 A search of ACEP clinical guidelines revealed no clinical policies regarding MetHgb or SulfHgb. The Underwater and Hyperbaric Medical Society published a set of guidelines in 2009 for the treatment of CO poisoning with HBO.12 The Centers for Disease Control and Prevention (CDC) clinical guidance for CO poisoning was also reviewed.13 Management recommendations made in this...
review are based upon both the existing literature and evidence-based reviews written by leading national experts.

## Carboxyhemoglobinemia

### Background

CO poisoning is a major cause of morbidity and mortality throughout the world. The CDC reported an incidence of more than 21,000 cases of unintentional, nonfire-related CO poisonings in 2007.\textsuperscript{14,15} The true incidence of CO poisoning is likely higher, due, in large part, to its nonspecific presentation and the high clinical suspicion required to make the diagnosis. Some authors estimate that up to one-third of all poisonings go unrecognized,\textsuperscript{16} with some placing the number of CO poisonings closer to 50,000 cases per year.\textsuperscript{17}

CO is formed after incomplete combustion of any carbon-containing compound. The most common sources include: house fires, automobiles, furnaces, ovens, heaters, grills, watercraft, gas-fueled generators, and cigarettes. Another source of CO is methylene chloride (dichloromethane), a solvent used in paint strippers, degreasers, and plastic welding adhesives. After ingestion or inhalation, methylene chloride undergoes biotransformation by hepatic mixed function oxidases to CO, leading to delayed and prolonged toxicity.\textsuperscript{18} CO is also endogenously produced both as a normal byproduct of the metabolism of protoporphyrin to bilirubin and with exposure to oxidant stress. Accordingly, elevated levels are measured in patients with higher rates of hemolysis, such as in patients with sickle cell disease and sepsis.\textsuperscript{19} Finally, significant amounts of CO have been observed in banked blood, with the highest measurement being 12%.\textsuperscript{20}

### Kinetics

CO is readily absorbed by the lungs and is largely bound by Hgb, with an affinity 200 to 250 times that of oxygen. CO intake increases with the following conditions: (1) increased ambient concentration, (2) prolonged duration of exposure, (3) higher ventilatory rate, and (4) increased pulmonary diffusing capacity. Given this strong affinity, the majority of CO is confined to the blood compartment; however, a portion of CO dissolved in the serum will distribute to tissues where it primarily binds to myoglobin, leading to cardiac dysfunction. CO also binds to cytochrome oxidase, cytochrome P450, catalases, and peroxidases, leading to disruption of normal cellular function. In fetal circulation, the half-life of CO is roughly 5 times that of the mother.\textsuperscript{21,22}

CO elimination changes as a function of both the concentration of inspired oxygen and atmospheric pressure. When breathing 21% oxygen in room air, the half-life of CO is approximately 4 hours, while inspiring 100% oxygen decreases the half-life to roughly 1 hour. Hyperbaric oxygen therapy decreases the half-life to 20 minutes.\textsuperscript{23}

### Pathophysiology

CO causes toxicity via multiple synergistic pathways, ultimately leading to decreased tissue oxygen delivery and utilization. First, CO binds to the oxygen-carrying site on Hgb, thereby decreasing the amount of oxygen bound by Hgb. Formation of COHgb also increases the affinity of Hgb for oxygen; this “left-shift” in the oxygen-hemoglobin dissociation curve impairs the divestment of oxygen to the tissues, further impairing oxygen delivery. (See Figure 1.)

At a cellular level, CO directly inhibits mitochondrial cytochrome c oxidase, which impairs oxygen utilization during oxidative phosphorylation. This inhibition is amplified in hypotensive and hypoxic states.\textsuperscript{8} Concurrent formation of reactive nitrogen species initiates a cascade of events at the microvasculature level, ultimately resulting in cerebral endothelial damage.

At a macroscopic level, CO causes myocardial depression and dysrhythmias by direct binding to myoglobin, resulting in myocyte hypoxia. Vasodilation results from simultaneous displacement of nitric oxide from platelets and direct activation of guanylate cyclase.\textsuperscript{24} The decreased cerebral blood flow caused by the cardiovascular effects of CO combined with cellular hypoxia and cerebral endothelial damage initiate and propagate an inflammatory cascade.

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### Figure 1. Effectors Of The Oxyhemoglobin Dissociation Curve

![Graph showing the effectors of the oxyhemoglobin dissociation curve](image_url)


Abbreviations: CO, carbon monoxide; COHgb, carboxyhemoglobin; O$_2$Hgb, oxyhemoglobin; PO$_2$, partial pressure of oxygen.
in the central nervous system that leads to neuronal cell death. (See Figure 2.)

Clinical Manifestations
Signs and symptoms exhibited by CO-poisoned patients primarily involve the central nervous system and cardiovascular system (See Table 1). Initial nonspecific symptoms are generally associated with lower exposure levels and include headache, dizziness, and nausea. The nonspecific nature of these complaints is very relevant to the emergency physician, as they are required to make the diagnosis of CO poisoning. Furthermore, the incidence of CO poisoning increases in the colder months (from the use of furnaces and other space heaters) at the same time viral illnesses are most prevalent. Chest pain, dyspnea, decreased exercise tolerance, hypotension, syncope, myocardial dysfunction, and dysrhythmias may develop with progressive exposure. Exposure to even higher CO concentrations may cause loss of consciousness, seizure, coma, and, ultimately, death. These severe clinical findings are generally associated with COHgb levels > 60%. It should be emphasized, however, that there is poor correlation between symptoms and COHgb levels, and COHgb levels should be interpreted with caution.

Myocardial injury and dysfunction are frequent in moderate-to-severe CO poisoning. Diagnostic testing may demonstrate ischemic changes on electrocardiogram (ECG) and decreases in ejection fraction on echocardiography, as well as elevations in serum troponins and B-type natriuretic peptide levels. Abnormalities can occur in the absence of clinically significant coronary artery disease and reflect direct CO-induced myocardial toxicity. Patients with coronary artery disease, congestive heart failure, or those with a history of myocardial infarction are at particularly increased risk of adverse events. Work-up should include ECG, chest x-ray, and echocardiogram along with cardiac enzymes and BNP levels.

Figure 2. Pathophysiology Of Carbon Monoxide Poisoning On The Brain

| COHgb, carboxyhemoglobin; MbCO, carboxymyoglobin; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NOS-1, neuronal nitric oxide synthase; O₂⁻, superoxide radical; RBC; red blood cell; WBC, white blood cell; XD, xanthine dehydrogenase; XO, xanthine oxidase. |
disease, anemia, or chronic pulmonary disease will become more symptomatic with lower CO fractions. More substantial exposures lead to cellular hypoxia with a resultant metabolic acidosis and increased lactate production. One study suggests that the degree of acidosis more accurately predicts poorer outcomes than COHgb concentration. Pulmonary edema, rhabdomyolysis, and retinal hemorrhages are frequently reported. Of note, cherry-red colored skin is classically described but is rarely encountered and is often a postmortem finding.

The central nervous system is the organ system most sensitive to the effects of CO and it is also the most studied regarding treatment. Both delayed neurologic sequelae (DNS) and persistent neurologic sequelae (PNS) syndromes have been described after CO poisoning. PNS are defined as symptoms found at presentation that persist throughout hospitalization. DNS occur up to 40 days after the original poisoning. These entities are an ill-defined and varied set of neurological signs and symptoms that can include any of the following: parkinsonism, dementia, apraxia, agnosia, cortical blindness, amnesia, personality changes, psychosis, paralysis, chorea, incontinence, persistent vegetative state, and peripheral neuropathy. The reported incidence of sequelae ranges from 3% to 68%, and spontaneous recovery has been reported from 75% to 100%. The true incidence is unknown, and estimates vary greatly, due, in part, to the lack of a consistent definition.

Observational studies have been used to retrospectively determine patient characteristics associated with development of DNS. Some of these include: coma or persistent altered mental status (Glasgow Coma Scale [GCS] score < 15); seizures, focal neurological deficit, a history of loss of consciousness or syncope, prolonged periods of exposure to CO, metabolic acidosis, age > 36 years, cardiovascular dysfunction, and serum markers of brain injury. Most of these risk factors, however, have not been evaluated in prospective trials. A preponderance of clinical studies suggests that the initial presentation of CO poisoning is variable and that no single risk factor uniformly predicts development of DNS. However, familiarity with these risk factors is important to the practicing physician, since they may impact definitive management.

**Diagnosis**

A diagnosis of CO poisoning is challenging and should be made clinically, based on the presence of typical symptoms and signs coupled with exposure to a CO source. COHgb level can be measured by co-oximeter to further assist with diagnosis. Noninvasive co-oximeters and breathalyzer devices can be readily used for screening purposes; however, CO poisoning should be confirmed with a COHgb blood level if the diagnosis is truly being considered. Either venous or arterial blood may be used to obtain levels. Normal levels range between 0% and 5% and even up to 15% in heavy smokers. Fetal hemoglobin may produce falsely elevated COHgb levels due to interference with standard analytic testing.

COHgb levels do not predict either clinical signs, symptoms, or outcome, as toxicity depends on several factors including duration of exposure, time from exposure, prehospital application of oxygen, co-ingestions, comorbid disease, and other genetic factors. As an example of the wide overlap of blood levels and symptoms, COHgb levels ranged between 1% and 53% in comatose patients and up to 47% in those with minimal symptoms. It should be emphasized that a poisoned patient can have a “normal” COHgb level, depending on the time since exposure and treatment with oxygen prior to obtaining levels. Thus, while elevated COHgb levels can be used to support the diagnosis of CO poisoning, the final diagnosis of CO poisoning is ultimately a clinical one. Of critical importance is the maintenance of a high index of suspicion for CO poisoning during the colder months, during which viral illnesses are prevalent. Key features indicating CO poisoning include: signs and symptoms only when around a CO source that resolve upon removal, pets that exhibit signs and symptoms at the same time as the patient, and other family members in the same household exhibiting similar symptomatology in a temporally related fashion. Furthermore, CO poisoning may occur in uncommon locations, such as the back of a boat, due to abnormal exhaust positioning. Therefore, the physician should always maintain a high index of suspicion for CO poisoning, especially given protein signs and symptoms that seemingly resolve away from a potential source.

Other useful initial diagnostics include: venous blood gas, lactate, troponin I, complete blood count.

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**Table 1. Symptoms Reported In Carbon Monoxide Exposure, By Frequency**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>85</td>
</tr>
<tr>
<td>Dizziness</td>
<td>69</td>
</tr>
<tr>
<td>Fatigue or generalized weakness</td>
<td>67</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>52</td>
</tr>
<tr>
<td>Trouble thinking or confusion</td>
<td>37</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>35</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2</td>
</tr>
</tbody>
</table>

This table was published in “Carbon Monoxide Poisoning” in Haddad and Winchester’s Clinical Management of Poisoning and Drug Overdose, by Eric Lavonas, page 1299, Copyright Elsevier, 2007. Used with permission.
(CBC), electrolytes, pregnancy test, serum toxicologic testing, ECG, chest radiograph, and noncontrast head computed tomography (CT). (See Table 2.) Changes in the hippocampus, basal ganglia, and central white matter can be demonstrated on both brain CT and magnetic resonance imaging (MRI). A neuropsychometric test for CO called the Carbon Monoxide Neuropsychological Screening Battery (CONSB) has been developed. Although it is an objective measure of cognitive function, its clinical utility has yet to be determined and is not commonly used in clinical practice.

**Treatment**

The general clinical pathway for managing a patient with CO poisoning is represented graphically. (See Clinical Pathway, page 10) As with all critically ill patients, initial resuscitation involves meticulous attention to airway, breathing, and circulation. Early intubation should be considered, especially in the setting of significant pulmonary or upper airway injury due to smoke inhalation or irritant gas exposure. Any burns should be treated in standard fashion. A complete history and physical examination should be performed, with emphasis on the neurologic examination. Concomitant evaluation for cyanide poisoning should be considered in cases of fire and smoke exposure, particularly in hypotensive patients with markedly elevated serum lactate levels. In the case of intentional CO exposure, evaluation and management of co-ingestions are warranted, with the goal of stabilizing the patient prior to performing HBO therapy. The desire to obtain a COHgb measurement should not delay delivery of 100% inspired oxygen. Although no trials exist that demonstrate improved outcomes with supplemental oxygen therapy, the therapy is safe, readily available, and will hasten CO elimination. Generally, subsequent COHgb measurements are unnecessary once the source is removed and oxygen therapy is administered. The patient should be maintained on supplemental oxygen until symptoms have resolved. In the case of CO poisoning resulting from methylene chloride exposure, because of continued endogenous production of CO, serial levels should be measured every 4 to 6 hours until undetectable. Patients with milder signs and symptoms, no evidence of significant end-organ toxicity, and unintentional exposure can be discharged from the hospital only after the source has been identified and remedied.

**Hyperbaric Oxygen Therapy**

HBO therapy is an often-utilized treatment for CO poisoning. HBO therapy involves placing patients in a chamber that increases the ambient pressure to higher levels than atmospheric pressure, which increases the partial pressure of oxygen and allows oxygen to displace CO from Hgb. This facilitates elimination of CO and shortens its half-life. In addition, the oxygen-carrying capacity of plasma (and, therefore, the overall oxygen-carrying capacity of blood) is increased, improving tissue oxygenation.

Both in vitro and animal studies have demonstrated multiple mechanisms by which HBO might reduce CO-induced central nervous system damage. HBO therapy may reduce CO binding to cytochrome c, preventing mitochondrial dysfunction. This treatment may also mitigate downstream effects of CO poisoning, including damage caused by activated neutrophil adhesion.

Clinical equipoise exists regarding the utilization of HBO for the prevention of DNS. Although animal and laboratory data suggest a mechanism for benefit of HBO therapy, improvement in outcomes in human subjects has not been reproducibly demonstrated. The largest and most often cited clinical studies addressing HBO therapy for CO poisoning are summarized in Table 3. There are 6 RCTs and 1 meta-analysis evaluating the effectiveness of HBO therapy for CO poisoning. Three RCTs demonstrated a decrease in neurologic sequelae with HBO, while 3 did not. These studies are notably varied in methodology, with differences in participant inclusion and exclusion criteria, choice of placebo, characteristics of HBO (depth, timing, length, and frequency), and outcome measures. The Cochrane group conducted a meta-analysis of the existing RCTs and concluded that the existing data “do not establish whether the administration of HBO to
patients with CO poisoning reduces the incidence of adverse neurologic outcome.”

The existing studies neither identify specific populations in whom HBO may be effective, nor the optimal timing, duration, and depth of HBO.

Akin to the conflicting findings in the available clinical trials, recommendations from national organizations are also somewhat inconsistent. ACEP issued a policy statement in 2008 that states, “[hyperbaric oxygen] is a therapeutic option for CO-poisoned patients; however, its use cannot be mandated...no clinical variables, including COHgb levels, identify a subgroup of CO-poisoned patients for whom HBO is most likely to provide benefit or cause harm.” In contrast, the CDC issued a statement more clearly recommending HBO, stating that physicians should... “consider HBO therapy when the patient has a COHgb level of > 25% to 30%; there is evidence of cardiac involvement, severe acidosis, transient or prolonged unconsciousness, or neurologic impairment.”

The Undersea and Hyperbaric Medical Society recommends referral for HBO in CO poisoning for: (1) unconsciousness (either persistent or by history), (2) prolonged exposure (> 24 hours), and (3) age > 36 years. They also recommend that HBO can be considered for patients with abnormal neuropsychological testing or CO levels > 25% to 30%.

Table 3. Summary Of Current Randomized Controlled Trials Evaluating Hyperbaric Oxygen For Carbon Monoxide Poisoning

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Type of Study</th>
<th>Treatment Groups</th>
<th>Conclusion</th>
<th>Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raphael et al</td>
<td>1989</td>
<td>343</td>
<td>Prospective randomized non-blinded</td>
<td>6 h NBO vs 2 h HBO at 2 ATA</td>
<td>No difference in patients that do not have LOC. Coma implies bad prognosis</td>
<td>Selection bias, inadequate HBO, treatment delays, nonblinded</td>
</tr>
<tr>
<td>Thom et al</td>
<td>1995</td>
<td>60</td>
<td>Prospective randomized non-blinded</td>
<td>NBO until symptoms resolved vs HBO at 2.8 ATA for 30 min followed by 2 ATA for 90 min</td>
<td>Decreased incidence of DNS in HBO group</td>
<td>Small N, nonblinded, questionable treatment in control group</td>
</tr>
<tr>
<td>Mathieu et al</td>
<td>1996</td>
<td>575</td>
<td>Prospective randomized non-blinded</td>
<td>12 h NBO vs HBO at 2.5 ATA</td>
<td>A difference in cognitive sequelae favoring HBO was found at 3 mo, but the difference lessened at 6 mo and disappeared at 12 mo</td>
<td>Interim analysis, multiple comparisons</td>
</tr>
<tr>
<td>Scheinkestel et al</td>
<td>1999</td>
<td>191</td>
<td>Prospective randomized blinded</td>
<td>NBO for 3 or 6 days vs daily HBO at 3 ATA with NBO for 3 or 6 days</td>
<td>No difference at 1 mo</td>
<td>Limited follow-up, poor study retention, lack of pretreatment neuropsychological testing, high incidence of intentional poisonings, unusual treatment regimen</td>
</tr>
<tr>
<td>Weaver et al</td>
<td>2002</td>
<td>152</td>
<td>Prospective randomized blinded</td>
<td>NBO vs 3 HBO sessions (3 ATA x 1 h, then 2 ATA for 1 h, the subsequent sessions at 2 ATA)</td>
<td>HBO decreased the incidence of cognitive sequelae at both 6 wk and 1 y</td>
<td>Questionable clinical significance</td>
</tr>
<tr>
<td>Annane et al</td>
<td>2010</td>
<td>179</td>
<td>Randomized non-blinded</td>
<td>6 h of NBO vs 4 h of NBO and a single HBO (2 ATA for 60-min plateau)</td>
<td>No difference at 1 mo</td>
<td>Inadequate HBO, limited follow-up</td>
</tr>
<tr>
<td>Buckley et al</td>
<td>2011</td>
<td>1335</td>
<td>Cochrane review</td>
<td>NA</td>
<td>Existing studies are inadequate to establish the efficacy of HBO therapy for CO poisoning</td>
<td>Meta-analysis, heterogeneous study populations and treatments</td>
</tr>
</tbody>
</table>

Abbreviations: ATA, atmosphere absolute; CO, carbon monoxide; DNS, delayed neurologic sequelae; HBO, hyperbaric oxygen; LOC, loss of consciousness; NA, not applicable; NBO, normobaric oxygen.
For patients who do receive HBO, the physician should be aware of a few practical considerations. HBO treatment should be guided specifically by providers trained in its use and according to institution-specific protocols. HBO therapy can make the treatment of an acutely unstable patient difficult, given the time required for a physician to gain physical access to the patient. All attempts to stabilize the patient must be made prior to placing the patient in the chamber. Hemodynamic instability and untreated pneumothorax are absolute contraindications for HBO. Most chambers are able to accommodate intubated patients, but all intubated patients should undergo myringotomy performed by an otolaryngologist prior to the first HBO treatment. Children who are to receive HBO therapy can be placed in adequately sized chambers along with their parents for comfort. The most common side effects of HBO treatment include anxiety, claustrophobia, barotrauma (middle ear, lung, teeth, and sinuses), and rarely, seizures. Awake patients may benefit from nasal decongestants to minimize barotrauma to the middle ear and the sinuses. Infants can be fed or myringotomy performed to decrease the possibility of tympanic membrane rupture. After each HBO therapy, patients should have their tympanic membrane visualized to evaluate for perforation and lung auscultation to evaluate for pneumothorax.

**Hyperbaric Oxygen Therapy in Pregnant Patients**

A fetus is much more susceptible to the effects of CO than other age groups. The increased toxicity is likely secondary to reduced arterial oxygen content and prolonged elimination -- roughly 5 times that of the mother. Early animal studies demonstrated a higher affinity of fetal Hgb for CO than adult Hgb, helping the fetal circulation act as a “CO sink.” However, more recent evidence suggests that the increased affinity is a result of lower oxygen partial pressures, rather than intrinsic properties of fetal Hgb. Likewise, CO has a prolonged half-life at lower oxygen partial pressures.

Fetal exposure to CO has been associated with high rates of fetal vertebral and limb abnormalities, brain injury, and demise. Maternal symptoms appear to correlate with fetal distress and morbidity. HBO appears to be safe during pregnancy, having been used in obstetric patients with diabetes, toxemia, and anemia without any perinatal complications. Case reports suggest that fetal distress may respond to HBO. In a case series, 38 patients with acute CO toxicity were prospectively followed after HBO at 2 atmosphere absolute (ATA). Two patients had spontaneous abortions (both within 15 days of the exposure). The remainder carried to term, and most delivered normal babies (1 baby was diagnosed with Down syndrome). Another series of 6 pregnant patients reported 3 cases of fetal mortality. No toxicity to the fetus from HBO has been demonstrated in humans.

The CDC has clearly identified obstetric patients as a population in whom HBO is appropriate. A current CDC Clinical Guidance Statement recommended that, “Hyperbaric oxygen is the treatment of choice for pregnant women, even if they are less severely poisoned. Hyperbaric oxygen is safe to administer and international consensus favors it as part of a more aggressive role in treating pregnant women.” In obstetric populations, the potential risks associated with untreated CO poisoning seem to outweigh the potential risks of HBO therapy. It should be noted that pregnant patients have been excluded from all current clinical trials, and there are no comparative studies evaluating different treatment modalities in this population. Regardless, based on the likely safety and potential benefits, pregnant patients with a CO level > 10% or with any symptoms attributable to CO poisoning should be considered HBO candidates.

**Summary of Recommendations For The Use Of Hyperbaric Oxygen Therapy**

Considerable controversy exists not only regarding the effectiveness of HBO therapy for CO poisoning, but which populations, if any, derive benefit. Significant limitations of the current literature prevent any strong recommendation either for or against the use of HBO for CO poisoning. Until more consistently beneficial evidence emerges, the emergency physician should be aware that recommendations for the use of HBO will vary greatly between individual practitioners and institutions. Given this wide practice variation among toxicologists, the care of CO-poisoned patients should be individually tailored. Physicians should maintain a low threshold to discuss the management of CO-poisoned patients with their institution’s medical toxicologist. Interdisciplinary care is particularly important for the pregnant patient with CO poisoning. In pregnant patients, the potential risks associated with untreated CO poisoning seem to outweigh the potential risks of HBO therapy, and HBO may be used more liberally than in the general population.

**Therapeutic Hypothermia**

Therapeutic hypothermia is currently utilized for the treatment of patients after cardiac arrest who have return of spontaneous circulation. This therapy has also been utilized in CO-poisoned patients either with or without HBO. The use of therapeutic hypothermia for CO poisoning has been reported in both isolated case reports and a small series. Theoretically, by slowing the deleterious effects induced by central nervous system cellular hypoxia, therapeutic hypothermia could potentially benefit a CO-poisoned patient who has suffered cardiac arrest. The decision to utilize this therapy should be
molecule contains 4 ferrous heme groups capable of binding and carrying oxygen. The loss of an electron from Fe$^{2+}$ to Fe$^{3+}$ creates MetHgb. (See Figure 3.) A small fraction of MetHgb (< 2%) is normal, given baseline endogenous red blood cell oxidative stress. The body relies on the cytochrome b5 reductase pathway to convert MetHgb back to normal Hgb. It is only when this pathway is overwhelmed by oxidant stress that excessive amounts of MetHgb result.

**Etiology**

The majority of acquired cases of methemoglobinemia are due to exposure to drugs and chemicals. Common causes of methemoglobinemia include: local anesthetics (eg, benzocaine, lidocaine, or prilocaine), nitrates and nitrites, phenazopyridine, aniline dyes, and metoclopramide. (See Table 4, page 11.)

Indeed, a common presentation is a patient sent to the emergency department (ED) for cyanosis after an endoscopic procedure during which a liberal dose of local anesthetic has been given. Dapsone is infamous for generating prolonged methemoglobinemia due to the long half-life of the drug and its metabolite. Outbreaks of methemoglobinemia have been reported in the setting of nitrite-containing water sources.

Methemoglobinemia has also been observed in acute diarrheal illnesses and sepsis in infants.

**Pathophysiology**

The main mechanism by which MetHgb causes morbidity and mortality is its inability to carry oxygen made in conjunction with appropriate physicians facile with the use of therapeutic hypothermia in a postarrest patient.  

**Disposition**

The source of CO exposure must be addressed and remedied prior to disposition. With unintentional exposures, asymptomatic patients or patients whose symptoms have resolved either prior to or during ED observation can be discharged. Proper education about sources of CO and the use of home detectors should be discussed with the patient prior to discharge. Patients with mild persistent symptoms may be admitted for 24-hour observation; patients who are hemodynamically unstable should be admitted to the intensive care unit (ICU). Furthermore, patients with abnormal diagnostic testing from end-organ injury due to CO poisoning (eg, abnormal ECG or elevated troponin) should be admitted and investigated further. Intentional CO poisoning, regardless of severity, mandates psychiatric evaluation. Regarding HBO therapy, the decision to proceed with HBO or to transfer the patient to an HBO-equipped facility should be made collectively between a toxicologist, a physician trained in HBO, and the emergency physician.

**Methemoglobinemia**

Methemoglobinemia is another toxic hemoglobinopathy that results from oxidative stress. Each Hgb molecule contains 4 ferrous heme groups capable of binding and carrying oxygen. The loss of an electron from Fe$^{2+}$ to Fe$^{3+}$ creates MetHgb. (See Figure 3.) A small fraction of MetHgb (< 2%) is normal, given baseline endogenous red blood cell oxidative stress. The body relies on the cytochrome b5 reductase pathway to convert MetHgb back to normal Hgb. It is only when this pathway is overwhelmed by oxidant stress that excessive amounts of MetHgb result.

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Methemoglobinemia has also been observed in acute diarrheal illnesses and sepsis in infants.

**Pathophysiology**

The main mechanism by which MetHgb causes morbidity and mortality is its inability to carry oxygen made in conjunction with appropriate physicians facile with the use of therapeutic hypothermia in a postarrest patient.  

**Disposition**

The source of CO exposure must be addressed and remedied prior to disposition. With unintentional exposures, asymptomatic patients or patients whose symptoms have resolved either prior to or during ED observation can be discharged. Proper education about sources of CO and the use of home detectors should be discussed with the patient prior to discharge. Patients with mild persistent symptoms may be admitted for 24-hour observation; patients who are hemodynamically unstable should be admitted to the intensive care unit (ICU). Furthermore, patients with abnormal diagnostic testing from end-organ injury due to CO poisoning (eg, abnormal ECG or elevated troponin) should be admitted and investigated further. Intentional CO poisoning, regardless of severity, mandates psychiatric evaluation. Regarding HBO therapy, the decision to proceed with HBO or to transfer the patient to an HBO-equipped facility should be made collectively between a toxicologist, a physician trained in HBO, and the emergency physician.
Clinical Pathway For Carbon Monoxide Poisoning

Detailed history and physical examination shows CO poisoning

- Apply high-concentration O₂
- Establish IV line, attach monitoring equipment
- Order ECG
- Order ABG or VBG with co-oximetry
- Consider renal function tests, cardiac biomarkers, and lactate, depending on clinical scenario
- Pregnancy test

Pregnant?

- NO
- YES

Presence of 1 or more?:
- Syncope or a period of unconsciousness
- Elevated troponin
- Metabolic acidosis
- Focal neurological deficits (especially cerebellar dysfunction)
- Seizures
- Altered mental status (GCS score < 15)
- Age > 36 y
- COHgb > 25%
- Prolonged CO exposure (> 24 h)
- Fetal distress
- Maternal COHgb level > 10%
- Chest pain
- Hypotension

• Suggested indications for HBO present or
- Fetal distress or
• CO level > 10%

Refer for HBO therapy (Class III)

• Supplementation O₂ x 4 h (Class I)
• Discharge with appropriate counseling after source identified and eliminated (Class I)

Abbreviations: ABG, arterial blood gas; CO, carbon monoxide; COHgb, carboxyhemoglobin; ECG, electrocardiogram; GCS, Glasgow Coma Scale; HBO, hyperbaric oxygen; IV, intravenous; LOC, loss of consciousness; O₂, oxygen; VBG, venous blood gas.

Class Of Evidence Definitions

Each action in the clinical pathways section of EM Critical Care receives a score based on the following definitions.

**Class I**
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

*Level of Evidence:*
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

**Class II**
- Safe, acceptable
- Probably useful

*Level of Evidence:*
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

**Class III**
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

*Level of Evidence:*
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

**Indeterminate**
- Continuing area of research
- No recommendations until further research

*Level of Evidence:*
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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oxygen to target tissue. Additionally, like COHgb, MetHgb shifts the oxyhemoglobin dissociation curve to the left, hindering the off-loading of oxygen by the normal heme. The result is a functional anemia. It should be emphasized that many of the agents that cause oxidant stress and methemoglobinemia can also produce sulfhemoglobinemia and hemolysis, both which contribute to toxicity. Patients with congestive heart disease, coronary artery disease, anemia, or chronic pulmonary disease will become symptomatic with relatively lower MetHgb fractions. Paradoxically, they may appear less cyanotic than patients with normal Hgb levels.

Clinical Manifestations
Because of MetHgb’s dark brown color, less is required to cause cyanosis (1.5 g/dL) than deoxyhemoglobin (5 g/dL). Skin discoloration or cyanosis it is usually present at levels between 15% and 20% and is usually well tolerated in healthy patients. In fact — although distressing to friends, family, and healthcare providers — cyanotic-appearing patients may be entirely asymptomatic. As MetHgb concentration increases, signs and symptoms include headache, dizziness, nausea, anxiety, dyspnea, chest pain, tachycardia, confusion, seizures, coma, and, eventually, death (70%).

Diagnosis
At the bedside, the astute clinician should consider methemoglobinemia in a cyanotic patient with abnormal pulse oximetry (approximately 85%, although it can be less) that does not improve with supplemental oxygen. The abnormal coloration (“chocolate”) of patient blood can also often lead to the diagnosis. The definitive manner by which methemoglobinemia is diagnosed is measurement of a methemoglobinemia level by co-oximetry. Unfortunately, some co-oximeters cannot differentiate between MetHgb and SulfHgb, and timely differentiation between the two may be difficult. Other useful diagnostics include: CBC, haptoglobin, lactate dehydrogenase, electrolytes, ECG, and chest radiograph.

Treatment Recommendations For Methemoglobinemia
Without exception, the source of oxidant stress should be identified and removed for patients with methemoglobinemia. Asymptomatic patients with methemoglobinemia do not generally require treatment or admission to the hospital. All symptomatic patients should have supplemental oxygen administered immediately. Patients with comorbid medical conditions (such as coronary artery disease, peripheral vascular disease, congestive heart failure, poor pulmonary function, or anemia) may develop more significant symptoms and require therapy at lower MetHgb levels. Symptomatic patients with methemoglobinemia who are not glucose-6-phosphate dehydrogenase (G6PD) deficient should receive methylene blue. Subsequent doses, or even a continuous infusion, may be required for methemoglobinemia with an inadequate response to methylene blue or due to xenobiotics with a longer duration of action (eg, dapsone). The initial dose of methylene blue is 1 mg/kg to 2 mg/kg administered intravenously over 5 minutes. Note that the pulse oximeter will read artificially low during administration of methylene blue; after infusion, the reading should then promptly return to baseline.

Administration of such a strongly blue dye will make the patient appear more cyanotic, but this is simply an artifact of methylene blue administration. Both clinical improvement and a reduction in MetHgb level should be evident within a few minutes to half an hour. Total methylene blue dosage should not exceed 5 mg/kg to 7 mg/kg during the first few hours of treatment due to the potential risk for hemolysis. As fetal Hgb is more sensitive to oxidant stress, physicians should consider using a lower dose of methylene blue (1 mg/kg) in obstetric patients. Serial MetHgb levels should be followed to ensure resolution and response to therapy. Red blood cell or exchange transfusions should be considered in select patients with known G6PD deficiency or worsening clinical status despite appropriate methylene blue administration. Cimetidine administration (1200 mg daily) may be considered as an adjunct treatment to block metabolism of dapsone.

Table 4. Signs And Symptoms Typically Associated With Methemoglobin Levels In A Healthy Patient With A Normal Hemoglobin Concentration

<table>
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<tr>
<th>Methemoglobin Level (%)</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 (normal)</td>
<td>None</td>
</tr>
<tr>
<td>3-15</td>
<td>Possibly none; slate-gray cutaneous coloration; pulse oximeter reads low SaO2</td>
</tr>
<tr>
<td>15-20</td>
<td>Cyanosis, chocolate-brown blood</td>
</tr>
<tr>
<td>20-50</td>
<td>Dyspnea, exercise intolerance, headache, fatigue, dizziness, syncope, weakness</td>
</tr>
<tr>
<td>50-70</td>
<td>Tachypnea, metabolic acidosis, dysrhythmias, seizures, CNS depression, coma</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>Grave hypoxic symptoms, death</td>
</tr>
</tbody>
</table>

Note: the list of signs and symptoms is not all-inclusive.
Abbreviation: CNS, central nervous system; SaO2, oxygen saturation.
Care should be initially directed towards supporting the patient’s airway, breathing, and circulation, as well as withdrawing the offending agent. The first-line treatment is administration of the antidote, methylene blue, and is predicated on the patient’s clinical signs and symptoms, physiologic state, and the cause of MetHgb. The indications for methylene blue administration include:

- Tachycardia
- Shortness of breath
- Chest pain
- Confusion or GCS score < 14
- Seizures
- MetHgb > 25% or with any of the above symptoms

Patients in extremis, with severe hemolysis, or with no response to methylene blue should be considered for immediate blood transfusion or exchange transfusion. Symptomatic patients should be admitted for observation to a monitored setting with serial MetHgb measurements and signs of hemolysis. Patients with known G6PD deficiency should not receive methylene blue; exchange transfusion should instead be considered, and consultation with a hematologist is warranted.

**Action Of Methylene Blue**

Methylene blue is a thiazine dye and, paradoxically, a weak oxidizing agent. When administered to a symptomatic patient with methemoglobinemia, methylene blue is reduced by nicotinamide adenine dinucleotide phosphate (NADPH) MetHgb reductase (with NADPH as a cofactor) to leukomethylene blue and subsequently reduces MetHgb to Hgb. (See Figure 4.) Under normal physiology, NADPH MetHgb reductase has no role in the maintenance of normal MetHgb levels. As a corollary, G6PD does not predispose to methemoglobinemia, but theoretically inhibits the ability of methylene blue to be reduced to leukomethylene blue given the absence of NADPH. Furthermore, because methylene blue is itself an oxidizing agent, it can lead to hemolysis in G6PD-deficient individuals. G6PD has many variants with respect to function; less functional G6PD variants that may be considered “deficient” retain sufficient function to respond appropriately to methylene blue administration. Thus, it is impossible to predict who will and will not respond to methylene blue therapy, and methylene blue should not be withheld based on unconfirmed clinical suspicion of G6PD. In most cases when exposed to methylene blue, NADPH MetHgb reductase activity dramatically increases and very effectively reverses MetHgb.

Since methylene blue inhibits monoamine oxidase A, the potential for serotonin syndrome or a hypertensive crisis exists. However, development of serotonin syndrome with methylene blue is rare.\(^4,6,71,72\) Given the rarity of such events and the life-threatening nature of acute and symptomatic methemoglobinemia, physicians should err on the side of treatment in those who require it.

**Figure 4. Suggested Algorithm For The Management Of Methemoglobinemia**

![Figure 4](image-url)

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; MetHgb, methemoglobin; NADPH, reduced nicotinamide adenine dinucleotide phosphate.
**Sulfhemoglobinemia**

Sulfhemoglobinemia is caused by the binding of elemental sulfur to an undetermined region of the heme Hgb, but it does not directly involve iron. SulfHgb is likewise unable to carry oxygen. SulfHgb is darker than MetHgb and, therefore, produces cyanosis at a lower fraction of total Hgb (0.5 g/dL) when compared with MetHgb (1.5 g/dL) and deoxyhemoglobin (5 g/dL). Agents that induce SulfHgb include laxatives (when abused), elemental sulfur, sulfur-containing compounds, trinitrotoluene, nitrates, phenacetin, and acetanilide.

Although SulfHgb is unable to transport oxygen, those who develop sulfhemoglobinemia are much less likely to become symptomatic for 2 reasons. First, only 1 heme group of the Hgb tetramer is affected. Second, unlike MetHgb, SulfHgb reduces the oxygen affinity of normal heme subunits, shifting the oxygen-Hgb dissociation curve to the right and facilitating oxygen delivery. Thus, most patients with sulfhemoglobinemia remain asymptomatic unless accompanied by methemoglobinemia or hemolysis. If a patient does become symptomatic from sulfhemoglobinemia, the symptoms are indistinguishable from methemoglobinemia.

Detection of sulfhemoglobinemia is challenging, since direct measurement in a timely fashion is usually not possible by co-oximetry. The diagnosis is frequently one of exclusion after the patient does not respond to methylene blue. Unlike MetHgb, SulfHgb is not amenable to methylene blue and persists for the life of the erythrocyte. There is no antidote for sulfhemoglobinemia, and treatment entails ensuring appropriate oxygen delivery and treating the accompanying methemoglobinemia and hemolysis. As with methemoglobinemia, transfusions should be considered for severe symptoms. Sulfhemoglobinemia is relatively benign, and, aside from removing the offending agent, no further therapy is required.

**Summary**

Toxic hemoglobinopathies are clinical syndromes resulting from exposure to certain drugs or chemicals that disrupt the normal function of Hgb. CO toxicity is a cause of serious morbidity and mortality. Clinical presentations range from asymptomatic COHgb elevations to multisystem organ dysfunction and death. Treatment options include elimination of exposure, high-flow oxygen therapy and HBO, and, potentially, therapeutic hypothermia. Both the heterogeneity of existing clinical trials regarding the use of HBO for CO poisoning and definitions of delayed neurologic injury preclude uniform and definitive recommendations. The risks and benefits of implementing HBO treatment should be tailored to the individual patient in consultation with a medical toxicologist. MetHgb is an oxidized version of Hgb that produces a functional anemia. It is readily recognized in the cyanotic patient with “rusted blood” whose oxygen saturation does not respond to supplemental oxygen administration. Methylene blue is the antidote for methemoglobinemia. Sulfhemoglobinemia is difficult to diagnose, and lack of response to methylene blue may be the initial clue to diagnosis. Exchange transfusion may be considered in severe cases of methemoglobinemia or sulfhemoglobinemia. MetHgb, SulfHgb, and hemolysis are all secondary to oxidant stress and may coexist together. For each of the 3 toxic hemoglobinopathies, the practicing physician must maintain a high index of suspicion to facilitate early recognition, appropriate intervention, and to reduce morbidity and mortality.

**Must-Do Markers Of Quality**

**Emergency Department Critical Care**

**Carboxyhemoglobinemia**
- Identify and eliminate the source.
- Administer high-flow oxygen.
- Assess end-organ damage.
- Determine need for HBO therapy in conjunction with a toxicologist or poison center.

**Methemoglobinemia**
- Discontinue source of oxidant stress.
- Administer methylene blue for symptomatic patients.
- Repeat methylene blue dose may be required, depending on oxidizing agent.
- Known G6PD deficiency is a contraindication for methylene blue, but suspicion is not.
- Methylene blue administration temporarily interferes with pulse oximetry readings.

**Sulfhemoglobinemia**
- Consider sulfhemoglobinemia in any patient with apparent methemoglobinemia that fails to respond to methylene blue.
- Laboratory detection of SulfHgb is problematic.

**Time And Cost-Effective Strategies**

- Every female patient of reproductive age requires a pregnancy test; this can be sent from triage, depending on mode of arrival.
- Any patient with suspected CO poisoning should be placed on 100% nonrebreather oxygen therapy.
- CO and MetHgb levels should be obtained from venous blood gas.
Case Conclusions

It was reported that the child was exposed to butyl nitrite, so in conjunction with her clinical findings, you made the diagnosis of methemoglobinemia and administered 2 mg/kg of methylene blue. Almost immediately, the pulse oximeter declined to 65%, but then it spontaneously improved. Within 5 minutes, the girl’s color returned to normal, and she awoke, crying, and later she sat comfortably in her mother’s arms. Her oxygen saturation was 98%. Initial co-oximetry measured 60% and MetHgb 60%; after methylene blue administration it measured 8%. Her Hgb was normal and there was no evidence of hemolysis. You transferred her to the local children’s hospital for further monitoring.

You empirically placed the 52-year-old man on high-flow oxygen during his ED stay. Serum electrolytes, CBC, and serum lactate were normal; however, his troponin I was elevated at 13 ng/mL. His headache resolved with acetaminophen, time, and oxygen. His neurological examination improved to normal. After you consulted with your institution’s toxicologist, you prescribed aspirin and admitted him for serial troponin enzyme testing. During his visit, a cardiologist evaluated him and recommended outpatient follow-up. He was counseled as to the potential for neurological sequelae. His wife had already turned off the car, but she asked the local fire department to check for CO in the house and garage. She also purchased a home CO detector.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.


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1. A contraindication to HBO therapy is:
   a. Pneumothorax
   b. Vasopressor infusion
   c. Elevated troponin
   d. Myringotomy tubes

2. Which of the following is an indication for HBO in a pregnant woman exposed to CO?
   a. Asymptomatic mother with CO level of 5% and no fetal distress
   b. Fetal distress
   c. Mother > 24 weeks gestation
   d. Elevated blood pressure and large proteinuria

3. What is the most important step prior to discharging a patient for CO toxicity?
   a. Repeating a level to ensure the CO level is < 2%
   b. Making sure the patient received 3 HBO treatments
   c. Identifying the source and ensuring a safe discharge environment
   d. Making sure the patient received 100% oxygen for 24 hours

4. Which of the following is commonly associated with formation of methemoglobinemia?
   a. Dapsone
   b. Ibuprofen
   c. Metoprolol
   d. Furosemide
5. Seizure and coma may present at MetHgb levels between:
   a. 3% and 15%
   b. 15% and 20%
   c. 20% and 50%
   d. 50% and 70%

6. Diagnostic clues for the presence of methemoglobinemia include which of the following?
   a. Decreased oxygen gap between arterial and venous blood
   b. Significant improvement of pulse oximeter oxygen saturation with administration of supplemental oxygen
   c. Cherry-red skin
   d. Dusky or cyanotic-appearing skin

7. If a patient with clinically significant methemoglobinemia does not respond to methylene blue, what is a treatment alternative?
   a. Exchange transfusion
   b. 100% oxygen by nonrebreather
   c. Plasma exchange
   d. Initiate epinephrine infusion

8. Known G6PD deficiency is a contraindication to methylene blue because it may lead to:
   a. Hemolysis
   b. Sulfhemoglobinemia
   c. Serotonin syndrome
   d. Cyanide toxicity

9. Methylene blue administration may induce the following clinical condition:
   a. Neuroleptic malignant syndrome
   b. Sulfhemoglobinemia
   c. Hypotension
   d. Serotonin syndrome

10. The most appropriate antidote for sulfhemoglobinemia is:
    a. Hydroxocobalamin
    b. HBO
    c. Methylene blue
    d. No antidote exists

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Use of Blood Products In The Critically Ill Patient

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It is imperative that emergency physicians have a basic understanding of blood products and the indications and risks associated with their use. This issue of EMCC will review the preparation of blood components and indications for their use, infusion of products, and the determination of stability after infusion. Infectious and immunologic risks associated with transfusion are reviewed, with special attention given to pulmonary complications (TRALI and TACO), as well as guidelines for comprehensive informed consent. Massive transfusion protocols and the use of oxygen-carrying substitutes are discussed as well.

Evidence-based, restricted use of blood components in critically ill patients can lead to decreased mortality while avoiding unnecessary risks for significant morbidity and complications. Recognition of the need for irradiated or leukoreduced components in special populations further reduces adverse events. Without safe and approved synthetic oxygen carrier solutions and a randomized trial suggesting otherwise, massive transfusion should continue with packed red blood cells, plasma, and platelets in the exsanguinating patient. The emergency physician must clearly understand risks and benefits associated with administration of blood products in order to obtain informed consent.

Sedation Of The Mechanically Ventilated Patient In The Emergency Department

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Critically ill patients frequently experience pain and undergo invasive procedures. The relief of pain, agitation, and delirium is correlated with improved outcomes and reduced ICU length of stay. This issue reviews current literature and guidelines that have contributed to a significant shift in sedation strategies. The article will highlight currently used sedatives, analgesics, and anesthetics utilized in the care of critically ill patients. Ongoing monitoring of sedation is of prime importance, and several validated sedation scales are discussed. A modern evidence-based sedation plan begins with pain relief, or analgosedation. This issue describes when supplemental medications are required and how to titrate these drugs to achieve the desired effect. Judicious and measured use of sedative medications helps to avoid untoward effects such as oversedation, hypotension, increased ICU length of stay, and increased mortality.

The treatment of pain is the first step in crafting a patient-centered sedation plan. Newer medicines (such as remifentanil) provide analgesia in addition to mild sedation. Physicians should evaluate their sedation plans according to validated sedation scales and administer additional medications (such as benzodiazepines) only when necessary. Critically ill patients have unique metabolic demands, and the utility of any single agent must be weighed against patient-specific factors such as organ dysfunction and age. Analgosedation focuses, first, on the relief of pain and is associated with improved patient outcomes.
Available Exclusively For EMCC Subscribers: Walking The Tightrope: Pain Management And Sedation In The Hypotensive Patient

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