HHS Public Access

Author manuscript

Ann Plast Surg. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

Ann Plast Surg. 2018 March ; 80(3 Suppl 2): S106–S112. doi:10.1097/SAP.0000000000001351.

Carbon monoxide and cyanide poisoning in the burned pregnant patient: an indication for hyperbaric oxygen therapy

Derek M. Culnan, M.D.[1], **Beretta Craft-Coffman, PA-C**[2], **Genevieve H. Bitz, B.S.**[1], **Karel D. Capek, M.D.**[3], **Yiji Tu, M.D.**[4], **William C. Lineaweaver, M.D., F.A.C.S.**[1], and **Maggie J. Kuhlmann-Capek, M.D.**[5]

[1]JMS Burn & Reconstruction Center at Merit Health Central Hospital, Jackson, MS, USA

[2]Burn & Reconstructive Centers of America, Augusta, GA, USA

[3]Shriners hospitals for children – Galveston, University of Texas medical branch, Galveston, TX, USA

[4]Department of Orthopedic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China

[5]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, TX, USA

Abstract

Carbon monoxide (CO) is a small molecule poison released as a product of incomplete combustion. CO binds hemoglobin, reducing oxygen delivery. This effect is exacerbated in the burned pregnant patient by fetal hemoglobin that binds carbon monoxide 2.5–3 fold stronger than maternal hemoglobin. With no signature clinical symptom, diagnosis depends on patient injury history, elevated carboxyhemoglobin levels, and alterations in mental status. The standard of care for treatment of CO intoxication is 100% normobaric oxygen, which decreases the half-life of CO in the bloodstream from 5 hours to 1 hour. Hyperbaric oxygen (HBO_2) is a useful adjunct to rapidly reduce the half-life of CO to 20 minutes and the incidence of delayed neurologic sequelae. Due to the slow disassociation of CO from hemoglobin in the fetus, there is a far stronger indication for HBO_2 in the burned pregnant patient than in other burn patient populations.

Cyanide intoxication is often a comorbid disease with CO in inhalation injury from an enclosed fire, but may be the predominant toxin. It acts synergistically with CO to effectively lower the lethal doses of both cyanide and CO. Diagnosis is best made in the presence of high lactate levels, carboxyhemoglobin concentrations greater than 10%, injury history of smoke inhalation from an enclosed fire, and alterations in consciousness. While treatment with hydroxocobalamin is the standard of care and has the effect of reducing concomitant CO toxicity, data indicate cyanide may also be displaced by HBO_2.

CO and cyanide poisoning presents potential complications impacting care. This review will address the mechanism of action, presentation, diagnosis, and treatment of CO and cyanide poisonings in the burned pregnant patient, and the use of HBO_2 therapy.

Corresponding Author: Derek M. Culnan, M.D., JMS Burn & Reconstructive Center at Merit Health Central, 1850 Chadwick Drive, Suite 1427, Jackson, MS 39204 USA, Phone: 601.824.3977, Fax: 601.824.3979, derek.culnan@burncenters.com.

Keywords

carbon monoxide poisoning; burn; pregnancy; hyperbaric oxygen; cyanide; hydroxocobalamin; inhalation injury; burn shock; lactic acidosis

INTRODUCTION

Carbon monoxide (CO) intoxication is a leading cause of poisoning worldwide and the third most common cause of accidental death in the United States, resulting principally from the inhalation of exhaust fumes.[1–4] In the context of burn patients, CO is liberated when any carbon-based material is incompletely oxidized or burned.[5] The severity of the inhalation injury is not directly proportional to the size of the cutaneous burn[6], and CO intoxication may go undiagnosed in a third of all burn patients with inhalation injury.[7] Among the pregnant population, accidental exposure in the domestic setting is the primary cause of CO poisoning.[8] A non-irritating, tasteless, and odorless gas, CO is difficult to detect. The exact incidence of CO intoxication of pregnant women is unknown but is estimated at 4.6–8.5% of all patients diagnosed with CO poisoning.[7,9]

In the burned pregnant patient population, maternal mortality and maternal survivors with fetal mortality are more common in those with concurrent smoke inhalation injury.[10] Maternal and fetal death strongly correlates with hypoxia resulting from inhalation injury.[11] Maternal mortality rates between 19–24% and fetal mortality rates between 36–67% are associated with CO intoxication during pregnancy.[12] In the burned pregnant patient, inhalation of toxic gases further increases the high morbidity and mortality of both mother and fetus, providing an indication for hyperbaric oxygen therapy.

Given the nonspecific symptoms of presentation, medical practitioners must maintain a high index of suspicion when pregnant patients present with thermal injuries, especially those derived from fires in enclosed spaces. In this review, we cover the mechanism of injury, presentation, diagnosis, and treatment modalities available to the burn team when presented with potential CO poisoning in the burned pregnant patient. Further, we will discuss another principle small molecule, poisonous gas product of combustion, cyanide, its association with CO and its ramifications for the burned pregnant patient with inhalation injury.

MECHANISM OF INJURY TO MOTHER AND FETUS

Inhalation injury is the second strongest predictor of mortality of both mother and fetus following burn injury.[10] In smoke generated from explosions and fires, the concentration of CO can reach 60%, magnitudes greater than atmospheric CO concentration of less than 0.001%.[13] CO is readily absorbed by the lungs whereupon it diffuses across the alveolar membranes into the blood, binding primarily to hemoglobin.[2] Systemic toxicity results from the binding of CO to hemoglobin with an affinity 200 to 250-fold greater than oxygen, displacing the oxygen.[14,15] This displacement results in tissue hypoxia by decreasing the oxygen-carrying capacity and shifting the oxygen dissociation curve to the left, thereby preventing the other three heme-oxygen binding sites from releasing oxygen from the blood to the tissues.[16,17]

CO intoxication also prevents oxygen from binding to cytochrome c oxidase and myoglobin, damaging cellular respiration and resulting in the impairment of mitochondrial function of all cells, most especially of the heart and central nervous system.[18–20] CO has an affinity for myoglobin between 20 to 25 times that of oxygen.[21,22] This binding induces arrhythmias and hypotension.[5] The binding of CO to cytochromes a3 and P450 as well as myoglobin creates an intracellular reservoir, prolonging the half-life of CO after the initiation of treatment.[23] Binding the cytochromes does not just interfere with cellular oxidative metabolism, but it also generates free radicals, which can create distant organ injury.[5,24]

Further, CO poisoning can result in delayed neurologic sequelae, such as Parkinson-like syndrome and dementia.[16,25–28] Due to nonspecific symptoms and the absence of diagnostic consensus, it is estimated that delayed neurologic sequelae (e.g., coma, depression, psychosis) present in 3–40% of patients with CO poisoning within 2 to 240 days of injury[26] and resolve in 75% of these patients.[27] These outcomes can result irrespective of COHb concentration at admission, potentially as a result of excess dopamine stimulated by CO.[29]

The binding affinity of CO to fetal hemoglobin is even stronger than CO binding to maternal hemoglobin.[2,9] CO crosses the placental barrier via passive diffusion.[30] Additionally, the partial pressure of fetal arterial oxygen is approximately 20 mm Hg, much lower than the partial pressure of maternal arterial oxygen of 100 mm Hg.[31] Thus, the fetus is more sensitive to shifts in the oxygen dissociation curve than the mother, and more vulnerable to CO poisoning.[32] CO has a binding affinity 2.5–3 times greater for fetal hemoglobin than for maternal hemoglobin, resulting in fetal carboxyhemoglobin (COHb) concentrations 10–15% greater than maternal COHb levels, and a half-life approximately four times greater in the fetus than the mother.[33–35] 60% fetal COHb is the approximate lethal level of CO in the fetus.[36]

While fetal hemoglobin has a greater affinity for CO than maternal hemoglobin, fetal uptake of CO lags significantly behind the mother.[32,35] The greater affinity of fetal hemoglobin to CO dictates that fetal COHb concentrations will continue to rise once maternal COHb concentrations reach a plateau.[32] Fetal COHb levels rise after the CO intoxication of the mother, who can suffer anoxic injury or death before fetal COHb levels increase.[37] Animal studies have shown that fetal concentrations of COHb to be approximately 58% higher than maternal COHb levels hours following acute CO exposure.[35] These data have never been demonstrated in human fetuses given the ethical and technical difficulties of collecting human fetal blood following CO exposure.

The impact of fetal tissue hypoxia depends on the severity of poisoning as well as fetal gestational age.[23,38] While alterations in psychomotor and mental development may result from insult at any gestational age, skeletal and anatomical malformations are more common if the fetus is exposed to CO during the first trimester. The later gestational ages are more susceptible to neurologic complications such as anoxic encephalopathy.[7,8,38,39]

PRESENTATION

CO intoxication does not have a signature symptom by which it is easily identified.[24,40] The clinical features depend on the concentration and chronicity of the exposure to CO gas.[41] Diagnosis of fetal CO poisoning is dependent on diagnosis of maternal CO poisoning. Maternal symptoms correlate to maternal concentration of CO bound to hemoglobin, COHb.[38] Of relevance to burned pregnant patients are acute levels of CO poisoning (30–50% COHb), life-threatening levels of CO poisoning (50–66% COHb), and lethal CO poisoning (>66% COHb).[38,42] These levels present with symptoms ranging from vomiting to psychiatric disorders to death. (Table 1) Headaches, vertigo, chest pain, malaise, shortness of breath, and nausea are common clinical signs of CO exposure.[43,44] Altered mental status and decreased level of consciousness are also signs of CO poisoning. Cherry red lips, considered a classical manifestation of CO poisoning, are rarely seen; as such, the absence of this sign should not be reassuring.[45] CO intoxication should be suspected of a lethargic or obtunded burn patient, or of any patient who has survived an enclosed fire.[46]

The risk from CO to the fetus is significant once the mother exhibits symptoms of altered consciousness.[38] The toxic effects on the fetus from CO are determined by concentration and duration of exposure, in addition to the gestational age of the fetus.[47] Fetal tachycardia, decreased fetal heart rate variability, and late decelerations on continuous external fetal monitoring are all signs of fetal distress that may manifest in the setting of CO poisoning.[23] The effects of CO poisoning may not present in the fetus for 36–48 hours following injury.[48] Consultation with a high-risk obstetrician over the course of care is necessary to monitor the status of the fetus. (Table 2)

DIAGNOSIS

Elevated levels of COHb as well as patient history and signs of exposure to CO from smoke inhalation are generally used to diagnose CO poisoning.[49] CO intoxication should be suspected when a burn patient presents with indicators of inhalation injury and an injury history of an entrapped fire. Signs and symptoms of inhalation injury include singed nasal hair; soot around the face, nose, and mouth; carbonaceous sputum; coughing; and shortness of breath. Environmental indicators of CO intoxication include exposure to the incomplete combustion of organic materials, especially in an enclosed space such as a structural fire.

In a non-smoking pregnant woman, the typical concentration of COHb ranges from 0.4% to 3%.[34,41,50] Routine tobacco use can cause baseline chronic CO levels of 0.4%–15%.[5,41] When COHb is greater than 4% in a non-smoking pregnant patient or 10% in a smoking pregnant patient, the diagnosis of CO poisoning should be made.[2,5,20,41,51] COHb levels, however, do not directly correspond to the degree of CO intoxication or potential outcomes.[52] To complicate assessment, burn patients with suspected inhalation injuries are typically intubated by and receive oxygen therapy from emergency medical personnel prior to arriving at the hospital emergency department or burn center.[16] This circumstance, as well as the time elapsed from delays in transfer, can lower the apparent concentration of COHb as measured at the time of admission to the burn unit. A low COHb concentration should not be used to eliminate CO poisoning as a potential diagnosis, making injury history and

physical examination crucial in establishing a diagnosis and course of care.[2] This consideration is particularly true for the burned pregnant patient where low levels of maternal COHb may belie high fetal COHb concentrations, necessitating treatment of the mother to treat the fetus.

To determine maternal COHb concentrations, medical practitioners rely on blood gas analyses.[51] Either venous or arterial COHb levels can be measured as results from venous and arterial blood gas analyses are generally within 2%.[53] Additionally, pulse CO-oximetry (Rad-57®, Massimo Corp, Irvine, CA) reads eight wavelengths of light, enabling it to discern between COHb and levels of oxygen bound to hemoglobin,[54] a performance beyond the capacity of conventional pulse oximetry.[55] Further, pulse CO-oximetry can be taken by fingertip measurement in the hospital or at the scene of injury, hastening diagnosis of CO poisoning.[56,57] This non-invasive diagnostic adjunct has limitations. Pulse CO-oximetry is unable to accurately determine COHb levels at low oxygen saturation, an effect enhanced by dark skin pigmentation and gender.[58–61] Thus, it may be unable to eliminate CO intoxication as a diagnosis and should be used in conjunction with patient injury history and evaluation obtained at admission and confirmed with laboratory testing.[62]

Currently, no method or diagnostic tool exists to determine the concentration of COHb of a fetus in utero. Diagnosis of fetal CO poisoning is dependent on diagnosis of maternal CO poisoning. No association has been made between maternal COHb levels and fetal outcomes; the fetus may suffer effects of CO poisoning even if maternal COHb concentrations are not at toxic levels.[63] Due to the delayed clearance by the fetus of CO, fetal COHb levels may require 40 hours to normalize once maternal COHb levels normalize.[5] Thus, typical diagnostic criteria to ascertain fetal health should be used. Moderate fetal heart rate variability is typically a sign of fetal well-being. The absence of or depressed variability (i.e., no fetal heart rate accelerations or decelerations) in conjunction with a higher baseline heart rate is an indication of fetal distress.[64] Additionally, tachycardia or late decelerations are indicative of fetal distress in the setting of CO poisoning.[23] Given that maternal vitals may not accurately reflect the condition of the fetus,[2,7] consultation with a high-risk obstetrician and possibly a neonatologist is necessary to best monitor the health of the fetus. In utero magnetic resonance imagining and ultrasounds are adjuncts that can permit the potential diagnosis of anoxic encephalopathy in the fetus, but only after delivery can determinations of neonatal outcomes following CO intoxication be made.[38]

TREATMENT

Despite the increased mortality risks at smaller burn sizes, the treatment of a burned pregnant patient does not differ greatly from that of a burned non-pregnant patient.[10,65] Except in rare circumstances, the optimal method to treat the fetus is to treat the mother, even in the setting of inhalation injury and CO intoxication. Reducing maternal COHb concentration is the only mechanism to reduce COHb levels in the fetus.

The foundation of treating CO poisoning is the administration of oxygen.[51] The classic treatment consists of 100% normobaric oxygen (NBO_2) administered via a tightly fitting, non-rebreather mask for a minimum of 6 hours.[18,54,66] When breathing normal ambient air,

the half-life of maternal COHb is 4–6 hours. In contrast, the half-life of maternal COHb is reduced to 40–75 minutes when 100% NBO_2 is administered.[16,18,54,67] The rate at which CO disassociates from hemoglobin increases due to the elevated partial pressure of oxygen, thereby raising the oxygen concentration of the blood and end-organs.[44,51,67] Given the extended duration required for fetal clearance of COHb, 100% NBO_2 may need to be administered at a rate of 15 L/min for 16 hours or more.[9] If maternal COHb concentration is in excess of 20% or the burned pregnant patient has at any time lost consciousness, pure oxygen in the setting of a burned pregnant patient may be inadequate for fetal survival, and hyperbaric oxygen therapy can be considered.[38,68]

Hyperbaric oxygen (HBO_2) therapy requires a specialized hyperbaric chamber to administer 100% oxygen to patients at pressures greater than 1 atmosphere, resulting in increasing blood and tissue oxygen levels, reduction of tissue and intravascular bubbles, and hastening the displacement of toxic gases.[49,69] In this environment, the half-life of maternal COHb is 20–40 minutes. HBO_2 therapy has been used since 1965 to treat CO poisoning when reports claimed a significant decrease in burn wound extension or demarcation following utilization of HBO_2 therapy.[70]

A recent survey of 68 centers in 23 European countries found a wide variance in HBO_2 therapy protocols and indications.[71] Given that fetal hemoglobin has a greater affinity for CO than maternal hemoglobin and the longer disassociation time of fetal COHb, burned pregnant patients might warrant receiving longer sessions or more sessions of HBO_2 therapy than non-pregnant patients.[38,68] To allow for the prolonged time for the fetus to eliminate CO, the duration of HBO_2 therapy administered to the mother may be up to five times longer than necessary to reduce the maternal COHb concentrations to near normal.[33] In addition to signs of fetal distress, maternal COHb levels greater than 20%, loss of consciousness, evidence of maternal end-organ ischemia, or neurological complications in the mother may lead practitioners to consider HBO_2 therapy.[68,69] Continued HBO_2 therapy may be indicated if the fetus shows signs of distress or the mother has further neurological complications 6–12 hours following the first HBO_2 administration.[2,48,68] HBO_2 therapy can be administered days after injury and have demonstrated therapeutic effect in patients with CO intoxication.[72]

For the burned pregnant patient with CO poisoning, case reports describe a range of protocols due to the lack of protocol standardization among HBO_2 providers worldwide. One report outlined a protocol requiring two sessions, one at 2.5 atmospheres for 30 minutes followed by a 60 minute treatment at 2 atmospheres.[68] A recent review recommends an initial HBO_2 treatment at pressure less than 2.7 atmospheres for 30–90 minutes followed by HBO_2 treatment of 90 minutes at pressure less than 2.2 atmospheres.[2] Greater study is required before one treatment algorithm can be established.

Pregnancy induces numerous physiologic changes including a decrease in vital lung capacity and increases in oxygen consumption, minute ventilation, and mucosal edema.[73,74] These alterations compound the inhalation injury. Additionally, the elevated temperature of the inhaled smoke can cause necrosis in regions of the trachea.[46] Typically, patients suspected to have suffered inhalation injury are intubated and receive oxygen therapy by emergency

medical personnel.[16] Burned pregnant patients with suspected inhalation injury can be considered for intubation to optimally manage the mother and the fetus.

During the period of acute poisoning, immediate emergency cesarean section prior to the administration of 100% oxygen therapy is not recommended unless no other recourse, such as HBO_2, exists to attempt to salvage the life of mother or child.[38] As with other clinical scenarios involving critical care in pregnancy, priority should be given to stabilization of maternal condition, as fetal condition will often follow maternal condition. During this time, emergency cesarean section correlates with a high risk of perinatal death.[38]

Possible adjuncts

Should a pregnant patient be severely burned and have suffered significant CO, use of NBO_2 may be insufficient for fetal survival, and delay in accessing the hyperbaric chamber may result in spontaneous abortion or fetal demise. In such situations where HBO_2 is unavailable or when its application is impractical due to other critical care priorities, other treatments are necessary. Studies have demonstrated that therapeutic red cell exchange can be effective in the management of a patient with severe CO poisoning.[75,76] There are no documented cases of red cell exchange in the CO-intoxiced pregnant patient, but with the limited side effect profile, relative ease of administration while addressing other critical care treatments, and rapid ability to replace COHb with normal hemoglobin, it may warrant further study in treating the burned pregnant patient with CO poisoning. Extarcorporeal membrane oxygenation (ECMO) has been used as a therapeutic adjunct in pregnant patients with severe respiratory distress as well as patients with severe CO poisoning.[77–80] While not yet reported in the burned pregnant population, ECMO is a potential treatment to manage CO intoxication.[54]

HBO_2 VERSUS NBO_2

The utility of HBO_2 therapy is debated. While several animal studies using HBO_2 therapy protocols at pressures greater than 3 atmospheres have indicated HBO_2 treatment poses significant risks to the fetus (e.g., prematurity, skeletal malformations, spontaneous abortions)[81], case studies have documented no such sequelae in human clinical practice, particularly at the more standard 2–2.5 atmospheres.[12,82] Analyses from Europe have shown a reduction in spontaneous abortions, fetal complications, and motor and cognitive impairments of the child when HBO_2 therapy is administered to the mother following acute CO exposure as compared to patients treated with conventional NBO_2 therapy.[71] A recent single-center 25-year-retrospective study showed no statistical difference between 412 children whose mothers had received HBO_2 treatment for CO poisoning in follow-ups of up to six years after the therapy in psychomotor development, height, or weight when matched with a control group not exposed to HBO_2 therapy, nor were there reported malformations among the children exposed at various gestational ages between the first and third trimesters to HBO_2.[83]

HBO_2 therapy has been shown to mitigate the inflammatory processes incited by CO intoxication.[44] Animal studies have demonstrated that HBO_2 therapy is more effective than NBO_2 in abrogating CO-induced brain and neurological injury, potentially by inhibiting

brain lipid peroxidation and preserving ATP tissue levels.[84–87] Studies of non-pregnant populations with CO poisoning showed a reduced incidence of delayed or long-term neurological sequelae (e.g., memory or attention problems) developing in the patients treated with HBO_2 than among patients treated with NBO_2.[88,89]

However, HBO_2 therapy is significantly more expensive than NBO_2 and is only available at a few specialized centers and hospitals. The logistics of HBO_2 therapy can delay management of other factors critical for maternal survival (e.g., resuscitation or escharotomy), and patients risk hyperoxic seizures and barotrauma from HBO_2 therapy.[51,90–92] One Cochrane Review found no evidence to support the use of HBO_2 therapy over NBO_2 to treat CO poisoning.[49] An earlier Cochrane Review found insufficient evidence to support the utilization of HBO_2 therapy in the management of burn injuries.[93] However, both reviews found sufficient evidence to warrant further study.

In most non-pregnant burn patients, CO poisoning is managed by placing patients on 100% NBO_2. NBO_2 therapy is done because at least one hour will have elapsed while the non-pregnant burn patient is assessed and stabilized prior to accessing a hyperbaric chamber, potentially lowering the patient out of the lethal CO range and obviating the need for HBO_2. However, the increased affinity of fetal hemoglobin for CO conspires with the slower fetal elimination rate to cause a greatly enhanced fetal toxigenesis. As such, 100% NBO_2 therapy can be inadequate to timely treat the fetus following acute CO exposure. As the best method to treat the fetus is to treat the mother, in the setting of the burned pregnant patient with significant CO poisoning, HBO_2 therapy may be indicated once the mother is stabilized to optimally eliminate CO potentially fatal to both mother and child.[2,16,17,24,28,38,41,44,49,51,54,56,66,68,71,83,89,93]

CYANIDE

Historically, CO was believed to be the agent principally responsible for morbidities and mortality associated with the inhalation toxic gases in smoke. Recently, the role of cyanide in the morbidity of inhalation injury has been explored. Cyanide is potentially the agent more responsible for complications and increased risk of death associated with inhalation injury.[94] Research regarding the incidence of cyanide toxicity versus CO poisoning is hampered by the short (1-hour) plasma half-life of cyanide whilst remaining a persistently-bound intrinsic toxin.[95] Difficulties in obtaining blood samples of inhalation injury victims at the scene of injury and of measuring both COHb and cyanide levels accurately in patients have stymied researchers. Regardless, their toxigenesis are synergistic, and they accrue from similar combustion sources, so it is likely cyanide will be present if CO is present in structural fires..

A consensus exists in the literature that, in enclosed fires, CO is likely to be inhaled with cyanide,[51,96,97] and that when a patient is poisoned by both CO and cyanide, the toxic gas molecules act synergistically to lower the lethal dose of each gas.[51] As animal studies have demonstrated, the combination of both cyanide and CO is more lethal to both mother and fetus at lower concentrations of CO and cyanide than either CO or cyanide poisoning alone. This effect is exacerbated in events such as domestic house fires.[98] Thus, if CO poisoning is

suspected derived from smoke inhalation of an entrapped fire, the medical practitioner should test for and prophylactically treat for cyanide intoxication.

Mechanism of Action

Acute cyanide intoxication results from the disruption of aerobic respiration by inactivating mitochondrial cytochrome c oxidase by binding with iron in cytochrome a_3, leading to potentially severe lactic acidosis, lethal hypoxia, and cytotoxic anoxia.[96,99] CO preferentially binds Fe^{2+} found in hemoglobin whereas cyanide preferentially binds Fe^{3+} found in cytochrome c oxidase.[100] Like CO, cyanide crosses the placental barrier, though to a lesser degree. Data from animal studies suggest that cyanide does not freely dissociate from maternal to fetal hemoglobin to the same extent as CO, and fetal levels of cyanide were found to be lower than maternal levels of cyanide.[101] The potentially higher levels of fetal COHb than maternal COHb concentrations may compound the toxic effect of cyanide in the fetus.[34]

Presentation

CO poisoning with concomitant cyanide intoxication will present with an advanced degree of alteration of consciousness and possibly changes in vital functions.[96] Similar to CO poisoning, patients with cyanide intoxication present with headaches, tachycardia, nausea, and weakness as well as cardiac arrest, coma, convulsions, and death at higher concentrations.[102] The sustained blockade of cellular respiration from cyanide intoxication leads to severe lactic acidosis and metabolic acidosis.[96,97] Cyanide is known to be significantly hepatotoxic and neurotoxic.[101] Cherry-red skin and urine may be used as a clinical sign of cyanide poisoning.[103,104] Animal studies have demonstrated fetal malformations and spontaneous abortions are associated with maternal cyanide exposure.[2]

Diagnosis

Cyanide poisoning can occur within seconds of exposure, and CO intoxication can mask the symptoms of cyanide poisoning, requiring the burn surgeon to maintain a high index of suspicion in burned pregnant patients presenting with confirmed or suspected inhalation injury.[96] Diagnosis of fetal cyanide poisoning rests on diagnosis of cyanide intoxication in the mother. Maternal serum lactate levels higher than 8 mmol/L, maternal pH less than 7.20, and maternal COHb concentrations greater than 10% strongly correlate with cyanide poisoning.[102,105] Additionally, a Glasgow Coma Scale below 14 and abnormal hemodynamics are also sensitive indicators of cyanide toxicity.[106] Should an obstetrical patient's blood be taken by emergency responders, a diagnosis of cyanide poisoning can be made if maternal cyanide levels return at greater than 1 mg/L.[107] Due to long time needed to run that test and short plasma half-life of cyanide, treatment should be initiated prior to the return of results in burned pregnant patients presenting with clinical symptoms of cyanide poisoning.

Treatment

Given the short half-life of cyanide in the bloodstream and rapid toxicology, oxygen therapy may be ineffective in the management of cyanide intoxication. Thus, if cyanide poisoning is

suspected in a burned pregnant patient, hydroxocobalamin (Cyanokit®, Merck Santé s.a.s., Semoy, France) should be administered to eliminate cyanide from mother and child prior to return of lab work, which may take hours to days to be analyzed and reported.[66,105,108,109]. Hydoxocobalamin binds cyanide, forming cyanocobalamin, otherwise known as vitamin B12, which is then excreted in the urine. Recent studies highlight concerns regarding a correlation of kidney injury and the administration of hydoxocobalamin.[110] Measurements of COHb are known to return falsely low after administration of hydroxocobalamin, obviating the utility of that diagnostic adjunct in concomitant CO poisoning.[111] The United States Food and Drug Administration approved the use of hydroxocobalamin in October 2010 in pregnant patients. It is classified as a pregnancy category C drug and should only be used when cyanide poisoning is suspected and the benefits to mother and fetus outweigh the risks of kidney injury and other complications.[66]

Another pregnancy category C drug, sodium thiosulfate has not been demonstrated in sheep studies to cross the placenta.[112] This drug may create a cyanide gradient toward the mother, conveying some protection against cyanide poisoning to the fetus.[112] However, a Task Force of the European Centre for Ecotoxicology and Toxicology of Chemicals concluded sodium thiosulfate to be inferior to hydroxocobalamin to treat cyanide poisoning derived from smoke inhalation.[113] Given the potential renal toxicity of hydroxocobalamin, further studies should analyze which therapy provides effective and safe treatment of cyanide poisoning in a burned obstetrical patient.

Other adjuncts to treat cyanide poisoning carry proven risks and significant toxicities to the fetus, including fetal death and methemoglobinemia.[114,115] Some of these, such as sodium nitrite, are also classified as pregnancy category C dugs,[115] but the potential complications should be strongly considered in determining if these treatments are appropriate in a pregnant patient, particularly with safer adjuncts currently available.

A recent rat study demonstrated that HBO_2 therapy displaced cyanide from cellular tissues into the blood, indicating therapeutic potentiality of HBO_2 therapy for cyanide toxicity.[116] Due to the synergistic toxicity of cyanide and CO, treating cyanide intoxication can be an indirect therapy of CO poisoning and can shorten the duration of NBO_2 or HBO_2 administration. Concomitant cyanide poisoning can be an indication for the administration of HBO_2 therapy for CO intoxication.[44]

CONCLUSION

Carbon monoxide and cyanide are poisonous, small-molecule gases elaborated as products of combustion, particularly from enclosed fires. While most non-pregnant burn patients with CO poisoning are managed with the administration of NBO_2 to reduce the half-life of CO from 4–6 hours to one hour, CO-intoxicated burned pregnant patients who present with altered mental status or consciousness as well as a COHb level greater than 20% can be considered candidates for HBO_2 therapy to better treat the fetus and mitigate delayed neurological sequelae in mother and child. If cyanide poisoning should be suspected, hydoxocobalamin should be administered immediately, and kidney function values tracked to monitor for kidney injury. Consultation and monitoring with a high-risk obstetrician is

necessary to best monitor the fetus in the setting of CO or cyanide poisoning. Given the nonspecific symptoms of presentation, burn surgeons must maintain a high index of suspicion of CO and cyanide poisonings when pregnant patients present with thermal injuries, especially those derived from fires in enclosed spaces.

Despite great advances in the management of burned patients that have significantly improved survival rates in other patient populations, maternal and fetal survival rates remain nearly unchanged from the 1960s.[117,118] While other patient populations routinely survive a 98% TBSA burn,[119] a 40% burn of a pregnant patient correlates to an obstetrical mortality rate of 50%.[10,65] Advancements in treating inhalation injury have lagged behind other aspects of burn care. When a burned pregnant patient has an inhalation injury, high mortality rates can be expected if the injury is not assessed and treated in a reasonable timeframe. Additional research into the care of both mother and fetus after burn injury and in the presence of CO and cyanide intoxications is requisite to develop better treatment algorithms.

References

1. Geehr EC, Salluzzo R, Bosco S, et al. Emergency health impact of a severe storm. Am J Emerg Med. 1989; 7(6):598–604. [PubMed: 2803354]
2. Gozubuyuk AA, Dag H, Kacar A, et al. Epidemiology, pathophysiology, clinical evaluation, and treatment of carbon monoxide poisoning in child, infant, and fetus. North Clin Istanb. 2017; 4(1): 100–107. [PubMed: 28752154]
3. Wolf SJ, Lavonas EJ, Sloan EP, et al. Clinical policy: Critical issues in the management of adult patients presenting to the emergency department with acute carbon monoxide poisoning. Ann Emerg Med. 2008; 51(2):138–152. [PubMed: 18206551]
4. Wolf SJ, Maloney GE, Shih RD, et al. Clinical policy: Critical issues in the evaluation and management of adult patients presenting to the emergency department with acute carbon monoxide poisoning. Ann Emerg Med. 2017; 69(1):98–107. e106. [PubMed: 27993310]
5. Ernst A, Zibrak JD. Carbon monoxide poisoning. N Engl J Med. 1998; 339(22):1603–1608. [PubMed: 9828249]
6. Shirani KZ, Pruitt BA Jr, Mason AD Jr. The influence of inhalation injury and pneumonia on burn mortality. Ann Surg. 1987; 205(1):82–87. [PubMed: 3800465]
7. Greingor JL, Tosi JM, Ruhlmann S, et al. Acute carbon monoxide intoxication during pregnancy. One case report and review of the literature. Emerg Med J. 2001; 18(5):399–401. [PubMed: 11559621]
8. Norman CA, Halton DM. Is carbon monoxide a workplace teratogen? A review and evaluation of the literature. Ann Occup Hyg. 1990; 34(4):335–347. [PubMed: 2240988]
9. Palmer J, Von Rueden K. Carbon monoxide poisoning and pregnancy: Critical nursing interventions. J Emerg Nurs. 2015; 41(6):479–483. [PubMed: 26409658]
10. Maghsoudi H, Samnia R, Garadaghi A, et al. Burns in pregnancy. Burns. 2006; 32(2):246–250. [PubMed: 16448763]
11. Karimi H, Momeni M, Momeni M, et al. Burn injuries during pregnancy in Iran. Int J Gynaecol Obstet. 2009; 104(2):132–134. [PubMed: 19022440]
12. Elkharrat D, Raphael JC, Korach JM, et al. Acute carbon monoxide intoxication and hyperbaric oxygen in pregnancy. Intensive Care Med. 1991; 17(5):289–292. [PubMed: 1939875]
13. Sinkovic A, Smolle-Juettner FM, Krunic B, et al. Severe carbon monoxide poisoning treated by hyperbaric oxygen therapy--a case report. Inhal Toxicol. 2006; 18(3):211–214. [PubMed: 16399663]
14. Coburn RF. The measurement of endogenous carbon monoxide production. J Appl Physiol (1985). 2012; 112(11):1949–1955. [PubMed: 22442030]

15. Sicoutris CP, Holmes JH. Fire and smoke injuries. Crit Care Nurs Clin North Am. 2006; 18(3): 403–417. [PubMed: 16962460]
16. Bleecker ML. Carbon monoxide intoxication. Handb Clin Neurol. 2015; 131:191–203. [PubMed: 26563790]
17. Ryter SW, Choi AM. Carbon monoxide: present and future indications for a medical gas. Korean J Intern Med. 2013; 28(2):123–140. [PubMed: 23525151]
18. Blumenthal I. Carbon monoxide poisoning. J R Soc Med. 2001; 94(6):270–272. [PubMed: 11387414]
19. Toon MH, Maybauer MO, Greenwood JE, et al. Management of acute smoke inhalation injury. Crit Care Resusc. 2010; 12(1):53–61. [PubMed: 20196715]
20. Turner M, Hamilton-Farrell MR, Clark RJ. Carbon monoxide poisoning: an update. J Accid Emerg Med. 1999; 16(2):92–96. [PubMed: 10191439]
21. Haab P. The effect of carbon monoxide on respiration. Experientia. 1990; 46(11–12):1202–1206. [PubMed: 2174793]
22. Schuwey D, Tempini A, Haab P. Carbon monoxide equilibrium curve of human umbilical cord blood. Adv Exp Med Biol. 1990; 277:209–214. [PubMed: 2096626]
23. Yildiz H, Aldemir E, Altuncu E, et al. A rare cause of perinatal asphyxia: maternal carbon monoxide poisoning. Arch Gynecol Obstet. 2010; 281(2):251–254. [PubMed: 19504116]
24. Huzar TF, George T, Cross JM. Carbon monoxide and cyanide toxicity: etiology, pathophysiology and treatment in inhalation injury. Expert Rev Respir Med. 2013; 7(2):159–170. [PubMed: 23547992]
25. Chang CC, Hsu JL, Chang WN, et al. Metabolic covariant network in relation to nigrostriatal degeneration in carbon monoxide intoxication-related parkinsonism. Front Neurosci. 2016; 10:187. [PubMed: 27199649]
26. Oh S, Choi SC. Acute carbon monoxide poisoning and delayed neurological sequelae: a potential neuroprotection bundle therapy. Neural Regen Res. 2015; 10(1):36–38. [PubMed: 25788913]
27. Pepe G, Castelli M, Nazerian P, et al. Delayed neuropsychological sequelae after carbon monoxide poisoning: predictive risk factors in the Emergency Department. A retrospective study. Scand J Trauma Resusc Emerg Med. 2011; 19:16. [PubMed: 21414211]
28. Thom SR, Bhopale VM, Fisher D. Hyperbaric oxygen reduces delayed immune-mediated neuropathology in experimental carbon monoxide toxicity. Toxicol Appl Pharmacol. 2006; 213(2): 152–159. [PubMed: 16325878]
29. Park EJ, Min YG, Kim GW, et al. Pathophysiology of brain injuries in acute carbon monoxide poisoning: a novel hypothesis. Med Hypotheses. 2014; 83(2):186–189. [PubMed: 24857260]
30. Delomenie M, Schneider F, Beaudet J, et al. Carbon monoxide poisoning during pregnancy: Presentation of a rare severe case with fetal bladder complications. Case Rep Obstet Gynecol. 2015; 2015:687975. [PubMed: 25834750]
31. Neuman, TS., Thom, SR. Physiology and medicine of hyperbaric oxygen therapy. Philadelphia, PA: Saunders Elsevier; 2008.
32. Longo LD. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. Am J Obstet Gynecol. 1977; 129(1):69–103. [PubMed: 561541]
33. Hill EP, Hill JR, Power GG, et al. Carbon monoxide exchanges between the human fetus and mother: a mathematical model. Am J Physiol. 1977; 232(3):H311–323. [PubMed: 842687]
34. Longo LD. Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. Ann N Y Acad Sci. 1970; 174(1):312–341. [PubMed: 4943972]
35. Longo LD, Hill EP. Carbon monoxide uptake and elimination in fetal and maternal sheep. Am J Physiol. 1977; 232(3):H324–330. [PubMed: 842688]
36. Farrow JR, Davis GJ, Roy TM, et al. Fetal death due to nonlethal maternal carbon monoxide poisoning. J Forensic Sci. 1990; 35(6):1448–1452. [PubMed: 2262778]
37. Cramer CR. Fetal death due to accidental maternal carbon monoxide poisoning. J Toxicol Clin Toxicol. 1982; 19(3):297–301. [PubMed: 7131616]
38. Aubard Y, Magne I. Carbon monoxide poisoning in pregnancy. BJOG. 2000; 107(7):833–838. [PubMed: 10901551]

39. Alehan F, Erol I, Onay OS. Cerebral palsy due to nonlethal maternal carbon monoxide intoxication. Birth Defects Res A Clin Mol Teratol. 2007; 79(8):614–616. [PubMed: 17584908]
40. Kao LW, Nanagas KA. Toxicity associated with carbon monoxide. Clin Lab Med. 2006; 26(1):99–125. [PubMed: 16567227]
41. Friedman P, Guo XM, Stiller RJ, et al. Carbon monoxide exposure during pregnancy. Obstet Gynecol Surv. 2015; 70(11):705–712. [PubMed: 26584719]
42. Gorman D, Drewry A, Huang YL, et al. The clinical toxicology of carbon monoxide. Toxicology. 2003; 187(1):25–38. [PubMed: 12679050]
43. Endorf FW, Dries DJ. Burn resuscitation. Scand J Trauma Resusc Emerg Med. 2011; 19:69. [PubMed: 22078326]
44. Weaver LK. Hyperbaric oxygen therapy for carbon monoxide poisoning. Undersea Hyperb Med. 2014; 41(4):339–354. [PubMed: 25109087]
45. Raw E, Hudsmith L, Aithal GP, Jaspan T. A not-so-simple collapse. J R Soc Med. 2003; 96(9): 459–460. [PubMed: 12949205]
46. Sabri A, Dabbous H, Dowli A, et al. The airway in inhalational injury: diagnosis and management. Ann Burns Fire Disasters. 2017; 30(1):24–29. [PubMed: 28592930]
47. Goldstein M. Carbon monoxide poisoning. J Emerg Nurs. 2008; 34(6):538–542. [PubMed: 19022078]
48. Hollander DI, Nagey DA, Welch R, et al. Hyperbaric oxygen therapy for the treatment of acute carbon monoxide poisoning in pregnancy. A case report. J Reprod Med. 1987; 32(8):615–617. [PubMed: 3656301]
49. Buckley NA, Juurlink DN, Isbister G, et al. Hyperbaric oxygen for carbon monoxide poisoning. Cochrane Database Syst Rev. 2011; (4):CD002041. [PubMed: 21491385]
50. Delivoria-Papadopoulos M, Coburn RF, Forster RE. Cyclic variation of rate of carbon monoxide production in normal women. J Appl Physiol. 1974; 36(1):49–51. [PubMed: 4809863]
51. Hampson NB, Piantadosi CA, Thom SR, et al. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. Am J Respir Crit Care Med. 2012; 186(11):1095–1101. [PubMed: 23087025]
52. Hampson NB, Dunn SL. Group UCCPS. Symptoms of carbon monoxide poisoning do not correlate with the initial carboxyhemoglobin level. Undersea Hyperb Med. 2012; 39(2):657–665. [PubMed: 22530449]
53. Touger M, Gallagher EJ, Tyrell J. Relationship between venous and arterial carboxyhemoglobin levels in patients with suspected carbon monoxide poisoning. Ann Emerg Med. 1995; 25(4):481–483. [PubMed: 7710152]
54. Rose JJ, Wang L, Xu Q, et al. Carbon monoxide poisoning: Pathogenesis, management, and future directions of therapy. Am J Respir Crit Care Med. 2017; 195(5):596–606. [PubMed: 27753502]
55. Barker SJ, Curry J, Redford D, et al. Measurement of carboxyhemoglobin and methemoglobin by pulse oximetry: a human volunteer study. Anesthesiology. 2006; 105(5):892–897. [PubMed: 17065881]
56. Hampson NB. Noninvasive pulse CO-oximetry expedites evaluation and management of patients with carbon monoxide poisoning. Am J Emerg Med. 2012; 30(9):2021–2024. [PubMed: 22626815]
57. Hampson NB, Weaver LK. Noninvasive CO measurement by first responders. A suggested management algorithm. JEMS. 2006; 31(5):S10–12. [PubMed: 16739272]
58. Bickler PE, Feiner JR, Severinghaus JW. Effects of skin pigmentation on pulse oximeter accuracy at low saturation. Anesthesiology. 2005; 102(4):715–719. [PubMed: 15791098]
59. Feiner JR, Rollins MD, Sall JW, et al. Accuracy of carboxyhemoglobin detection by pulse CO-oximetry during hypoxemia. Anesth Analg. 2013; 117(4):847–858. [PubMed: 23477959]
60. Feiner JR, Severinghaus JW, Bickler PE. Dark skin decreases the accuracy of pulse oximeters at low oxygen saturation: the effects of oximeter probe type and gender. Anesth Analg. 2007; 105:S18–23. [PubMed: 18048893]
61. O'Malley GF. Non-invasive carbon monoxide measurement is not accurate. Ann Emerg Med. 2006; 48(4):477–478. [PubMed: 16997690]

62. Weaver LK, Churchill SK, Deru K, et al. False positive rate of carbon monoxide saturation by pulse oximetry of emergency department patients. Respir Care. 2013; 58(2):232–240. [PubMed: 22782305]
63. Levasseur L, Galliot-Guilley M, Richter F, et al. Effects of mode of inhalation of carbon monoxide and of normobaric oxygen administration on carbon monoxide elimination from the blood. Hum Exp Toxicol. 1996; 15(11):898–903. [PubMed: 8938485]
64. Towers CV, Corcoran VA. Influence of carbon monoxide poisoning on the fetal heart monitor tracing: a report of 3 cases. J Reprod Med. 2009; 54(3):184–188. [PubMed: 19370905]
65. Rezavand N, Seyedzadeh A, Soleymani A. Evaluation of maternal and foetal outcomes in pregnant women hospitalized in Kermanshah Hospitals, Iran, owing to burn injury, 2003–2008. Ann Burns Fire Disasters. 2012; 25(4):196–199. [PubMed: 23766753]
66. Roderique EJ, Gebre-Giorgis AA, Stewart DH, et al. Smoke inhalation injury in a pregnant patient: a literature review of the evidence and current best practices in the setting of a classic case. J Burn Care Res. 2012; 33(5):624–633. [PubMed: 22293595]
67. Weaver LK, Howe S, Hopkins R, et al. Carboxyhemoglobin half-life in carbon monoxide-poisoned patients treated with 100% oxygen at atmospheric pressure. Chest. 2000; 117(3):801–808. [PubMed: 10713010]
68. Silverman RK, Montano J. Hyperbaric oxygen treatment during pregnancy in acute carbon monoxide poisoning. A case report. J Reprod Med. 1997; 42(5):309–311. [PubMed: 9172124]
69. Weaver LK. Hyperbaric medicine for the hospital-based physician. Hosp Pract (1995). 2012; 40(3): 88–101.
70. Wada J, Ikeda T, Kamata K. Oxygen hyperbaric treatment for carbon monoxide poisoning and severe burns in coal mine gas explosion. Igakunoayumi (Japan). 1965; 54:68.
71. Mutluoglu M, Metin S, Ibrahim A, et al. The use of hyperbaric oxygen therapy for carbon monoxide poisoning in Europe. Undersea Hyperb Med. 2016; 43(1):49–56. [PubMed: 27000013]
72. Gibson AJ, Davis FM, Ewer T, et al. Delayed hyperbaric oxygen therapy for carbon monoxide intoxication--two case reports. N Z Med J. 1991; 104(906):64–65. [PubMed: 2020446]
73. Practice Bulletin No. 170 Summary: Critical Care in Pregnancy. Obstet Gynecol Surv. 2016; 128(4):929–930.
74. Ramos ESM, Martins NR, Kroumpouzos G. Oral and vulvovaginal changes in pregnancy. Clin Dermatol. 2016; 34(3):353–358. [PubMed: 27265073]
75. Hexdall A, McGee W. Red cell exchange transfusion for severe carbon monoxide poisoning merits further study. J Clin Apher. 2013; 28(5):335–336. [PubMed: 23804457]
76. Zengin S, Yilmaz M, Al B, et al. Therapeutic red cell exchange for severe carbon monoxide poisoning. J Clin Apher. 2013; 28(5):337–340. [PubMed: 23749385]
77. Anselmi A, Ruggieri VG, Letheulle J, et al. Extracorporeal Membrane Oxygenation in Pregnancy. J Card Surg. 2015; 30(10):781–786. [PubMed: 26307595]
78. Cunningham JA, Devine PC, Jelic S. Extracorporeal membrane oxygenation in pregnancy. Obstet Gynecol. 2006; 108(3 Pt 2):792–795. [PubMed: 17018505]
79. Saad AF, Rahman M, Maybauer DM, et al. Extracorporeal Membrane Oxygenation in Pregnant and Postpartum Women With H1N1-Related Acute Respiratory Distress Syndrome: A Systematic Review and Meta-analysis. Obstet Gynecol. 2016; 127(2):241–247. [PubMed: 26942349]
80. Teerapuncharoen K, Sharma NS, Barker AB, et al. Successful Treatment of Severe Carbon Monoxide Poisoning and Refractory Shock Using Extracorporeal Membrane Oxygenation. Respir Care. 2015; 60(9):e155–160. [PubMed: 25922545]
81. Van Hoesen KB, Camporesi EM, Moon RE, et al. Should hyperbaric oxygen be used to treat the pregnant patient for acute carbon monoxide poisoning? A case report and literature review. JAMA. 1989; 261(7):1039–1043. [PubMed: 2644457]
82. Thorsen E, Aanderud L, Aasen TB. Effects of a standard hyperbaric oxygen treatment protocol on pulmonary function. Eur Respir J. 1998; 12(6):1442–1445. [PubMed: 9877506]
83. Wattel F, Mathieu D, Mathieu-Nolf M. A 25-year study (1983–2008) of children's health outcomes after hyperbaric oxygen therapy for carbon monoxide poisoning in utero. Bull Acad Natl Med. 2013; 197(3):677–694. [PubMed: 25163349]

84. Thom SR. Antagonism of carbon monoxide-mediated brain lipid peroxidation by hyperbaric oxygen. Toxicol Appl Pharmacol. 1990; 105(2):340–344. [PubMed: 2219124]
85. Thom SR. Functional inhibition of leukocyte B2 integrins by hyperbaric oxygen in carbon monoxide-mediated brain injury in rats. Toxicol Appl Pharmacol. 1993; 123(2):248–256. [PubMed: 8248932]
86. Piantadosi CA. Diagnosis and treatment of carbon monoxide poisoning. Respir Care Clin N Am. 1999; 5(2):183–202. [PubMed: 10333448]
87. Weaver LK. Carbon monoxide poisoning. Crit Care Clin. 1999; 15(2):297–317. viii. [PubMed: 10331130]
88. Thom SR, Taber RL, Mendiguren II, et al. Delayed neuropsychologic sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen. Ann Emerg Med. 1995; 25(4):474–480. [PubMed: 7710151]
89. Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med. 2002; 347(14):1057–1067. [PubMed: 12362006]
90. Weaver LK. Clinical practice. Carbon monoxide poisoning. N Engl J Med. 2009; 360(12):1217–1225. [PubMed: 19297574]
91. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. N Engl J Med. 1996; 334(25):1642–1648. [PubMed: 8628361]
92. Hampson NB, Simonson SG, Kramer CC, et al. Central nervous system oxygen toxicity during hyperbaric treatment of patients with carbon monoxide poisoning. Undersea Hyperb Med. 1996; 23:215–219. [PubMed: 8989851]
93. Villanueva E, Bennett MH, Wasiak J, et al. Hyperbaric oxygen therapy for thermal burns. Cochrane Database Syst Rev. 2004; (3):CD004727. [PubMed: 15266540]
94. Baud F, Boukobza M, Borron SW. Cyanide: an unreported cause of neurological complications following smoke inhalation. BMJ Case Rep. 2011; 2011
95. Baud FJ, Barriot P, Toffis V, et al. Elevated blood cyanide concentrations in victims of smoke inhalation. N Engl J Med. 1991; 325(25):1761–1766. [PubMed: 1944484]
96. Baud FJ. Acute poisoning with carbon monoxide (CO) and cyanide (CN). Ther Umsch. 2009; 66(5):387–397. [PubMed: 19401990]
97. Hampson NB, Hauff NM. Risk factors for short-term mortality from carbon monoxide poisoning treated with hyperbaric oxygen. Crit Care Med. 2008; 36(9):2523–2527. [PubMed: 18679118]
98. Norris JC, Moore SJ, Hume AS. Synergistic lethality induced by the combination of carbon monoxide and cyanide. Toxicology. 1986; 40(2):121–129. [PubMed: 3726889]
99. Ballantyne, B. Toxicology of cyanides. In: Ballantyne, B., Marrs, TC., editors. Clinical and Experimental Toxicology of Cyanides. Bristol, UK: Wright Publishers; 1987. p. 41-126.
100. Chang, R. Physical chemistry for the biosciences. Sausalito, CA: University Science Books; 2005.
101. Soto-Blanco B, Gorniak SL. Prenatal toxicity of cyanide in goats--a model for teratological studies in ruminants. Theriogenology. 2004; 62(6):1012–1026. [PubMed: 15289044]
102. Baud FJ. Cyanide: critical issues in diagnosis and treatment. Hum Exp Toxicol. 2007; 26(3):191–201. [PubMed: 17439922]
103. Jang DH, Shofer FS, Weiss SL, et al. Impairment of mitochondrial respiration following ex vivo cyanide exposure in peripheral blood mononuclear cells. Clin Toxicol (Phila). 2016; 54(4):303–307. [PubMed: 26846815]
104. Hampson NB. When is the urine “cherry red” in carbon monoxide poisoning? J Clin Toxicol. 2014; 4:215.
105. Hamad E, Babu K, Bebarta VS. Case files of the University of Massachusetts toxicology fellowship: Does this smoke inhalation victim require treatment with cyanide antidote? J Med Toxicol. 2016; 12(2):192–198. [PubMed: 26831054]
106. Dries DJ, Endorf FW. Inhalation injury: epidemiology, pathology, treatment strategies. Scand J Trauma Resusc Emerg Med. 2013; 21:31. [PubMed: 23597126]
107. Grabowska T, Skowronek R, Nowicka J, et al. Prevalence of hydrogen cyanide and carboxyhaemoglobin in victims of smoke inhalation during enclosed-space fires: a combined toxicological risk. Clin Toxicol (Phila). 2012; 50(8):759–763. [PubMed: 22882141]

108. Anseeuw K, Delvau N, Burillo-Putze G, et al. Cyanide poisoning by fire smoke inhalation: a European expert consensus. Eur J Emerg Med. 2013; 20(1):2–9. [PubMed: 22828651]
109. MacLennan L, Moiemen N. Management of cyanide toxicity in patients with burns. Burns. 2015; 41(1):18–24. [PubMed: 24994676]
110. Legrand M, Michel T, Daudon M, et al. Risk of oxalate nephropathy with the use of cyanide antidote hydroxocobalamin in critically ill burn patients. Intensive Care Med. 2016; 42(6):1080–1081. [PubMed: 26891675]
111. Baud F. Clarifications regarding interference of hydroxocobalamin with carboxyhemoglobin measurements in victims of smoke inhalation. Ann Emerg Med. 2007; 50(5):625–626. [PubMed: 17963991]
112. Graeme KA, Curry SC, Bikin DS, et al. The lack of transplacental movement of the cyanide antidote thiosulfate in gravid ewes. Anesth Analg. 1999; 89(6):1448–1452. [PubMed: 10589625]
113. Baud, FJ. Efficacy and safety of antidotes for acute poisoning by cyanides. Brussels, Belgium: European Centre for Ecotoxicology and Toxicology of Chemicals; 2013. Technical Report No. 121
114. Doucet, JJ., Boedeker, B., Jagminas, L. Weapons of mass destruction: chemical, biological, and radiological warfare agents. In: Wilson, WC.Grande, CM., Hoyt, DB., editors. Trauma: Emergency resuscitation perioperative anesthesia surgical management. Vol. 1. Boca Raton, FL: Taylor & Francis Group, LLC; 2007. p. 783-784.
115. Herndon DN, Rodriguez NA, Diaz EC, et al. Long-term propranolol use in severely burned pediatric patients: a randomized controlled study. Ann Surg. 2012; 256(3):402–411. [PubMed: 22895351]
116. Lawson-Smith P, Jansen EC, Hilsted L, et al. Effect of acute and delayed hyperbaric oxygen therapy on cyanide whole blood levels during acute cyanide intoxication. Undersea Hyperb Med. 2011; 38(1):17–26. [PubMed: 21384760]
117. Rode H, Millar AJ, Cywes S, et al. Thermal injury in pregnancy--the neglected tragedy. S Afr Med J. 1990; 77(7):346–348. [PubMed: 2181702]
118. Vaghardoost R, Kazemzadeh J, Rabieepoor S. Epidemiology of burns during pregnancy in Tehran, Iran. Burns. 2016; 42(3):663–667. [PubMed: 26691644]
119. Herndon DN, Rutan RL. Comparison of cultured epidermal autograft and massive excision with serial autografting plus homograft overlay. J Burn Care Rehabil. 1992; 13(1):154–157. [PubMed: 1572848]

Table 1

Symptoms of maternal carbon monoxide intoxication

CO Poisoning	Symptoms
Acute	Respiratory distress, visual & physical impairment, exertional dyspnea, angina, confusion, changes in consciousness, convulsions, disorientation, hypotension, arrhythmia, tachycardia, tachypnea, dysrhythmias and other electrocardiogram changes (e.g., ST segment depressions), acute myocardial infarction, fever, vomiting, severe headache, increased heart rate, increased respiratory rate, dizziness, fatigue, problematic decision-making, vertigo
Life-threatening	Changes in consciousness, fainting, comas, delusions, amnesia and other psychiatric difficulties, disorientation, apathy, apraxia, incontinence, intestinal problems, muscular hypertonia, seizures, syncope, severe acidosis, delayed neurologic sequelae (e.g., Parkinson-like syndrome and dementia)
Lethal	Death

Table 2

Fetal outcomes due to acute carbon monoxide poisoning

Outcome	Gestational Age	Notes
Anatomical malformations (skeletal & limb abnormalities), low birth weight,	1st trimester	
Brain malformations (anoxic encephalopathy), down syndrome, cerebral palsy, mental & psychomotor development functional changes, fetal brain dysgenesis	2nd and 3rd trimester	Neurological changes can be incited during the first trimester if cyanide exposure is significant