Carbon monoxide poisoning

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epidemiology

epidemiology: tends to occur in specific situations

https://emcrit.org/ibcc/co/
• (1) Heating in the winter (CO generated by burning any fuel with inadequate oxygen)
  • Malfunctioning furnaces
  • Wood- or coal-burning stoves
  • Gasoline-powered generators used in enclosed spaces
  • Propane-powered forklifts or ice-resurfacing machines
  • Gas kitchen stoves used as a source of heat
  • Pear. CO can diffuse through drywall between adjacent apartments! The fact that your patient isn't burning fuel in their own apartment doesn't exclude CO exposure.
• (2) Suicide attempt using automobile exhaust
• (3) Burn victims with smoke inhalation
• (4) Exposure to methylene chloride (metabolism yields carbon monoxide)
  • Paint remover
  • Unique in that CO production occurs in a delayed fashion (levels peak 8 hours after exposure)

symptoms & presentation

useful diagnostic clues:

• Simultaneous illness among people living or working together (or animals experiencing syncope!)

neurologic

• Headache
• Visual alterations
• Ataxia, dizziness
• Delirium – Stupor – Coma
• Seizure

cardiopulmonary

• Dyspnea
• Chest pain due to myocardial ischemia
• Arrhythmia (acute mortality is usually due to VT/VF).
• Syncope
• Hypertension (initially), eventually may see hypotension (with systolic heart failure)

gastrointestinal:

• Nausea, vomiting
• Abdominal pain

tests that may provide clues

These tests are insensitive, late, and not preferred methods of detecting CO poisoning.

oxygen saturation gap

• Carbon monoxide "tricks" the pulse oximeter into reporting a high oxygen saturation, regardless of what the oxygen saturation actually is.
• Oxygen saturation gap refers to a patient with carbon monoxide poisoning and hypoxemia. This produces a "gap" between the pulse oximetry (which is close to 100%) compared to the PaO2 on ABG (which may be low).
• This may be helpful if you stumble over it, but it shouldn't be used intentionally as a diagnostic test for carbon monoxide.
  • In practice, this gap will generally be assumed to be a venous blood sample (rather than a true arterial blood specimen).
CO may increase lactate levels (due to reduced oxygen delivery and impaired tissue oxygen utilization).

Carboxyhemoglobin levels should be included in the investigation of undifferentiated hyperlactatemia (https://emcrit.org/ibcc/agma/#evaluation_&_treatment_of_lactate_elevation) (in patients with potential exposure).

**neuroimaging**

- Not the preferred mode of diagnosis of CO poisoning! (Changes are revealed too late make a significant impact in management).
- Over time, CT or MRI scanning may show decreased density in central white matter (e.g. globus pallidus, putamen, and caudate nuclei).
- Unfortunately, by the time these findings are detected, CO levels may have normalized (making definitive diagnosis impossible).

**specific testing for CO**

Different hospital systems test for carbon monoxide in different ways. You must know how your hospital does it.

**noninvasive co-oximetry**

- A specifically designed pulse oximeter (http://www.masimo.com/spco/) can detect carbon monoxide by simultaneously measuring absorption at seven wavelengths of light (instead of two, as in most oximeters).
- Performance is good but not perfect. This is well suited for use as a screening tool among undifferentiated emergency department patients.
  - This device is expensive and unavailable at most centers (but will probably come down in price soon).

**central laboratory processing of ABGs**

- Some hospitals analyze ABGs and VBGs in a central laboratory, with routine measurement of carbon monoxide and methemoglobin levels in all samples (using spectrophotometry).
- However, hospitals are increasingly using point-of-care testing – which don't measure carbon monoxide levels.

**specific laboratory test for carboxyhemoglobin**

- At most hospitals, the only way to obtain a carbon monoxide level is to specifically order this test.
- This doesn't have to be performed on arterial blood, nor need the sample be kept on ice. The carboxyhemoglobin level will be the same in any sample of blood drawn, arterial or venous.
- The test may be confounded by use of hydroxycobalamin for treatment of cyanide in smoke inhalation victims.
- Refrigerated, heparinized blood samples have a stable carboxyhemoglobin level for months, so CO level can be retrospectively added onto admission blood samples (18272101 (https://www.ncbi.nlm.nih.gov/pubmed/18272101)).

**interpreting carboxyhemoglobin levels**

- Normal levels:
- Nonsmokers: 0-3%
- Smokers: 0-10% (upper limit isn’t well defined, may extend as high as 15%?)(29435715).

- Although many references relate carboxyhemoglobin level to symptoms, this appears to be a myth. There is no validated relationship between carboxyhemoglobin levels and specific symptoms (26632018). Reasons that CO levels may not track with symptoms:
  - (a) Symptoms reflect tissue and blood levels of CO, not just blood levels.
  - (b) Chronic or subacute CO exposure may cause a greater amount of tissue CO, relative to blood CO.
  - (c) Hemoglobin concentration and overall cardiopulmonary fitness may also affect symptomatology.
- Severe intoxication is usually associated with carboxyhemoglobin level > 25%.

Cognitive schema for diagnosis?

Diagnosing CO poisoning is difficult due to its many possible manifestations. The schema above suggests some situations where testing may be considered. This obviously isn’t perfect, nor is it intended to replace medical judgement. This is merely included merely as a cognitive aid for considering the possibility of carbon monoxide poisoning.

Physiologic avenues of therapy

Two physiologic problems involved in carbon monoxide poisoning:
1. Carbon monoxide bound to erythrocytes prevents oxygen transfer to the tissues.
2. Carbon monoxide bound to the tissues may prevent oxygen utilization. In some ways, this may be a thornier issue than #1.

**physiologic maneuvers which could theoretically improve matters:**

- Manipulate end-organ oxygen utilization (to reduce oxygen utilization). A primary concern here is the brain.
  - Avoid fever or hyperthermia (this is generally bad for the brain, and also will increase metabolic rates and oxygen demand).
  - Sedation may decrease brain activity and thereby reduce the oxygen demand.
- Maintaining adequate cardiac output is important for two reasons:
  - Cardiac output drives CO from the tissues into the lungs.
  - Cardiac output will increase the oxygen delivery to the tissues.
- RBC transfusion (or exchange transfusion).
  - Anemia is problematic because this will impair both tissue oxygen delivery and tissue CO removal.
  - Exchange transfusion will remove erythrocytes which are bound to CO and deliver new erythrocytes.
- Adequate ventilation.
  - CO is removed from the body via ventilation across the lungs.
  - Hypoventilation should be avoided; the optimal pCO2 target might be on the low end of normal. (Hyperventilation will decrease cerebral perfusion, so that's not great either.)
- Aggressive oxygenation.
  - Oxygen administration plays multiple roles here (it competes with CO and provides oxygenation to the tissues).
  - Patients should be treated with 100% inhaled FiO2 at a minimum. In some situations, hyperbaric oxygen may be considered to push this even farther.

**risk stratification?**

Carbon monoxide poisoning has a spectrum of severity, ranging from mild to lethal. One challenge is determining where the patient lies along this spectrum, in order to determine the appropriate aggressiveness of our therapies.

Patients with severe carbon monoxide poisoning might benefit from intubation and sedation, to provide 100% oxygen and reduce metabolic activity. Although the precise criteria to define severe intoxication aren’t well defined, the following features may be useful.

**features suggestive of severe poisoning**

- Carboxyhemoglobin level is generally >25%. However, as discussed above, there is only a weak relationship between carboxyhemoglobin levels and symptoms so this isn’t an absolute cutoff.
- Significant neurologic dysfunction (seizure or obtundation).
  - For most patients, the brain is the end-organ which we are most concerned with resuscitating properly.

**mild CO intoxication**

Oxygen competes with carbon monoxide for binding to hemoglobin. Thus, the most basic treatment for carbon monoxide is flooding the patient with oxygen. This may be initiated empirically while awaiting testing for carbon monoxide.

**100% FiO2 should be provided by one of the following methods:**

https://emcrit.org/ibcc/co/
Carbon monoxide poisoning - EMCrit Project

- (a) High-flow nasal cannula set to 100% FiO2 with moderate or high flow rate (e.g. ~40 L/min or more).
  - One study found a reduction in carbon monoxide half-life to ~40 minutes using high flow rates (~60 liters/min) (https://www.ncbi.nlm.nih.gov/pubmed/30689450).
- (b) Combination of a nasal cannula beneath a non-rebreather facemask, both set to 15 liters/minute flow.
- (c) CPAP or BiPAP device with good mask seal, set to 100% FiO2.
  - One small RCT found CPAP to be more effective than HFNC at 15 liters/minute. The limitation to this study is that 15 liters/minute flow may not be adequate to truly achieve the benefits of HFNC (https://www.ncbi.nlm.nih.gov/pubmed/31637993).

Severe CO intoxication

High-quality evidence doesn't really exist for this condition, so no solid recommendations can be made. The following treatments may be considered, based on the clinical context and on bedside judgement.

Intubation & Sedation

- Provide 100% FiO2 (regardless of what the patient's PaO2 is).
- Provide adequate ventilation.
  - Increasing the minute ventilation will increase CO clearance from the body.
  - However, also desirable to avoid hypoventilation, which may delay CO clearance from the body.
  - A sensible target CO2 level could be in the low-normal range (pCO2 35-40 mm).
- Deep sedation.
  - Propofol may be an excellent sedative, if tolerated hemodynamically. Propofol reduces cerebral metabolic activity, which may reduce cellular oxygen deficiency in the brain.
  - Dissociative ketamine may be considered as a sedative choice, if the patient isn't hemodynamically able to tolerate propofol. Ketamine has been shown to protect against CO poisoning in rats, due to inhibition of the NMDA receptor which blocks glutamate excitotoxicity (https://www.ncbi.nlm.nih.gov/pubmed/8854215).
  - Deep sedation (more than is necessary to tolerate the ventilator) could be beneficial as a supportive therapy until enough time has passed to clear the CO.

Temperature Control

- Fever is extraordinarily problematic here for many reasons:
  - Fever is generally bad for the anoxic brain (admittedly, a generalization from other conditions).
  - Fever will increase metabolic oxygen demands, thereby exacerbating oxygen demand/supply mismatch.
- Therapeutic temperature control may be a reasonable intervention. This isn't supported by any high-level evidence, but may be indirectly supported by evidence regarding anoxic brain injury (which is mechanistically somewhat similar to CO poisoning).
  - Based on the dictum of *primum non nocere*, TTM at 36°C might currently be the best strategy, as this is safer overall and requires less physiologic manipulation. Additionally, one animal study suggested that hypothermia could increase mortality in carbon monoxide poisoning (https://www.ncbi.nlm.nih.gov/pubmed/2378003).

PRBC Transfusion

- Exchange transfusion
  - Some case series have described exchange transfusion. However, there is no high-level evidence to support this.
  - Given that the half-life of carbon monoxide is roughly an hour (at 100% FiO2), exchange transfusion probably doesn't make sense for most patients. By the time of the exchange transfusion, the carbon monoxide levels will be falling anyway.
- Simple transfusion (a.k.a. "straight" transfusion)
  - For patients with anemia, it could make sense to target a somewhat higher hemoglobin level than usual (e.g. hemoglobin target > 10 g/dL).

Defend Perfusion

https://emcrit.org/ibcc/co/
Reasons that hemodynamics are important:
- Maintaining adequate perfusion is required to encourage CO transport out of the tissues and oxygen transport into the tissues.
- Animal studies suggest that chronic neurologic sequelae may require two hits – CO exposure plus hypotension.
- Adequate brain perfusion is probably the most important hemodynamic target (as this may affect long-term sequelae).
- Patients may have myocardial stunning due to carboxyhemoglobinemia, which could theoretically benefit from inotropic support. As always, resuscitation should be guided by bedside evaluation (e.g. with echocardiography).

**hyperbaric oxygen?**

**potential benefits of hyperbaric oxygen**
- Oxygen competes with CO for binding to tissues and erythrocytes, thereby decreasing the half-life of carbon monoxide in the body.
- The half-life of carbon monoxide under various conditions:
  - Half-life of carbon monoxide at 21% FiO2 is ~5 hours.
  - Half-life of carbon monoxide at 100% FiO2 is ~1 hour.
  - Half-life of carbon monoxide at 250% FiO2 is ~20 minutes.
- In pregnancy, hyperbaric oxygen could promote fetal oxygenation.

**potential risks of hyperbaric oxygen**
- (1) Hyperoxia-induced free radical production
  - Part of the pathogenesis of CO toxicity involves free radical production in the brain.
  - High levels of oxygen may increase free radical generation, which is potentially detrimental to patients with brain injury.
  - Hyperoxia seems to be harmful among post-arrest patients, and may also be detrimental among post-CO patients.
- (2) Logistic barriers to care
  - Placement in a hyperbaric chamber may interfere with other components of management.
- (3) Transportation risks
  - Most hospitals don't have a hyperbaric chamber, so this therapy may involve inter-hospital transfer (with the risks attendant in that process).

**effect of timing in the use of hyperbaric oxygen**
- If hyperbaric oxygen therapy is beneficial, it's probably most useful initially (before there has been substantial brain injury).
- Provision of hyperbaric oxygen probably becomes increasingly unhelpful as time progresses:
  - The level of CO in the brain will fall over time, making this intervention relatively less beneficial.
  - Although many studies have included repeated hyperbaric sessions over a period of days, the theoretical basis of applying hyperbaric oxygen after the initial CO has been washed out seems questionable. (More hyperbaric oxygen is probably not better – especially when provided in a delayed fashion.)

**evidentiary basis of hyperbaric oxygen**
RCTs regarding hyperbaric oxygen are shown above. Overall, this data is relatively unimpressive. The largest trials are negative (including every trial with >152 patients).

Timing to treatment may be important – the study with the shortest delay to intervention had a positive outcome (Thom et al. 1993).

Some studies detected evidence of harm:
- Scheinkestel et al. concluded that hyperbaric therapy may have worsened patient outcomes and cannot be recommended.

Advocates for hyperbaric oxygen emphasize the Weaver trial as the study that got things right (analogous to the NINDS trial in stroke research). However, this trial has numerous limitations:
- At baseline, patients in the control group had significantly higher rates of cerebellar dysfunction (15/76 vs. 4/76).
- The study was prematurely terminated, due to perceived benefit. Premature termination is a notorious cause of false-positive studies. This trial was subject to four interim analyses, so based on a Haybittle-Peto stopping rule (https://en.wikipedia.org/wiki/Haybittle–Peto_boundary) it should have been stopped only if the results were extremely significant (p < 0.001).
- Five patients were lost to follow-up (four in the control arm and one in the hyperbaric arm). These five patients were assumed to have poor outcomes.
- Some p-values seem to have been obtained with an uncorrected Pearson Chi-squared test, which will tend to over-estimate the statistical significance of results. When re-calculated using a Fisher Exact test, results are less impressive (table below).
- Change in the primary endpoint between study inception and publication (CoreEM [https://coreem.net/journal-reviews/hyperbaric-oxygen-for-acute-carbon-monoxide-poisoning/]).

**Table 2. Outcomes at 6 Weeks, 6 Months, and 12 Months after Enrollment.***

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hyperbaric Oxygen (N=76)</th>
<th>Normobaric Oxygen (N=76)</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Fisher Exact Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive sequelae</td>
<td>19/76 (25.0)</td>
<td>31/76 (41.0)</td>
<td>0.39 (0.20–0.78)</td>
<td>0.007</td>
<td>0.04</td>
</tr>
<tr>
<td>Intention-to-treatment population</td>
<td>18/79 (23.7)</td>
<td>31/72 (40.3)</td>
<td>0.41 (0.21–0.81)</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Abnormal</td>
<td>1/7 (14.3)</td>
<td>9/11 (81.8)</td>
<td>0.01 (0.01–1.92)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td>16/76 (21.1)</td>
<td>26/76 (34.2)</td>
<td>0.43 (0.21–0.88)</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Intention-to-treatment population</td>
<td>18/78 (17.2)</td>
<td>31/89 (34.6)</td>
<td>0.38 (0.16–0.89)</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>At 12 months</td>
<td>14/76 (18.4)</td>
<td>26/76 (32.9)</td>
<td>0.46 (0.22–0.98)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td>9/62 (14.5)</td>
<td>18/66 (27.3)</td>
<td>0.43 (0.19–1.08)</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

*The five patients who did not have data on neuropsychological tests at 6 weeks were not included in the primary endpoint. Cognitive sequelae present at 6 or 12 months were not included in the primary endpoint.

**ACEP clinical policy (2017)**

This includes a detailed summary of available literature. However, it’s a short document which is highly recommended reading (the PDF is available right [here](https://emcrit.org/wp-content/uploads/2017/01/PII2016064416313452.pdf)).
Perhaps this is the most trustworthy and non-biased assessment of the topic available. The authors conclude that "It remains unclear whether hyperbaric therapy is superior to normobaric oxygen therapy for improving long-term neurocognitive outcomes." ACEP recommends that either hyperbaric oxygen or high-flow normobaric oxygen should be used.

**my opinion on hyperbaric oxygen**

1. Any benefit from hyperbaric oxygen is likely greatest *early* on in the disease course, while carbon monoxide levels remain high. After carbon monoxide levels have fallen, risks of hyperoxia might outweigh the benefits of hyperbaric therapy.
2. If hyperbaric therapy can be instituted very rapidly (e.g. <6 hours), it's probably beneficial.
3. If hyperbaric therapy requires inter-hospital transfer with substantially delayed initiation, then it's probably not beneficial.
4. Hyperbaric therapy should be considered more strongly in pregnancy, to improve fetal oxygenation.
5. Additional RCTs are needed to clarify whether hyperbaric oxygen is effective.
6. Local toxicologists should be consulted for cases of severe CO poisoning given controversy in the literature and variable resources in different geographic areas.

**the future: isocapneic hyperventilation?**

Carbon monoxide clearance from the body can be accelerated with the use of hyperventilation. However, hyperventilation is generally limited by the generation of respiratory alkalosis (low pCO2 levels). Hyperventilation with *normocapnia* can be achieved if the patient inhales a gas with elevated CO2 levels. This has been shown to greatly accelerate CO clearance (achieving a clearance rate similar to that of hyperbaric oxygen) ([28107437](https://www.ncbi.nlm.nih.gov/pubmed/28107437)).

Isocapneic hyperventilation was utilized historically, before the advent of hyperbaric oxygen. This method was often effective, although if not instituted properly there could be a risk of promoting hypercapnia. In the 1960s, due to a growth in popularity of hyperbaric oxygen, this technique fell out of favor. With the wisdom of hindsight, that transition may have been a mistake. Specifically, isocapneic hyperventilation is potentially cheaper, easier, and more widely applicable than hyperbaric oxygen therapy.

Currently, achieving isocapneic hyperventilation at the bedside may be logistically challenging. For intubated patients, this would likely involve:

- Immediate availability of tanks of CO2 gas
- Bleeding CO2 gas into the ventilator at a controlled rate
- Up-titration of CO2 bleed-in rate, with simultaneous increase in minute ventilation
- Monitoring of end-tidal CO2 and patient's PaCO2 (with a goal of pCO2 ~35-40 mm)
- Maximization of minute ventilation while maintaining a stable pCO2 level
- Sedation or paralysis (to avoid excessive work of breathing)

For non-intubated patients, a commercial device ([ClearMate](https://thornhillmedical.com/clearmate/)) has been developed which utilizes variable CO2 administration to promote isocapneic hyperventilation ([28107437](https://www.ncbi.nlm.nih.gov/pubmed/28107437)). This device generates different inhaled levels of CO2 depending on the patient's minute ventilation, thereby avoiding a risk of hypercapnia. The device is portable and requires no power source, allowing for immediate application anywhere.

**summary**

**podcast**

The primary mistake is failing to consider and screen for carbon monoxide intoxication. Testing for carbon monoxide poisoning may be considered in patients with possible exposure and any of the following presentations:

- Neurologic abnormalities (e.g. seizure, delirium, coma, cerebellar signs).
- Suspected intoxication (e.g. presentation with acutely altered mental status without alternative explanation).
- Elevated lactate (especially in a hemodynamically stable patient without an obvious cause for this).
- Flu-like symptoms (e.g. headache, nausea, vomiting, dyspnea) – especially in the absence of fever.
- Simultaneous illness in multiple people living together.

- Failure to immediately initiate 100% FiO2 if carbon monoxide poisoning is identified or strongly suspected. This may be achieved in numerous ways, perhaps the most effective being noninvasive ventilation.

Going further:

- [Hyperbaric oxygen for acute carbon monoxide poisoning](https://coreem.net/journal-reviews/hyperbaric-oxygen-for-acute-carbon-monoxide-poisoning/) (Brent Dibble, CoreEM)
- [Neuroimaging in Carbon Monoxide poisoning](https://radiopaedia.org/articles/carbon-monoxide-poisoning-1?lang=us) (Daniel Bell and Yuranga Weerakkody, Radiopaedia)
- [Carbon Monoxide toxicity](https://wikem.org/wiki/Carbon_monoxide_toxicity) (WikEM)
- [Carbon Monoxide Poisoning](http://www.emdocs.net/carbon-monoxide-poisoning/) (Zach Radwine, emDocs)