Cyanide poisoning

INTRODUCTION — Cyanide is a mitochondrial toxin that is among the most rapidly lethal poisons known to man. Used in both ancient and modern times as a method of execution, cyanide causes death within minutes to hours of exposure. Though significant cyanide poisoning is uncommon, it must be recognized rapidly to ensure prompt administration of life-saving treatment. A summary table to facilitate emergent management is provided (table 1).

This topic review will discuss the toxicity and management of cyanide poisoning. A general approach to the poisoned patient is found elsewhere. (See "General approach to drug poisoning in adults".)

EPIDEMIOLOGY — According to the Toxic Exposure Surveillance System, there were 3165 human exposures to cyanide from 1993 to 2002. Of these, 2.5 percent were fatal [1]. Cyanide poisoning may result from a broad range of exposures (table 2).

- Fire — In industrialized countries, the most common cause of cyanide poisoning is domestic fires [2]. Cyanide can be liberated during the combustion of products containing both carbon and nitrogen. These products include wool, silk, polyurethane (insulation/upholstery), polyacrylonitriles (plastics), melamine resins (household goods), and synthetic rubber [3-5]. Vehicular fires can also expose victims to cyanide. Toxicologic evaluation of passengers following the explosion in 1985 of a Boeing 737 during take-off in Manchester, England, revealed that 20 percent of the 137 victims who escaped had dangerously elevated levels of carbon monoxide, while 90 percent had dangerously elevated levels of cyanide [6]. Overall, it is reported that significant levels of cyanide are present in up to 35 percent of all fire victims [7].

- Industrial — Worldwide industrial consumption of cyanide is estimated to be 1.5 million tons per year, and occupational exposures account for a significant number of cyanide poisonings [8]. Metal extraction in mining, electroplating in jewelry production, photography, plastics and rubber manufacturing, hair removal from hides, and rodent pesticide and fumigants have all been implicated in cyanide poisonings. Skin contact with cyanide salts can result in burns, which allow for enhanced absorption of cyanide through the skin. The combination of cyanide salts and acid, as utilized in electroplating, results in the release of cyanide gas, which can lead to lethal inhalational exposures. Splashes of cyanide solutions can result in dermal as well as mucosal absorption [2,9].

- Medical — Cyanide exposures can result from alternative and standard medical treatments. Amygdalin (trade name Laetrile), a substance derived from apricot and peach kernels, and introduced as an antineoplastic agent in the 1950s, can cause severe cyanide toxicity [10-12]. The drug is alleged to kill cancer cells selectively via its metabolite, hydrocyanic acid. Laetrile is available as a 500 mg oral tablet that contains 30 to 150 mg of amygdalin [13]. Intestinal beta-d-glucosidase digests the amygdalin, releasing hydrogen cyanide (HCN). This enzymatic reaction explains why only gastrointestinal exposure, in contrast to intravenous administration, results in toxicity [10].

Sodium nitroprusside, a medication used in the treatment of hypertensive emergencies, contains five cyanide groups per molecule. Toxic levels of cyanide may be reached in patients who receive prolonged infusions of sodium nitroprusside, in patients with chronic renal failure, or in pediatric patients [14,15]. Treatment for 3 to 10 hours with 5 to 10 mcg/kg/min has resulted in fatalities [16]. Methods for preventing nitroprusside-induced cyanide poisoning include using silver foil on IV tubing (preventing light from decomposing the nitroprusside molecule), using maximal infusion rates of 2 mcg/kg/min, and adding sodium thiosulfate to the nitroprusside solution [17].

- Diet — The family Rosaceae, which includes the bitter almond, cherry laurel, apricot, plum, peach, pear, and...
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PATHOPHYSIOLOGY — In normal cellular metabolism, most adenosine triphosphate (ATP) is generated from oxidative phosphorylation. An important part of this process is the shuttling of electrons through the mitochondrial cytochrome complex (also known as the electron transport chain) (figure 1).

Cyanide avidly binds to the ferric ion (Fe3+) of cytochrome oxidase a3, inhibiting this final enzyme in the mitochondrial cytochrome complex. When this enzyme’s activity is blocked, oxidative phosphorylation ceases. The cell must then switch to anaerobic metabolism of glucose to generate ATP.

Anaerobic metabolism leads to the formation of lactic acid and the development of metabolic acidosis. Hydrogen ions produced by ATP hydrolysis are no longer consumed in aerobic ATP production, exacerbating this acidosis. Bicarbonate decreases as it buffers excess acid, leading to an increased anion gap.

Despite an ample oxygen supply, cells cannot utilize oxygen because of their poisoned electron transport chain. This functional (or “histotoxic”) hypoxia is particularly deleterious to the cardiovascular and central nervous systems (especially the basal ganglia).

A number of other mechanisms may exacerbate brain injury. Cyanide’s nonspecific inhibition of antioxidants (such as catalase, glutathione reductase, and superoxide dismutase) results in the accumulation of toxic oxygen free-radicals. Cyanide stimulates N-methyl-D-aspartate (NMDA) receptors, inducing apoptotic cell death. It also inhibits glutamic acid decarboxylase (GAD), the enzyme responsible for the formation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) from glutamic acid. Consequently, cyanide increases the risk of seizures as GABA levels fall.

Although cyanide has a primary affinity for ferric (Fe3+) iron, a small amount may bind to the ferrous (Fe2+) iron of hemoglobin, forming cyanohemoglobin, which is unable to transport oxygen, thereby further exacerbating tissue hypoxia.

KINETICS AND METABOLISM — Cyanide is rapidly absorbed through the respiratory tract and mucous membranes, and it can also be absorbed through the gastrointestinal tract and skin. Symptoms and signs of poisoning begin at blood cyanide concentrations of approximately 40 μmol/L. Once absorbed, cyanide is quickly distributed in the body with an estimated volume of distribution of 1.5 L/kg. Approximately 60 percent is protein bound.

In vivo, cyanide metabolism and neutralization involve a number of mechanisms. The most important is the detoxification of cyanide via rhodanese. Rhodanese is an enzyme found abundantly in many tissues, particularly the liver and muscle. Thiosulfate serves as a sulfur donor in the reaction catalyzed by rhodanese that converts cyanide to thiocyanate, a water soluble molecule excreted in the urine.

A minor pathway for cyanide detoxification involves hydroxocobalamin, the precursor to vitamin B12. Circulating hydroxocobalamin combines with cyanide to form cyanocobalamin, which is safely excreted in the urine. Finally, a small amount of unmetabolized cyanide is eliminated through urine, sweat, and expiration.

CLINICAL PRESENTATION — Clinical features of cyanide poisoning are dependent upon the route, duration, and amount of exposure. Central nervous system and cardiovascular system dysfunction are most prominent. Symptoms and signs can include the following:

- Central nervous system – Headache, anxiety, confusion, vertigo, coma, seizures
- Cardiovascular – Initial tachycardia and hypertension, then bradycardia and hypotension, atrioventricular block, ventricular dysrhythmias
- Respiratory – Initial tachypnea then bradypnea, pulmonary edema
- Gastrointestinal – Vomiting, abdominal pain
- Skin – Flushing (cherry-red color), cyanosis (late finding), irritant dermatitis (itching, erythema, edema, vesicles)
- Other – Miscellaneous exposure to cyanide may occur during illicit synthesis of phencyclidine, terrorist attacks, ingestion of acetonitrile (artificial nail polish remover), product tampering, and cigarette smoking. Because of the natural cyanide found in tobacco, cigarette smokers have more than 2.5 times the mean whole blood cyanide level of nonsmokers (table 1).
Of note, because of the decreased utilization of oxygen by tissues, the venous oxyhemoglobin concentration will be high, making venous blood appear bright red. Therefore, despite hypotension, apnea, and/or bradycardia, the patient does not usually appear cyanotic in the setting of cyanide poisoning [16].

Symptoms depend on the severity and route of cyanide poisoning (table 3). After inhaling hydrogen cyanide (HCN), the victim may detect a bitter, almond odor (discernible to approximately 60 percent of the population) [28]. Initially, inhalation of small amounts of HCN causes headache, anxiety, nausea, and a metallic taste [9]. In contrast, cyanogen chloride (CNCl) exposure predominantly results in eye and mucous membrane irritation and then pulmonary symptoms, namely bronchorrhea, cough, and dyspnea [22]. Inhalation of 100 ppm for 30 minutes or 300 ppm for five minutes is usually fatal [9].

While toxicity from parenteral exposure begins within seconds, toxicity from ingestion or dermal exposure is from minutes to hours, depending on the extent of exposure. Ingestion of cyanide salts results in gastric irritation, frequently causing vomiting and abdominal pain [16]. The lethal oral dose is 50 mg of hydrogen cyanide (HCN) or 200 mg of potassium cyanide (KCN) in an adult [9,22]. The lethal dermal exposure is estimated to be 100 mg/kg (table 3) [7].

Delayed sequelae — Survivors of severe cyanide poisoning may develop delayed-onset Parkinsonism or other neurologic sequelae. The basal ganglia are particularly sensitive to cyanide toxicity [28]. Basal ganglia injury may be due to either direct cellular injury or secondary to hypoxic effects. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain may demonstrate radiologic changes several weeks after the exposure. Resolution of symptoms is variable, and treatment is supportive.

Chronic cyanide exposure — Chronic cyanide exposure results in vague symptoms, such as headache, dysgeusia (abnormal taste), vomiting, chest pain, abdominal pain, and anxiety [9]. There are at least three insidious syndromes associated with chronic, low-level cyanide exposure: tobacco amblyopia, tropical ataxic neuropathy, and Leber hereditary neuropathy.

Tobacco amblyopia occurs predominantly in male cigarette smokers and manifests as progressive visual loss. It may result from an inherent inability to detoxify cyanide, and symptoms may reverse following smoking cessation or hydroxocobalamin (Cyanokit) administration.

Tropical ataxic neuropathy (TAN) is a demyelinating condition associated with excessive cassava consumption, usually in the poor and malnourished. The cassava plant contains a cyanogen, linamarin, which may not be removed with inadequate processing. Signs and symptoms of TAN include paresthesias, ataxia, hearing loss, and optic atrophy. Vitamin B12 deficiency may contribute to the condition. Cessation of dietary cassava and administration of vitamin B12 ameliorate symptoms.

Leber’s hereditary optic neuropathy is a rare, gradual loss of central vision that appears to be due to a defect in cyanide metabolism. A deficiency of rhodanese is one proposed mechanism.

LABORATORY EVALUATION

General testing — Routine laboratory evaluation in the potentially poisoned patient should include the following:

- Point-of-care (eg fingerstick) glucose concentration, to rule out hypoglycemia as the cause of any alteration in mental status
- Acetaminophen and salicylate levels, to rule out these common coingestions
- Electrocardiogram, to rule out conduction system poisoning by drugs that effect the QRS or QTc intervals
- Pregnancy test in women of childbearing age

Specific testing — Specific testing in cases of potential cyanide poisoning should also include the following:

- Basic chemistries (eg, Na+, Cl−, K+, HCO3−) and arterial blood gas to assess for anion gap metabolic acidosis
- Serum lactate concentration to confirm lactic acidosis
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A patient with altered mental status, seizures, hypotension, and lactic acidosis may be poisoned with:

- Carbon monoxide poisoning
- Inhalation injury from heat, smoke, or chemical irritants

Lactate — Cyanide-poisoned patients have an elevated blood lactate concentration. A retrospective study of 11 ICU patients with cyanide poisoning found that plasma lactate concentrations correlated closely with the severity of cyanide toxicity [29]. There were significant inverse correlations between lactate and systolic blood pressure, respiratory rate, and arterial pH. In fact, lactate concentrations of 10 mmol/ L or greater have been shown to be sensitive and specific for cyanide poisoning in smoke inhalation victims [30]. Consequently, a normal serum lactate level should lead the clinician to entertain other diagnoses, while serial lactate measurements can be used to monitor progress of patients being treated for cyanide poisoning.

Venous PO2 — A narrowing of the venous-arterial PO2 gradient (ie, venous hyperoxia) may be seen in the cyanide-poisoned patient [31]. Cyanide inhibits cellular oxidative phosphorylation resulting in a marked decrease in peripheral tissue oxygen extraction from the blood. This results in elevated central venous oxygenation. On examination, the skin may appear flushed and the venules in the retina bright red. Laboratory evaluation may reveal a decreased arterial–venous oxygen gradient. Clinicians should keep in mind that a decreased oxygen gradient is nonspecific and can result from other inhibitors of oxidative phosphorylation, such as carbon monoxide, hydrogen sulfide, and azides.

Cyanide concentration (level) — Blood cyanide concentrations may be obtained for diagnostic confirmation but results are not available in time to be clinically useful. Even when available, the results of direct testing may be unreliable as both proper storage conditions and prompt blood draws are required. Furthermore, blood cyanide concentrations do not correlate directly with survival. Nonetheless, blood cyanide concentrations of 0.5 to 1 mg/L (12 to 23 μmol/L) generally correlate with tachycardia and flushing, 1 to 2.5 mg/L (23 to 58 μmol/L) with obtundation, 2.5 to 3 mg/L (58 to 69 μmol/L) with coma, and greater than 3 mg/L (>69 μmol/L) with death [22].

Cyantesmo test strips are colorimetric strips used in the testing of waste water and during autopsies. One in vitro study assessed the ability of these strips to detect cyanide in simulated samples [32] and found they were accurate only at markedly elevated cyanide levels. Additional work is needed before this test can be considered for routine clinical use.

Given the limitations of cyanide concentration testing, antidotal treatment should be administered empirically based on the clinical presentation, and blood cyanide levels should serve mainly as confirmation.

DIAGNOSIS — Cyanide poisoning is an uncommon entity. Therefore, making the diagnosis requires that the clinician maintain a high index of suspicion based on history and clinical presentation. Patients who are victims of fires or reported ingestions, are exposed at work, or have recently been treated with sodium nitroprusside should all be considered potentially cyanide poisoned. When a clear history is unavailable, clinicians should consider any patient with altered mental status and a metabolic acidosis of unknown etiology a possible victim of cyanide poisoning. Blood cyanide concentrations are not available in time to guide the clinical management of acute poisoning.

DIFFERENTIAL DIAGNOSIS — Carbon monoxide poisoning is similar to cyanide in presentation. (See "Carbon monoxide poisoning").

Due to cyanide's wide range of possible symptoms and signs, the clinician must consider a number of potential diagnoses, including those listed below. Generally, the diagnosis is made based on a history of exposure and a consistent clinical presentation, since very few of these intoxicants have a rapidly available diagnostic test. If the diagnosis is in doubt, clinicians should seek assistance from a medical toxicologist or regional poison center. (See 'Additional resources' below.)

A patient with altered mental status, seizures, hypotension, and lactic acidosis may be poisoned with:

- Tricyclic antidepressants (see "Tricyclic antidepressant poisoning")
- Isoniazid (see "Isoniazid: An overview")
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- Methemoglobin producing agents (see "Clinical features, diagnosis, and treatment of methemoglobinemia")
- Strychnine (see "Strychnine poisoning")

A patient who suddenly collapsed after exposure to a gas may be poisoned with:

- Carbon monoxide (see "Carbon monoxide poisoning")
- Hydrogen sulfide gas
- Phosphpine
- Arsine (see "Chemical terrorism: Rapid recognition and initial medical management")
- Asphyxiants (eg, methane)

Also, exposure to cyanogen chloride can mimic exposure to any chemical irritant (eg, chlorine) [28].

**MANAGEMENT** — Untreated, cyanide poisoning is rapidly lethal. If clinical history and examination are suggestive of cyanide poisoning, antidotal therapy must be given immediately, barring any contraindications. Management should also include resuscitation and decontamination. A summary table to facilitate emergent management is provided (table 2). (See 'Antidotal treatment guidelines' below.)

Care must be taken when evaluating victims of smoke inhalation. Carbon monoxide poisoned patients present similarly to those also poisoned by cyanide, and clinicians may focus on easily obtained carboxyhemoglobin levels, inadvertently neglecting to manage co-existent cyanide toxicity [18]. Cyanide toxicity should be considered in all smoke inhalation patients with two or more of the following: carbonaceous material in the oropharynx, neurologic dysfunction, metabolic acidosis on arterial blood gas, and serum lactate >8 mmol/L [33]. (See "Inhalation injury from heat, smoke, or chemical irritants").

The recognition and management of cyanide poisoning can be difficult, and clinicians should seek assistance from a medical toxicologist or a regional poison center if they have any questions or concerns. (See 'Additional resources' below.)

**Resuscitation** — First, clinicians must stabilize the patient's airway, breathing, and circulation. The patient's airway should be secured as necessary and high-flow oxygen should be given, regardless of pulse oximetry readings. Mouth-to-mouth resuscitation is contraindicated in cyanide poisoning due to the risk of exposure to the provider of cardiopulmonary resuscitation (CPR) [16]. Otherwise, CPR should be provided as per advanced cardiac life support protocols. (See "Advanced cardiac life support (ACLS) in adults" and "Basic life support (BLS) in adults" and "Pediatric basic life support for healthcare providers").

In unresponsive patients, point of care testing of serum glucose should be performed and supplemental dextrose administered if the patient is hypoglycemic. Naloxone should be administered if opioid toxicity is suspected in addition to cyanide poisoning. Thiamine is a benign antidote and its administration should be considered, particularly in patients with a history of alcohol abuse. (See "Stupor and coma in adults".)

Seizures associated with cyanide poisoning are treated with benzodiazepines. Hypotension is treated with fluids and vasopressors as needed. Comorbid conditions and concurrent exposures are treated as necessary. Detailed discussions of the general management of the poisoned patient are provided separately. (See "Initial management of the critically ill adult with an unknown overdose" and "General approach to drug poisoning in adults").

**Decontamination** — Patients poisoned by cyanide through inhalation or topical exposure must be rapidly removed from the source, and their clothing taken off and appropriately discarded. In dermal exposures, wounds must be cleansed with soap and water to prevent further absorption. Rescuers should wear protective suits and respirators until proper decontamination is completed [34]. (See "Topical chemical burns").

Gastrointestinal decontamination should be performed rapidly in cases of oral ingestion, as cyanide is quickly absorbed. Although laboratory studies have demonstrated that cyanide binds poorly to activated charcoal (AC), animal studies report decreased mortality among rats given AC after lethal potassium cyanide ingestions [35]. Therefore, we suggest that a single dose of AC be administered (50 g in adults; 1 g/kg, up to 50 g maximum, in children). There is no role for multiple doses of AC or cathartics. such as magnesium citrate or sorbitol. Charcoal should be withheld in

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Orogastric lavage is not recommended. It may be attempted only if ingestion occurred within 60 minutes of presentation and a large amount of cyanide is thought to be present in the upper gastrointestinal tract [36].

**Antidotes** — If clinical history and examination are suggestive of cyanide poisoning, antidotal therapy must be given immediately, barring any contraindications. (See 'Antidotal treatment guidelines' below.)

Antidotal treatment of cyanide poisoning involves three strategies: binding of cyanide, induction of methemoglobinemia, and use of sulfur donors. In Europe, the combination of sodium thiosulfate and hydroxocobalamin has provided successful treatment of severe poisoning. In the United States, the Cyanide Antidote Kit may still be used in some locations to provide the cyanide antidotes if hydroxocobalamin is not available. The traditional kit (which is no longer manufactured) includes amyl nitrite (12 0.3 mL ampules) and sodium nitrite (two 300 mg/10 mL ampules) to induce methemoglobinemia, and sodium thiosulfate (two 12.5 g/50 mL vials) to act as a sulfur donor. This kit is designed to treat two adult patients or one adult patient twice. An alternative kit containing sodium nitrite and sodium thiosulfate (Nithiodote), but again hydroxocobalamin is the preferred treatment.

Treatment with amyl nitrite or sodium nitrite is contraindicated in cases of concurrent carbon monoxide toxicity (see 'Induction of methemoglobinemia' below).

**Direct cyanide binding** — One strategy in cyanide neutralization involves direct binding of cyanide, preferably using hydroxocobalamin (Cyanokit). Dicobalt edetate also binds cyanide but can cause severe side effects.

**Hydroxocobalamin** — Hydroxocobalamin, a precursor of vitamin B12, contains a cobalt moiety that avidly binds to intracellular cyanide (with greater affinity than cytochrome oxidase) forming cyanocobalamin [37]. This molecule is stable and readily excreted in the urine. Because hydroxocobalamin acts rapidly, does not adversely affect tissue oxygenation, and is relatively safe, many investigators recommend it be used as the first line agent in cyanide poisoning and we concur with this approach [38,39].

The dose of hydroxocobalamin is 70 mg/kg (typical adult dose is 5 g) given intravenously (IV). This dose is effective for the majority of adult patients. A second half-dose may be given depending upon the severity of poisoning or the clinical response to treatment. Although optimum pediatric dosing is not well established, some recommend 70 mg/kg IV (maximum dose 5 g) [22]. The half-life is 24 to 48 hours.

In France, hydroxocobalamin is commonly used in conjunction with sodium thiosulfate, a combination shown to be effective and safe in severe cyanide poisoning [7,40-42]. One study of heavy smokers found that hydroxocobalamin decreased cyanide levels by 59 percent [43].

Hydroxocobalamin, when given at the recommended dose, may cause a temporary reddish discoloration of the skin, plasma, urine, and mucous membranes [44,45]. These changes last for approximately two to three days, altering the laboratory values of tests performed using cooximetry or spectrophotometry. Blood tests that may be affected include creatinine, lactate, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), bilirubin, and magnesium [18,46-48]. Common urinalysis tests may also be affected (eg, glucose, protein, ketones, and leukocyte and erythrocyte counts).

Of note, IV infusion of hydroxocobalamin appears to interfere with co-oximetry measurements of total hemoglobin, carboxyhemoglobin, methemoglobin, and oxyhemoglobin [49,50]. This may complicate the assessment of smoke inhalation victims (who may suffer from both cyanide and carbon monoxide poisoning) if hydroxocobalamin is administered before blood is obtained for testing.

In one study of hydroxocobalamin administration in adults, adverse effects from high doses included rash, headache, nausea, chest discomfort, decreased lymphocyte percentage, and dyspnea [51]. At the recommended dose, both transient hypertension and slowing of the heart rate have been reported [7,43,47]. Overall, hydroxocobalamin is considered safe and effective [37,52].

**Dicobalt edetate** — Dicobalt edetate is an intravenous chelator of cyanide, with a rapid onset of action, used in the United Kingdom. The dose is 20 mL of a 1.5 percent solution given over one minute. It is associated with multiple severe side effects including seizures, anaphylaxis, hypotension, and cardiac dysrhythmias [2]. As a result, it is administered only when the diagnosis of cyanide is nearly certain and alternative treatments are unavailable.

**Induction of methemoglobinemia** — Another antidotal strategy involves the induction of methemoglobin. The
The induction of methemoglobinemia is accomplished by the administration of amyl nitrite, sodium nitrite, or dimethylaminophenol. Amyl nitrite ampules are crushed and then inhaled by the patient (either from under the patient’s nose or via the endotracheal tube) for 30 seconds of each minute. Thirty second pauses allow for adequate oxygenation during treatment. Amyl nitrite induces only a 5 percent methemoglobinemia, and is thus only a temporizing measure. It may be used when intravenous access is unavailable, such as in the prehospital setting [16].

Sodium nitrite 300 mg (or 10 mg/kg) is administered intravenously, inducing a 15 to 20 percent methemoglobinemia [51]. This level of methemoglobinemia is easily tolerated by most patients. However, methemoglobin shifts the oxygen-hemoglobin dissociation curve to the left further hindering oxygen delivery to tissues (figure 2). A decreased dose is required for children weighing less than 25 kg and patients with anemia. A 20 to 30 percent level of methemoglobinemia, the goal of cyanide treatment in the average adult patient, may be lethal in children or anemic patients, who have little reserve. Nitrites should be avoided in pregnant women.

The appropriate dose of sodium nitrite given to adult patients incapable of tolerating significant methemoglobinemia adjusted according to the patient’s hemoglobin. A medical toxicologist or regional poison center should be consulted for appropriate dosing. Approximate initial dosing is as follows:

- Hemoglobin 7 g/dL, dose is 0.19 mL/kg of 3 percent sodium nitrite
- Hemoglobin 8 g/dL, dose is 0.22 mL/kg of 3 percent sodium nitrite
- Hemoglobin 9 g/dL, dose is 0.25 mL/kg of 3 percent sodium nitrite
- Hemoglobin 10 g/dL, dose is 0.27 mL/kg of 3 percent sodium nitrite
- Hemoglobin 11 g/dL, dose is 0.30 mL/kg of 3 percent sodium nitrite

Patients receiving nitrites may develop hypotension and tachycardia [16]. These side effects are somewhat rate dependent. Arthralgias, myalgias, vomiting, and psychosis may also occur.

In addition to inducing a methemoglobinemia, nitrites may provide benefit by causing vasodilation. Nitrites release nitrous oxide, a vasodilator, leading to increased blood flow to the liver and other organs, thereby enhancing the metabolism of cyanide. This proposed effect is supported by the success of other vasodilators in protecting the body from cyanide toxicity [22, 53].

Dimethylaminophenol (4-DMAP), an agent introduced in Germany, is another inducer of methemoglobin. 4-DMAP is given in a dose of 5 mL of a 5 percent solution IV over one minute. It is potent and rapidly acting, achieving peak levels of methemoglobin within five minutes of administration. The potency of 4-DMAP, which can require methylene blue to reverse the extent of methemoglobinemia, is problematic. Methylene blue, the recommended reversal agent for methemoglobinemia, should be avoided in the setting of cyanide poisoning because its use can release free cyanide [54]. Other potential adverse effects of 4-DMAP include reticulocytosis, nephrotoxicity, and hemolysis [2]. (See "Clinical features, diagnosis, and treatment of methemoglobinemia").

Of special note, patients who are victims of fires may be suffering from both carbon monoxide and cyanide toxicity. Carboxyhemoglobin causes the oxygen-hemoglobin dissociation curve to be shifted to the left creating tissue hypoxia. In these patients, the induction of methemoglobinemia could be lethal [55]. (See "Carbon monoxide poisoning", and "Inhalation injury from heat, smoke, or chemical irritants").

Sulfur donors — A third antidotal strategy involves maximizing the availability of sulfur donors for rhodanese, a ubiquitous enzyme that detoxifies cyanide by transforming it to thiocyanate. Thiocyanate is then renally excreted. Sodium thiosulfate is the therapeutic sulfur donor of choice.

In theory, a 3:1 ratio of sodium thiosulfate to cyanide is required for complete detoxification. The standard adult dose of sodium thiosulfate is 50 mL of a 25 percent solution, or 12.5 g [16, 22]. The onset of action may be slow (up to 30 minutes). Because thiocyanate levels of 10 mg/dL or higher may cause psychosis, arthralgias, vomiting, and myalgias, patients with renal failure may require hemodialysis to remove it from the blood stream [7]. However, in most patients sodium thiosulfate is safe and well tolerated.

In an animal experiment, nitrite treatment alone tripled the dose of cyanide needed to cause death, while thiosulfate treatment alone quadrupled the dose. In combination, however, nitrites and thiosulfate increased the dose of cyanide required to cause death 13-fold [22], suggesting synergy between the two treatments.
inconsistent findings in the literature overall, the use of HBO therapy in cyanide poisoning remains controversial. Further research and controlled studies in humans are needed.

**Antidotal treatment guidelines** — Cyanide poisoning is rare, but when present requires decisive action. We recommend treatment with sodium thiosulfate and hydroxocobalamin when available. In hospitals without hydroxocobalamin, treatment with nitrates may be life-saving, but induction of 20 to 30 percent methemoglobinemia in a patient who is critically ill from another cause may prove catastrophic. When the history strongly suggests cyanide toxicity, we recommend prompt treatment with both nitrates and sodium thiosulfate. In such cases, the benefits of therapy outweigh the risks of methemoglobinemia. Note that methemoglobinemia may be lethal in children or anemic patients, who have little reserve, and nitrates should be avoided in pregnant women. (See ‘Induction of methemoglobinemia’ above.)

**Probable cyanide intoxication** — Availability of treatment varies by region and hospital. Immediately below is a series of antidotal management recommendations, based upon treatment availability, for patients with probable cyanide intoxication:

- For patients in locations where hydroxocobalamin is available, it is the preferred treatment and we recommend:
  - Sodium thiosulfate 25 percent, 1.65 mL/kg IV (maximum dose 12.5 g) **AND**
  - Hydroxocobalamin 70 mg/kg IV (5 g is the standard adult dose)
- For patients without contraindication to nitrates, in locations where hydroxocobalamin is not available, we recommend the Cyanide Antidote Kit, if available, which consists of the following three medications:
  - Amyl nitrite inhaled by the patient (held under the patient’s nose or via the endotracheal tube) for 30 seconds of each minute, for three minutes
  - Sodium nitrite 10 mg/kg IV **AND**
  - Sodium thiosulfate (25 percent) 1.65 mL/kg IV (maximum dose 12.5 g)

Some kits do not contain amyl nitrite. In such cases, give sodium nitrite and sodium thiosulfate in the same doses.

- For patients with contraindications to nitrates or with smoke inhalation (pending test results for carboxyhemoglobin), in locations where hydroxocobalamin is not available, we recommend:
  - Sodium thiosulfate (25 percent) 1.65 mL/kg IV (maximum dose 12.5 g) only
- In locations where 4-dimethylaminophenol (4-DMAP) or dicobalt edetate is available, and there are no contraindications to either drug, and neither hydroxocobalamin nor the Cyanide Antidote Kit is available, we recommend:
  - 4-DMAP (5 percent) 5 mL IV over one minute **OR**
  - If 4-DMAP is unavailable and the diagnosis is clear, dicobalt edetate (1.5 percent) 20 mL IV over one minute, **ONLY** if cyanide poisoning is highly suspected or confirmed

**Questionable cyanide intoxication** — Immediately below is a series of antidotal management recommendations, based on treatment availability, for patients with questionable cyanide intoxication:

- For patients in locations where hydroxocobalamin is available, we recommend:
  - Sodium thiosulfate (25 percent) 1.65 mL/kg IV (maximum dose 12.5 g) **AND**
  - Hydroxocobalamin 70 mg/kg IV (5 g is the standard adult dose)
- For patients in locations where hydroxocobalamin is not available, but the Cyanide Antidote Kit is available, we recommend:
  - Sodium thiosulfate (25 percent) 1.65 mL/kg IV (maximum dose 12.5 g) **without** the use of nitrates

After sodium thiosulfate is administered, further testing (eg, mixed central venous oxygen saturation, blood gas analysis, and co-oximetry for carboxyhemoglobin and methemoglobin) should be obtained promptly. If ancillary data strongly support cyanide toxicity over other potential causes of the patient’s symptoms, we recommend the administration of nitrates as described above. (See ‘Probable cyanide intoxication’ above.)
Empiric treatment for smoke inhalation — Clinicians should consider the possibility of cyanide toxicity and maintain a low threshold for initiating treatment in victims of smoke inhalation. Frequently, victims of house fires have a depressed level of consciousness, which may be caused by cyanide, carbon monoxide, other inhaled or ingested toxins, traumatic shock, or head injury. The pathophysiology and general management of smoke inhalation is discussed elsewhere. (See "Inhalation injury from heat, smoke, or chemical irritants".)

We suggest empiric treatment for cyanide toxicity be initiated in victims of smoke inhalation with an unexplained lactic acidosis or a low or declining end-tidal CO2 (EtCO2) level. If these measurements are unavailable, we suggest treatment be initiated in any patient demonstrating a depressed level of consciousness, cardiac arrest, or hemodynamic decompensation [58].

We suggest the following antidotal treatment:

- **Sodium thiosulfate** (25 percent) 1.65 mL/kg IV (maximum dose 12.5 g) AND
- **Hydroxocobalamin** 70 mg/kg IV (5 g is the standard adult dose)

Treatment with **amyl nitrite** or **sodium nitrite** is **contraindicated** in cases of potential carbon monoxide toxicity (eg, from a fire), until carbon monoxide toxicity has been excluded.

Serum lactate and EtCO2 monitoring may provide useful information when determining management of smoke inhalation victims. Cyanide toxicity poisons mitochondria, forcing cells to use anaerobic metabolism. This results in a lactic acidosis and a compensatory drop in EtCO2. (See 'Pathophysiology' above.)

**PEDIATRIC CONSIDERATIONS** — The pathophysiology and clinical manifestations of acute cyanide poisoning are similar for children and adults [59]. However, pediatric patients appear to be more vulnerable to cyanide poisoning from smoke inhalation. This is thought to be due to their immature metabolism, lower body mass, and higher respiratory rate. (See 'Clinical presentation' above.)

As young children have higher concentrations of fetal hemoglobin and less methemoglobin reductase than adults, induced methemoglobinemia can reduce oxygen-carrying capacity to dangerously low levels. Therefore, hydroxocobalamin is the preferred treatment for cyanide intoxication, and it is considered safe in children [60]. Although optimum pediatric dosing is not well established, some recommend 70 mg/kg IV (maximum 5 g) [22,60].

The major concern in pediatric patients with cyanide poisoning involves management using the Cyanide Antidote Kit, when hydroxocobalamin is unavailable.

In order to avoid dangerously high methemoglobin levels, **sodium nitrite** should be dosed according to the patient’s hemoglobin. A medical toxicologist or regional poison center should be consulted for dosing details and assistance with management. The approximate initial dose of sodium nitrite, to be given no faster than 5 mL/min, is as follows [9]:

- Hemoglobin 7 g/dL, dose is 0.19 mL/kg of 3 percent sodium nitrite
- Hemoglobin 8 g/dL, dose is 0.22 mL/kg of 3 percent sodium nitrite
- Hemoglobin 9 g/dL, dose is 0.25 mL/kg of 3 percent sodium nitrite
- Hemoglobin 10 g/dL, dose is 0.27 mL/kg of 3 percent sodium nitrite
- Hemoglobin 11 g/dL, dose is 0.30 mL/kg of 3 percent sodium nitrite
- Hemoglobin 12 g/dL, dose is 0.33 mL/kg of 3 percent sodium nitrite
- Hemoglobin 13 g/dL, dose is 0.36 mL/kg of 3 percent sodium nitrite
- Hemoglobin 14 g/dL, dose is 0.39 mL/kg of 3 percent sodium nitrite

Point of care hemoglobin testing makes this approach easier to perform. In emergency departments where a rapid hemoglobin level is difficult to obtain, pediatric patients can be dosed on the basis of weight. Sodium nitrite is given 10 mg/kg IV, or 0.33 mL/kg of a 3 percent solution IV. The dose should not exceed 10 mL and should not be given at a rate greater than 5 mL/min in order to avoid significant hypotension.

Sodium thiosulfate is given IV 1.65 mL/kg of a 25 percent solution, up to a maximum of 12.5 g (50 mL). Sodium thiosulfate appears to cause fewer adverse effects than sodium nitrite and is considered safe for use in children [9,16]. Gastrointestinal symptoms and localized burning at the injection site were noted in one volunteer study [43].
Cyanide poisoning

30/08/2016

Ingestions or overdoses. The World Health Organization provides a listing of international poison centers at its website: [www.who.int/gho/chemical_safety/poisons_centres/en/index.html](http://www.who.int/gho/chemical_safety/poisons_centres/en/index.html)

**SUMMARY AND RECOMMENDATIONS** — Cyanide is among the most rapidly lethal poisons known to man. A summary table to facilitate emergent management is provided (table 1). Clinicians should seek assistance from a medical toxicologist or a regional poison center. (See 'Additional resources' above.)

Acute cyanide poisoning may result from a broad range of exposures (table 2). In industrialized countries, the most common cause is domestic fires. Poisoning can also occur from industrial exposure (eg, mining, electroplating, plastic manufacturing), standard and alternative medical treatments (eg, nitroprusside, laetrile), and certain foods (eg, Rosaceae family). (See 'Epidemiology' above.)

Cyanide toxicity occurs from cellular hypoxia, which results in an anion gap metabolic acidosis. (See 'Pathophysiology' above.)

Clinical findings

- Clinical features of cyanide poisoning are dependent upon the route, duration, and amount of exposure. Central nervous system and cardiovascular system dysfunction are most prominent. Symptoms and signs are described in detail above. (See 'Clinical presentation' above.)

- Because of the decreased utilization of oxygen by tissues, venous oxyhemoglobin concentration will be high, making venous blood appear bright red. Therefore, despite hypotension, apnea, and/or bradycardia, the patient does not appear cyanotic in the setting of cyanide poisoning. (See 'Clinical presentation' above.)

- Toxicity from parenteral exposure begins within seconds, toxicity from an ingestion or dermal exposure is delayed from minutes to hours (table 3). Delayed and chronic sequelae are discussed above. (See 'Clinical presentation' above.)

- Patients who are victims of fires or reported ingestions, are exposed to cyanide at work, or have recently been treated with sodium nitroprusside are all potentially cyanide poisoned. In the event that history is unavailable, clinicians should consider any patient with altered mental status and a severe anion gap metabolic acidosis of unknown etiology a possible cyanide poisoning. (See 'Diagnosis' above.)

Testing

- Routine laboratory evaluation in potential cyanide intoxication should include the following: point-of-care (eg, fingerstick) glucose, acetaminophen and salicylate levels, electrocardiogram, and a pregnancy test in women of childbearing age. (See 'Laboratory evaluation' above.)

- Specific testing in potential cyanide intoxication should include the following:
  - Basic chemistries (Na+, Cl−, K+, HCO3−) and arterial blood gas to assess for anion gap metabolic acidosis
  - Serum lactate to confirm lactic acidosis and assess severity of exposure
  - Central venous blood gas, if possible, to assess for a diminished venous-arterial PO2 gradient
  - Carboxyhemoglobin and methemoglobin levels (measured by co-oximetry), particularly if there is any concern for concomitant carbon monoxide exposure (eg, house or vehicle fire) or exposure to drugs that produce methemoglobinemia (table 4). IV infusion of hydroxocobalamin may interfere with co-oximetry measurements of total hemoglobin, carboxyhemoglobin, methemoglobin, and oxyhemoglobin. (See 'Laboratory evaluation' above and "Inhalation injury from heat, smoke, or chemical irritants".)

Treatment — Clinicians should seek assistance from a medical toxicologist or a regional poison center. (See 'Additional resources' above.)

- The clinician's first responsibility is to stabilize the patient's airway, breathing, and circulation. Mouth-to-mouth resuscitation is contraindicated due to the potential for provider exposure. Otherwise, cardiopulmonary resuscitation should be provided as per advanced cardiac life support protocols. (See "Advanced cardiac life support (ACLS) in adults".) (See 'Resuscitation' above.)

http://www.uptodate.com/contents/cyanide-poisoning?topicKey=EM%2F299&elapsedTimeMs=0&source=search_result&searchTerm=cianeto&selectedTitle=1%7E65&view=print&displayedView=full
Gastrointestinal decontamination should be performed in cases of oral ingestion. Due to the rapid absorption of cyanide, oral decontamination should be performed rapidly. We recommend that a single dose of activated charcoal (AC) be administered (Grade 1B); the typical dose is 50 g in adults and 1 g/kg in children. There is no role for multiple dose charcoal or charcoal cathartics, such as magnesium citrate or sorbitol. Charcoal should be withheld in patients who are sedated or may not be able to protect their airway, unless tracheal intubation is performed first. (See "Gastrointestinal decontamination of the poisoned patient".)

Antidotal treatment of cyanide poisoning involves three strategies: binding of cyanide, induction of methemoglobinemia, and use of sulfur donors. Each is described in the text. (See ‘Antidotes’ above.)

Based upon treatment availability, we recommend the following approaches to antidotal therapy for patients with probable cyanide intoxication. Treatment for patients in whom cyanide poisoning is possible but unlikely is described in detail above. (See ‘Antidotal treatment guidelines’ above):

For patients in locations where hydroxocobalamin is available it is the preferred therapy, and we recommend the following treatment (Grade 1B):

- Sodium thiosulfate (25 percent) 1.65 mL/kg IV (maximum dose 12.5 g), and
- Hydroxocobalamin 70 mg/kg IV (5 g is the standard adult dose)

For patients without contraindication to nitrites, in locations where hydroxocobalamin is not available, and the Cyanide Antidote Kit is available, we recommend the following treatment (Grade 1B):

- Amyl nitrite inhaled by the patient (held under the patient’s nose or via the endotracheal tube) for 30 seconds of each minute, for three minutes
- Sodium nitrite 10 mg/kg IV, and
- Sodium thiosulfate (25 percent) 1.65 mL/kg IV (maximum dose 12.5 g)

Some kits do not contain amyl nitrite. In such cases, give sodium nitrite and sodium thiosulfate in the same doses.

For patients with contraindications to nitrites or with smoke inhalation (pending test results for carboxyhemoglobin), in locations where hydroxocobalamin is not available, we recommend the following treatment (Grade 1B):

- Sodium thiosulfate (25 percent) 1.65 mL/kg IV (maximum dose 12.5 g) only

In locations where 4-dimethylaminophenol (4-DMAP) or dicobalt edetate is available, and there are no contraindications to either drug, and neither hydroxocobalamin nor the Cyanide Antidote Kit is available, we recommend the following treatment (Grade 1B):

- 4-DMAP (5 percent) 5 mL IV over one minute
- OR, if 4-DMAP is unavailable,
- Dicobalt edetate (1.5 percent) 20 mL IV over one minute, ONLY if cyanide poisoning is highly suspected or confirmed

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REFERENCES


27. Rajashekar Ts, Okade R. Irritant contact dermatitis to accidental exposure of cyanide. Indian J Dermatol 2013; 58:162.


37. Lambot R, Kuttler R, Schaeffer D. The efficacy of superactivated charcoal in treating rats exposed to a
Cyanide poisoning: Rapid overview

To obtain emergent consultation with a medical toxicologist, call the United States Poison Control Network at 1-800-222-1222, or access the World Health Organization's list of international poison centers (www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html).

General information
Cyanide poisoning is rapidly lethal unless treated with antidote

Clinical features

<table>
<thead>
<tr>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascertain if patient has access to cyanide, or if patient was part of a high-risk event (eg, fire, industrial exposure)</td>
</tr>
<tr>
<td>Initial symptoms are nonspecific: headache, anxiety, confusion, abdominal pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs: initial hypertension/tachycardia/tachypnea progresses to respiratory and circulatory collapse</td>
</tr>
<tr>
<td>Skin: may be flushed with &quot;cherry red&quot; color</td>
</tr>
<tr>
<td>Neurologic: seizures and coma as poisoning progresses</td>
</tr>
</tbody>
</table>

Laboratory evaluation

<table>
<thead>
<tr>
<th>Obtain the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingerstick glucose, acetaminophen and salicylate levels, electrocardiogram, and pregnancy test (when appropriate)</td>
</tr>
<tr>
<td>Basic chemistries and serum lactate</td>
</tr>
<tr>
<td>Elevated anion gap acidosis, with elevated lactate, expected in cyanide poisoning</td>
</tr>
<tr>
<td>Venous blood appears bright red</td>
</tr>
<tr>
<td>Central venous blood gas with concomitant arterial blood gas</td>
</tr>
<tr>
<td>Narrowed venous-arterial PO2 gradient supports cyanide toxicity</td>
</tr>
<tr>
<td>Carboxyhemoglobin and methemoglobin levels</td>
</tr>
<tr>
<td>Rule out dyshemoglobinemias</td>
</tr>
<tr>
<td>Use nitrates (see below) cautiously or not at all in presence of dyshemoglobinemias</td>
</tr>
<tr>
<td>Cyanide poisoning can cause: renal failure, hepatic failure, rhabdomyolysis, pulmonary edema; obtain relevant studies as indicated</td>
</tr>
</tbody>
</table>

General treatment

Secure airway, breathing, and circulation. Intubation is usually required. Administer high-flow oxygen by nonrebreather face mask regardless of pulse oximetry reading.

Do NOT perform mouth to mouth resuscitation in cases of suspected cyanide toxicity. Patients with dermal exposure must be decontaminated using proper precautions.

Give a single dose of activated charcoal if the airway is adequately protected (50 g in adults; 1 g/kg in children with maximum dose of 50 g)

Treat hypotension with rapid IV boluses of isotonic fluid and vasopressors as needed. Treat seizures with a benzodiazepine (eg, diazepam 5 mg IV).
## Antidotal treatment

**Administer cyanide antidote** when cyanide poisoning is clinically suspected. Hydroxocobalamin is the preferred antidote.

If hydroxocobalamin is available, give the following:

- Hydroxocobalamin 70 mg/kg up to 5 g IV (5 g is standard adult dose)
- Sodium thiosulfate (25 percent): 1.65 mL/kg up to 50 mL IV; may repeat once (maximum dose 12.5 g)

If hydroxocobalamin is not available, cyanide toxicity is known or strongly suspected, and there are no contraindications to nitrites, give the following:

- Sodium nitrite 10 mg/kg - up to 300 mg - by slow IV infusion; may repeat once
- Sodium thiosulfate (25 percent) 1.65 mL/kg up to 50 mL IV; may repeat once

If hydroxocobalamin is not available and cyanide toxicity is possible but not certain, or the patient has contraindications to nitrites, give the following:

- Sodium thiosulfate (25 percent) 1.65 mL/kg up to 50 mL IV; may repeat once

Refer to topic for details about nitrite treatment for children and patients with anemia, and for treatment in cases of unlikely cyanide poisoning.
### Sources of cyanide

#### Industrial exposures
- Plastics production
- Photography
- Fumigation
- Pesticides/ Rodenticides
- Synthetic rubber production
- Fertilizer production
- Metal polish
- Hair removal from hides
- Electroplating
- Metallurgy

#### Plants and fruits
- Bamboo sprout
- Macadamia nuts
- Hydrangea
- Rosaceae family (plum, peach, pear, apple, bitter almond, cherry)

#### Miscellaneous
- Cigarette smoking
- Phencyclidine synthesis
- Artificial nail glue remover
- Product tampering
- Suicide/ Terrorist attack

#### Drugs
- Sodium Nitroprusside
- Laetrile

#### Combustion
- Wool
- Silk
- Polyurethanes
- Polycrylonitriles
- Nylon
- Melamine resins
- Plastics
Mitochondrial metabolism

Schematic representation showing the steps within the mitochondria in which energy stored in fatty acids, pyruvate, and amino acids is transformed into ATP. Energy substrates are first transported into the mitochondria where, after conversion into acetyl CoA, they enter the tricarboxylic acid cycle (TCA). The reduced forms of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD) are formed from the citric acid cycle and the beta-oxidation of fatty acids in the mitochondrial matrix. Subsequently, oxidative phosphorylation or the respiratory chain, which is composed of four multi-subunit complexes (I, II, III, and IV) linked by the mobile electron carriers coenzyme Q and cytochrome c. The respiratory chain transfers electrons from NADH (via complex I) and from reduced flavoproteins (via complex II and electron transfer flavoprotein-coenzyme Q oxidoreductase [ETF-Qo]) to coenzyme Q10, then complex III, cytochrome c and finally complex IV, where they combine with molecular oxygen to form water.

CoQ: Coenzyme Q; NADH: Nicotinamide adenine dinucleotide reduced; FMN: Flavin mononucleotide; FES: Non-heme iron-sulfur protein; Pi: Inorganic phosphate; TCA: Tricarboxylic acid cycle.


Graphic 78699 Version 1.0
## Toxic cyanide doses

<table>
<thead>
<tr>
<th>Route of Exposure</th>
<th>Toxic Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation</td>
<td>100 ppm x 30 min</td>
</tr>
<tr>
<td></td>
<td>300 ppm x 5 min</td>
</tr>
<tr>
<td>Oral</td>
<td>50 mg (HCN)</td>
</tr>
<tr>
<td></td>
<td>200 mg (KCN)</td>
</tr>
<tr>
<td>Dermal</td>
<td>100 mg/kg</td>
</tr>
<tr>
<td>Intravenous</td>
<td>5-10 µg/kg/ min x 3-10 hrs</td>
</tr>
</tbody>
</table>
Depicted here is the oxyhemoglobin dissociation curve for normal adult hemoglobin (Hemoglobin A, solid line). Note that hemoglobin is 50 percent saturated with oxygen at a partial pressure of 27 mmHg (ie, the P50 is 27 mmHg) and is 100 percent saturated at a PaO₂ of approximately 100 mmHg. Depicted here are curves that are "left-shifted" (blue line, representing increased oxygen affinity) and "right-shifted" (red line, decreased oxygen affinity). The effect of right- or left-shifting of the curve is most pronounced at low oxygen partial pressures. In the examples shown, the right-shifted curve means that hemoglobin can deliver approximately 70 percent of its attached oxygen at a PaO₂ of 27 mmHg. In contrast, the left-shifted hemoglobin can deliver only about 35 percent of its attached oxygen at this PaO₂. A high proportion of fetal hemoglobin, which has high oxygen affinity, shifts this curve to the left in newborns.

Graphic 81216 Version 6.0
### Agents known to cause methemoglobinemia

<table>
<thead>
<tr>
<th>Acetanilide</th>
<th>Naphthoquinone</th>
<th>Naphthalene</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Amino salicylic acid</td>
<td>Nitrites</td>
<td>Nitrites</td>
</tr>
<tr>
<td>Aniline, aniline dyes</td>
<td>Amyl nitrite</td>
<td>Farrl nitrite</td>
</tr>
<tr>
<td>Benzene derivatives</td>
<td>Sodium nitrite</td>
<td>Nitroglcerin</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Nitric oxide</td>
<td>Nitrobenzene</td>
</tr>
<tr>
<td>Chlorates</td>
<td></td>
<td>Paraquat</td>
</tr>
<tr>
<td>Chloroquine</td>
<td></td>
<td>Phenacetin</td>
</tr>
<tr>
<td>Dapsone</td>
<td></td>
<td>Phenazopyridine</td>
</tr>
<tr>
<td>Local anesthetic agents</td>
<td></td>
<td>Primaquine</td>
</tr>
<tr>
<td>Benzocaine</td>
<td></td>
<td>Rasburicase</td>
</tr>
<tr>
<td>Lidoecaine</td>
<td></td>
<td>Resorcinol</td>
</tr>
<tr>
<td>Prilocaine</td>
<td></td>
<td>Sulfonamides</td>
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<tr>
<td>Menadione</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylene blue*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*While methylene blue is a recognized treatment for methemoglobinemia, it is an agent with oxidant potential, and may worsen the clinical situation, since in individuals with glucose-6-phosphate dehydrogenase deficiency it induces acute hemolysis that can further decrease oxygen delivery to the tissues. Paradoxically, in high doses methylene blue can also increase methemoglobinemia.*
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