Agency for Toxic Substances and Disease Registry
Case Studies in Environmental Medicine
Nitrate/Nitrite Toxicity

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Key Concepts	• Nitrate toxicity is a preventable cause of methemoglobinemia. • Infants younger than 4 months of age are at particular risk of nitrate toxicity from contaminated well water. • The widespread use of nitrate fertilizers increases the risk of well-water contamination in rural areas.
About This and Other Case Studies in Environmental Medicine	This educational case study document is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to promote the adoption of medical practices that aid in the evaluation and care of potentially exposed patients. The complete series of Case Studies in Environmental Medicine is located on the ATSDR Web site at http://www.atsdr.cdc.gov/csem/. In addition, the downloadable PDF version of this educational series and other environmental medicine materials provides content in an electronic, printable format, especially for those who may lack adequate Internet service.
How to Apply for and Receive Continuing Education Credit	See Internet address www2.cdc.gov/atsdrce/ for more information about continuing medical education credits, continuing nursing education credits, and other continuing education units.

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Disclaimer

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How to Use This Course

Introduction	The goal of *Case Studies in Environmental Medicine* (CSEM) is to increase the primary care provider's knowledge of hazardous substances in the environment and to help in evaluating and treating potentially exposed patients. This CSEM focuses on Nitrate/Nitrite Toxicity.
Available Versions	Two versions of the Nitrate/Nitrite Toxicity CSEM are available • the HTML version http://www.atsdr.cdc.gov/csem/nitrate/ provides content through the Internet; • the downloadable PDF version provides content in an electronic, printable format, especially for those who may lack adequate Internet service. The HTML version offers interactive exercises and prescriptive feedback to the user.
Instructions	To make the most effective use of this course, we recommend that you • take the initial check to assess your current knowledge about Nitrate/Nitrite Toxicity • read the title, learning objectives, text, and key points in each section • complete the progress check exercises at the end of each section and check your answers • complete and submit your assessment and posttest responses online if you wish to obtain continuing education credit. Continuing education certificates can be printed immediately upon completion.
Instructional Format	This course is designed to help you learn efficiently. Topics are clearly labeled so that you can skip sections or quickly scan sections you are already familiar with. This labeling will also allow you to use this training material as a handy reference. To help you identify and absorb important content quickly, each section is structured as follows:

Section Element	Purpose
Title	Serves as a "focus question" that you should be able to answer after completing the section
Learning Objectives	Describes specific content addressed in each section and focuses your attention on important points
Text	Provides the information you need to answer the focus question(s) and achieve the learning objectives
Key Points	Highlights important issues and helps you review
Progress Check exercises	Enables you to test yourself to determine whether you have mastered the learning objectives
Progress Check answers	Provides feedback to ensure you understand the content and can locate information in the text

Learning Objectives	Upon completion of the Nitrate/Nitrite Toxicity CSEM, you will be able to

Content Area	Objectives
Overview	• Describe what nitrates/nitrites are
Exposure Pathways	• Identify sources of nitrates/nitrites • Describe drinking water exposure risk to nitrates/nitrites
Who Is at Risk	• Identify the population most susceptible to nitrates/nitrites
Standards and Regulations	• Describe the U.S. Environmental Protection Agency's recommended limit for nitrates/nitrites in drinking water
Biologic Fate	• Describe the mean intake of nitrates by persons in the United States • Describe how nitrates are metabolized and excreted
Physiologic Effects	• Describe the physiologic and pathologic effects of nitrates and nitrites
Clinical Evaluation	• Describe the clinical assessment of an infant exposed to nitrates or nitrites • Describe the signs and symptoms of methemoglobinemia • Identify the laboratory test results that indicate methemoglobinemia
Treatment and Management	• Describe two treatments for methemoglobinemia caused by nitrates/nitrites toxicity

Initial Check

Instructions	This Initial Check will help you assess your current knowledge about nitrate/nitrite toxicity. To take the initial check, read the case below, and then answer the questions that follow.
Case Study	***A 2-month-old infant is vomiting and has diarrhea, tachypnea, and cyanosis.***

A two-month-old female infant is brought to your clinic in a rural area for a routine well-baby checkup. According to the child's chart, she was delivered two weeks early because of maternal toxemia. There was no neonatal distress; her birth weight was 7 pounds and 2 ounces.

Today, the mother states that she has noticed an intermittent bluish discoloration of the baby's lips, tip of the nose, and ears. Physical examination of the infant is negative for cardiac murmurs and abnormalities on lung auscultation. You note a below-average weight gain. Feedings consist of 4 ounces of diluted formula every two hours. The infant has occasional loose stools. You instruct the parents to increase caloric feedings, which should include vitamin and mineral supplements. You tell the parents to call you immediately if any further episodes of the bluish discoloration occur.

Approximately three weeks later, the baby's frantic parents call your office; the infant is crying incessantly and has vomiting and profuse diarrhea.

Vital Signs

When the baby is brought to your clinic a few minutes later, she is afebrile but has tachypnea, central cyanosis, and drowsiness. You note her vital signs as follows

- blood pressure (BP) = 78/30 mm Hg (normal 50th percentile for her age is 80/46 mm Hg)
- heart rate = 140 beats/minute
- respiration = 40 breaths/minute

Additional Information

An ambulance is summoned and 100% oxygen is administered by face mask. No improvement in the cyanosis is noted on her arrival at the hospital emergency department.

Emergency Treatment

The examining emergency physician now notes a grade II/VI systolic murmur and central cyanosis, which has not improved despite administration of 100% oxygen for nearly 1 hour. The infant shows no evidence of cardiac failure, atelectasis, pneumonitis, or pneumothorax. Therapy with methylene blue is started, which results in a dramatic resolution of the cyanosis. The infant is discharged on the second hospital day with no evidence of central nervous system hypoxic damage.

Initial Check

1. What is the most likely cause of this infant's cyanosis?
2. What laboratory tests, either obtained during the hospitalization or ordered subsequently, would help confirm the diagnosis?
3. What steps, if any, can be taken to prevent a recurrence of cyanosis and distress in this infant?
4. What questions will you ask the parents of the infant in the case study to help determine the cause of the cyanosis?
5. If well water used to dilute formula is implicated in the cyanosis, what are some possible causes of its nitrate contamination?
6. What recommendations can you make to the infant's family in the case study to prevent further cyanotic episodes?
7. What factors make infants younger than 4 months of age more susceptible to developing methemoglobinemia when exposed to nitrates?
8. What laboratory tests are useful for screening a patient with suspected methemoglobinemia?
9. Why might some patients with methemoglobinemia not respond to treatment with methylene blue?
10. What options are available to treat significant methemoglobinemia in a patient who has glucose 6-phosphate dehydrogenase (G6PD) deficiency?

Initial Check Answers

1. In an infant with no known cardiopulmonary disease, cyanosis that is unresponsive to oxygen therapy is most likely due to methemoglobinemia. Carboxyhemoglobinemia and sulfhemoglobinemia should also be considered.

   The information for this answer comes from section "How should patients exposed to nitrates or nitrites be evaluated?"

2. The clinical and laboratory tests that should be interpreted in diagnosing methemoglobinemia are

   - blood color,
   - methemoglobin (MHg) levels and total hemoglobin, and
   - arterial blood gases.

   When a drop of blood is placed on filter paper, the chocolate brown appearance of blood does not change with time because MHg does not change when it comes in contact with atmospheric oxygen. Deoxyhemoglobin appears dark red or violet initially, but it brightens after exposure to atmospheric oxygen. The level of MHg in the blood can be measured and should be interpreted in light of the total hemoglobin. Analysis of arterial blood gases will reveal normal or slightly low partial pressure of oxygen with falsely elevated oxygen saturation values. Pulse oximetry results will be inaccurate; they will show a constant oxygen saturation close to 85%. Co-oximetry may

be used to directly measure oxygen saturation, rather than the "calculated" level on arterial blood gases.

The information for this answer comes from section "What laboratory tests can assist with diagnosis of nitrate/nitrite toxicity?"

3. The initial step in preventing a recurrence of the infant's cyanosis and distress is to identify the cause of the cyanosis. The next step is to correct or eliminate the cause. If the infant is suffering from acquired methemoglobinemia, the agent must be identified and removed from the infant's environment. In the case of infantile acquired methemoglobinemia, well water used to prepare formula should be tested for the presence of nitrates. Ingestion of nitrate-containing water is a common cause of methemoglobinemia in infants, especially those living in rural areas.

   The information for this answer comes from section "Who is at risk?"

4. Questions that may help define the cause of the cyanosis include

   - Where is the home located?
   - What activities have been occurring around the home?
   - What type of sewer system connects to the home?
   - What are family members' occupations, avocations, and hobbies?
   - What is the source of the family's drinking water and how is it supplied?

   Information to gather from families with infants includes

   - the type of formula, feeding regimen, and source of dilution water;
   - the infant's history of recent gastroenteritis; and
   - family history, including recent use of all medications by both infant and mother.

   For information on taking a complete exposure history, see *Case Studies in Environmental Medicine: Taking an Exposure History* (1).

   The information for this answer comes from section "How should patients exposed to nitrates or nitrites be evaluated?"

5. Causes of high nitrate concentrations in well water include runoff from the use of nitrogen-containing agricultural fertilizers (including anhydrous ammonia) and seepage of organic nitrogen-containing material from animal wastes or septic sewer systems.

   The information for this answer comes from section "What are Nitrates/Nitrites?"

6. The well water should be tested for nitrate concentration and the presence of coliform bacteria. The family can contact the local health

department to perform these tests. It is most important to identify the source of the methemoglobin-inducing agent and to preclude any further exposure. If nitrate-contaminated well water is the source, you should recommend using bottled water or an alternative water source other than the contaminated well to dilute formula.

The information for this answer comes from section "Who is at risk?"

7. Infants younger than 4 months of age are more susceptible to developing methemoglobinemia because the pH of their gut is normally higher than in older children and adults. The higher pH enhances the conversion of ingested nitrate to the more potent nitrite. The bacterial flora of a young infant's gut is also different from that found in older children and adults and might be more likely to convert ingested nitrate to nitrite. Gastroenteritis can increase in vivo transformation of nitrate to nitrite and systemic absorption of nitrite from the large intestine.

   A large proportion of hemoglobin in young infants is in the form of fetal hemoglobin. Fetal hemoglobin is more readily oxidized to methemoglobin (MHg) by nitrites than is adult hemoglobin. In addition, in infants, NADH-dependent methemoglobin reductase, the enzyme responsible for reduction of induced MHg back to normal hemoglobin, has only about half the activity it has in adults.

   The information for this answer comes from section "Who is at risk?"

8. Laboratory tests useful for screening a patient with suspected methemoglobinemia include

   - examination of blood color with bedside "filter paper,"
   - arterial blood gases (ABGs) with co-oximetry,
   - MHg level,
   - complete blood counts (CBC) with peripheral blood smear,
   - serum-free hemoglobin, and
   - serum haptoglobin.

   The information for this answer comes from section "What laboratory tests can assist with diagnosis of nitrate/nitrite toxicity?"

9. The most common cause of a poor response to methylene blue treatment is unrecognized G6PD deficiency.

   The information for this answer comes from section "How should patients exposed to nitrates/nitrites be treated and managed?"

10. Treatment options for patients with G6PD deficiency might include exchange transfusion and/or hyperbaric oxygen therapy.

    The information for this answer comes from section "How should patients exposed to nitrates/nitrites be treated and managed?"

What Are Nitrates and Nitrites?

Learning Objective	Upon completion of this section, you will be able to • describe what nitrates/nitrites are • identify sources of nitrates/nitrites
Introduction	Nitrate (NO_3^-) and nitrite (NO_2^-) are naturally occurring inorganic ions that are part of the nitrogen cycle. Microbial action in soil or water decomposes wastes containing organic nitrogen into ammonia, which is then oxidized to nitrite and nitrate. Because nitrite is easily oxidized to nitrate, nitrate is the compound predominantly found in groundwater and surface waters. Contamination with nitrogen-containing fertilizers (e.g. potassium nitrate and ammonium nitrate), or animal or human organic wastes, can raise the concentration of nitrate in water. Nitrate-containing compounds in the soil are generally soluble and readily migrate with groundwater (2, 3).
Water Contamination	Shallow, rural domestic wells are those most likely to be contaminated with nitrates, especially in areas where nitrogen-based fertilizers are in widespread use (4). Approximately 13 million households in the United States use private wells to supply their drinking water (5). In agricultural areas, nitrogen-based fertilizers are a major source of contamination for shallow groundwater aquifers that provide drinking water (6). A recent United States Geological Survey study showed that more than 8,200 wells nationwide were contaminated with nitrate levels above the U.S. Environmental Protection Agency (EPA) drinking water standard of 10 parts per million (ppm) (7). EPA has estimated that approximately 1.2% of community water wells and 2.4% of private wells exceed the nitrate standard (8). Other sources of nitrate contamination are organic animal wastes and contamination from septic sewer systems, especially in wells less than 100 feet deep. During spring melt or drought conditions, both domestic wells and public water systems using surface water can show increased nitrate levels (9–11). Drinking water contaminated by boiler fluid additives may also contain increased levels of nitrites (12).
Food Contamination	Contaminated foodstuffs, prepared baby foods, and sausage preserved with nitrates and nitrites have caused exposure in children (13–15). Although vegetables are seldom a source of acute toxicity, they account for more than 70% of the nitrates in a typical human diet. Cauliflower, spinach, collard greens, broccoli, and root vegetables have naturally greater nitrate content than other plant foods do (16, 17). The remainder of the nitrate in a typical diet comes from drinking water (about 21%) and from meat and meat products (about 6%) in which sodium nitrate is used as a preservative and color-enhancing agent (18, 19). For infants who are bottle-fed, however, the major source of nitrate exposure is drinking water used to dilute formula.
Other Sources of Exposure	Nitrate or nitrite exposure can occur from certain medications and volatile nitrite inhalants. Accidental exposures to nitrites in chemical laboratories and ingestion in suicide attempts have been reported. Deliberate abuse of volatile nitrites (amyl, butyl, and isobutyl nitrites) frequently occurs. Nitrate or nitrite exposure also can occur from certain medications. Infants and children are especially susceptible to nitrate

exposure through topical silver nitrate used in burn therapy.

Other medications implicated in cases of nitrate or nitrite toxicity are quinone derivatives (antimalarials), nitroglycerine, bismuth subnitrite (antidiarrheal), ammonium nitrate (diuretic), amyl and sodium nitrites (antidotes for cyanide and hydrogen sulfide poisoning), and isosorbide dinitrate/tetranitrates (vasodilators used in coronary artery disease therapy). Ammonium nitrate found in cold packs and nitrous gases used in arc welding are other possible sources of exposure. An ethyl nitrite folk remedy called "sweet spirits of nitre" has caused fatalities (20, 21).

Key Points

- Shallow, rural domestic wells are those most likely to be contaminated with nitrates, especially in areas where nitrogen based fertilizers are in widespread use.
- Other nitrate sources in well water include seepage from septic sewer systems, or other contaminants.
- Contaminated foodstuffs, prepared baby foods, and sausage preserved with nitrates and nitrites have caused exposure in children.
- Nitrate or nitrite exposure can occur from certain medications and volatile nitrite inhalants.

Progress Check

1. Nitrites and nitrates

   A. are naturally occurring organic ions
   B. are relatively insoluble in water
   C. readily migrate in ground water
   D. all of the above.

   To review relevant content, see "Introduction" in this section.

2. Which of the following water sources would most likely contain nitrates or nitrites?

   A. bottled water
   B. large municipal water supplies
   C. shallow, rural domestic wells
   D. water from deep wells.

   To review relevant content, see "Water Contamination" in this section.

3. Medications which have been implicated in nitrate/nitrite toxicity include

   A. nitroglycerin
   B. antimalarials
   C. silver nitrate burn cream
   D. all of the above.

   To review relevant content, see "Other Sources of Exposure" in this section.

Who Is at Risk?

Learning Objective	Upon completion of this section, you will be able to • describe drinking water exposure risk to nitrates and nitrites and • identify the population most susceptible to nitrates and nitrites.
Introduction	About 1% to 2% of the U.S. population that uses drinking water from public water systems might be exposed to nitrates in excess of the EPA-recommended maximum concentration. EPA has estimated that approximately 1.2% of community water wells and 2.4% of private wells exceed the nitrate standard. Residents in as many as 603,000 homes may consume drinking water from nitrate-contaminated domestic wells. Although suppliers of public water sources are required to monitor nitrate concentrations regularly, few rural wells are routinely tested for nitrates (8).
Infants Are at Highest Risk	Infants younger than 4 months of age who are fed formula diluted with water from rural domestic wells are especially prone to developing health effects from nitrate exposure (21). The high pH of the infant gastrointestinal system favors the growth of nitrate-reducing bacteria, particularly in the stomach and especially after ingestion of contaminated waters. The stomach of adults is typically too acidic to allow for significant bacterial growth and the resulting conversion of nitrate to nitrite. A proportion of hemoglobin in young infants is still in the form of fetal hemoglobin. Fetal hemoglobin is more readily oxidized to methemoglobin (MHg) by nitrites than is adult hemoglobin. Therefore, infants, and especially premature infants, are particularly susceptible. In addition, NADH-dependent methemoglobin reductase, the enzyme responsible for reduction of induced MHg back to normal hemoglobin, has only about half the activity in infants as in adults (22, 23). Infection and inflammatory reactions can increase endogenous synthesis of nitrate in both infants and adults (4). Gastroenteritis with vomiting and diarrhea can exacerbate nitrite formation in infants. It has been reported to be a major contributor to MHg risk in infants independent of nitrate/nitrite ingestion (24–26). These factors combine to place young infants with diarrhea, who are fed formula diluted with nitrate-contaminated well water, at the greatest risk for toxicity (10, 27).
Pregnancy	The pregnant woman and her fetus represent another high-risk group. Reproductive outcome studies done at sites with high nitrate levels in the water supply provide some evidence of maternal transfer of nitrate and nitrite. The pregnant woman and her fetus might be more sensitive to toxicity from nitrites or nitrates at or near the 30th week of pregnancy (28, 29).

Key Points	• About 1% to 2% of the U.S. population that uses drinking water from public water systems might be exposed to nitrates in excess of the EPA-recommended maximum concentration. • Infants younger than 4 months of age are the highest risk group.
Progress Check	4. In the U.S., what percent of private wells exceed the EPA nitrate standard? A. 0% B. 1% C. 2.4% D. 10% *To review relevant content, see "Introduction" in this section.* 5. High risk populations for nitrate/nitrite toxicity include A. infants younger than 4 months old B. infants with diarrhea or vomiting C. infants fed formula diluted with private well water D. all of the above *To review relevant content, see "Infants are at Highest Risk" in this section.*

What Are U.S. Standards for Nitrate/Nitrite Levels?

Learning Objectives	After completing this section, you will be able to • describe EPA's recommended limit for nitrates and nitrites in drinking water.
Introduction	EPA has set an enforceable standard called a maximum contaminant level (MCL) for nitrates at 10 ppm, and for nitrites at 1 ppm. EPA believes that exposure below this level is not expected to cause health problems. Given present technology and resources, this is also a level to which water systems can reasonably be required to remove this contaminant should it occur in drinking water. All public water supplies must abide by these regulations. Once a water source is contaminated, the costs of protecting consumers from nitrate exposure can be significant. Nitrate is not removed by conventional drinking water treatment processes; its removal requires additional, relatively expensive treatment units (30).
Intake Limits	The Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization of the United Nations/World Health Organization and the European Commission's Scientific Committee on Food have set an acceptable daily intake (ADI) for nitrate of 0–3.7 mg nitrate ion/kg body weight. This intake appears to be safe for healthy neonates, children, and adults. The same is also true of the EPA reference dose (RfD) for nitrate of 1.6 mg nitrate nitrogen/kg body weight per day (equivalent to about 7.0 mg nitrate ion/kg body weight per day). JECFA has proposed an ADI for nitrite of 0–0.07 mg nitrite ion/kg body weight. EPA has set an RfD of 0.l mg nitrite nitrogen/kg body weight per day (equivalent to 0.33 mg nitrite ion/kg body weight per day) (31, 32).
Environmental Standards	The current water standard for nitrate is based on levels considered low enough to protect infants from methemoglobinemia. Some published results suggest an association between nitrate in drinking water and human malformations. However, a review of the toxicology in relation to possible adverse effects on reproduction and development offers no evidence for teratogenic effects attributable to nitrate or nitrite ingestion. The present maximum contaminant level appears to adequately protect even sensitive populations from nitrate-induced toxicity (33). Nitrate, however, has not undergone an evaluation of carcinogenic potential by EPA (34).
Key Points	• The current water standard for nitrate is based on protection of infants from methemoglobinemia. • In vivo conversion of nitrates to nitrites significantly enhances nitrates' toxic potency.

Progress Check	6. EPA's maximum contaminant level (MCL) for nitrates in drinking water is which of the following? A. 1 ppm B. 10 ppm C. 100 ppm D. 1,000 ppm *To review relevant content, see "Introduction" in this section.* 7. The present maximum contaminant level appears to adequately protect even sensitive populations from nitrate-induced toxicity. A. true B. false. *To review relevant content, see "Environmental Standards" in this section.*

What Is the Biologic Fate of Nitrates/Nitrites?

Learning Objectives	Upon completion of this section, you will be able to describe • the mean intake of nitrates by persons in the U.S. and • how nitrates are metabolized and excreted.
Introduction	Nitrate and nitrite levels in the body are the result of internal nitrate production and external sources. Intake of some amount of nitrates is a normal part of the nitrogen cycle in humans. The mean intake of nitrate per person in the United States is about 40–100 mg/day (in Europe it is about 50–140 mg/day). In the proximal small intestine, nitrate is rapidly and almost completely absorbed (bioavailability at least 92%) (31). Approximately 60% to 70% of an ingested nitrate dose is excreted in urine within the first 24 hours. About 25% is excreted in saliva through an active blood nitrate transport system and potentially is reabsorbed. Half-lives of parent nitrate compounds are usually less than 1 hour; half-lives of metabolites range from 1 hour to 8 hours (35, 36). Nitrate may also be synthesized endogenously from nitric oxide (especially in the case of inflammation), which reacts to form nitrite (22, 31).
Metabolism of Nitrates to Nitrites	In vivo conversion of nitrates to nitrites significantly enhances nitrates' toxic potency. The major metabolic pathway for nitrate is conversion to nitrite, and then to ammonia. Approximately 5%–10% of the total nitrate intake is converted to nitrite by bacteria in the saliva, stomach, and small intestine. This reaction is pH dependent, with no nitrate reduction occurring below pH 4 or above pH 9. This is the main reason why infants are more susceptible to nitrite toxicity from elevated nitrate/nitrite ingestion. Another potential metabolic pathway is the reaction of nitrite with endogenous molecules to form N-nitroso compounds, which may have toxic or carcinogenic effects (22).
Key Points	• Intake of some amount of nitrates is a normal part of the nitrogen cycle in humans. • In vivo conversion of nitrates to nitrites significantly enhances nitrates' toxic potency.
Progress Check Answers	8. The mean intake of nitrate per person in the U.S. is about: A. 40–100 mg/day B. 1 cup/ day C. 5 grams/day D. 1 pound/day *To review relevant content, see "Introduction" in this section.* 9. The toxicity of nitrates is enhanced by in vivo conversion to A. urea B. CO_2 C. protein D. nitrites *To review relevant content, see "Metabolism of Nitrates to Nitrites" in this section.*

What Are the Physiologic Effects of Exposure to Nitrates/Nitrites?

Learning Objective	Upon completion of this section, you will be able to • describe the physiologic and pathologic effects of nitrates/nitrites.
Introduction	Unless conditions exist for reducing nitrate to nitrite in the gut (i.e., high pH and proper intestinal microbial flora), ingested nitrate (NO_3^-) is metabolized and excreted without producing apparent adverse effects. Nitrate in the diet may even enhance host defenses against gastrointestinal pathogens by modulating platelet activity, and possibly even gastrointestinal motility and microcirculation (37–39). The known toxic effects of nitrate exposure result from the conversion of nitrate to nitrite (22). The effects of nitrite (NO_2^-) are the same whether nitrite-containing compounds are ingested or inhaled, or nitrite is produced in vivo from nitrate.
Hematologic Effects	Acute acquired methemoglobinemia is the most important adverse health effect caused by excessive nitrate or nitrite exposure. Methemoglobinemia may arise from various etiologies (40), including • ingestion or skin exposure to an oxidizing drug or chemical • systemic acidosis as a result of diarrhea and dehydration • nitrate or nitrite ingestion in water • genetic disorders presenting as cyanosis shortly after birth Methemoglobinemia is a well-recognized hazard of ingestion of nitrates and nitrites (41, 42). The first reported case of fatal acquired methemoglobinemia in an infant due to ingestion of nitrate-contaminated well water occurred in 1945 (43). In the following 25 years, about 2,000 similar cases of acquired methemoglobinemia in young infants were reported worldwide; about 10% of such cases resulted in death (44). Sporadic cases and occasional fatalities occurred through the 1980s and 1990s, most often resulting from ingestion of nitrate-contaminated well water by infants (33, 45, 46). Hemoglobin molecules contain iron within a porphyrin heme structure. The iron in hemoglobin is normally found in the Fe^{++} state. The iron moiety of hemoglobin can be oxidized to the Fe^{+++} state to form methemoglobin. Once it is formed, the molecule loses its ability to carry molecular oxygen. Because red blood cells are bathed in oxygen, a certain amount of physiologic methemoglobin formation occurs continuously. Several endogenous reduction systems exist to maintain methemoglobin in the reduced state. In normal individuals only about 1% of total hemoglobin is methemoglobin at any given time (40, 47). Methemoglobin can be reduced back to hemoglobin by both spontaneous (NADH-dependent and to a lesser degree by NADPH-dependent) methemoglobin reductase enzymes. Depending on the percentage of total methemoglobin, the clinical picture is one of oxygen deprivation with cyanosis, cardiac dysrhythmias and circulatory failure, and progressive central nervous system (CNS) effects. CNS effects can range from mild dizziness and lethargy to coma and convulsions (33, 48, 49).

Cardiovascular Effects	Hypotension is the main cardiovascular effect seen with nitrate and nitrite medications. It is not commonly seen with ingestion of nitrates and nitrites in food and water.
Reproductive and Developmental Effects	Maternal exposure to environmental nitrates and nitrites may increase the risk of pregnancy complications such as anemia, threatened abortion/premature labor, or preeclampsia (29, 50). Recent epidemiologic data have suggested an association between developmental effects in offspring and the maternal ingestion of nitrate from drinking water; however, a definite conclusion on the cause-and-effect relationship cannot be drawn (33). The maternal transfer of nitrate, nitrite, and N-nitroso compounds, and the potential effect on fetal death and malformation have been described (51). A few studies have hinted at a role for nitrate intake in the risk for developing diabetes mellitus in childhood (52–54). All of these reproductive and developmental effects require further study.
Carcinogenicity	Some study results have raised concern about the cancer-causing potential of nitrates and nitrites used as preservatives and color-enhancing agents in meats (55). Nitrates can react with amino acids to form nitrosamines, which have been reported to cause cancer in animals (51). Elevated risk of non-Hodgkin's lymphoma and cancers of the esophagus, nasopharynx, bladder, and prostate have been reported (56–59). An increased incidence of stomach cancer was observed in one group of workers with occupational exposures to nitrate fertilizer; however, the weight of evidence for gastric cancer causation is mixed (60, 61). Epidemiological investigations and human toxicological studies have not shown an unequivocal relationship between nitrate intake and the risk of cancer (31).
Key Points	• Acute acquired methemoglobinemia is the most important adverse health effect caused by excessive nitrate/nitrite exposure. • Maternal exposure to environmental nitrates and nitrites may increase the risk of pregnancy complications such as anemia, threatened abortion/premature labor, or preeclampsia.
Progress Check	10. Effects of methemoglobinemia include which of the following A. cyanosis B. coma or convulsions C. dysrhythmias D. all of the above *To review relevant content, see "Hematologic Effects" in this section.* 11. In methemoglobinemia, the oxidized Fe^{3+} of the hemoglobin molecule A. turns the blood bright red B. decreases its ability to carry oxygen C. activates the clotting cascade D. produces fever *To review relevant content, see "Hematologic Effects" in this section.*

How Should Patients Exposed to Nitrates/Nitrites Be Evaluated?

Learning Objectives

Upon completion of this section, you will be able to

- describe the clinical assessment of an infant exposed to nitrates/nitrites and
- describe the signs and symptoms of methemoglobinemia.

Introduction

The evaluation of nitrate/nitrite-related health effects most often presents as a clinical evaluation of an infant with cyanosis. Symptomatic methemoglobinemia is much less common in older children and adults.

Exposure History

The evaluation of a patient with suspected nitrate or nitrite exposure includes a complete medical and exposure history (1). Clues to potential exposure are often obtained by questioning the patient or family about the following topics (see **Table 1** for a select list of methemoglobin inducers)

- location of the home (urban, suburban, or rural),
- drinking water source and supply (if well water: depth, location, type of well construction, and frequency of microbiologic and nitrate testing),
- nearby activities (agricultural or industrial) and proximity to drinking-water source,
- type of sewer system (municipal or septic) and proximity to drinking-water source,
- proximity of neighboring septic tanks or others upgradient to drinking water source,
- recent flooding,
- occupations, avocations, and hobbies of family members,
- type of formula consumed by infant, feeding regimen, and source of dilution water,
- types of food eaten, with a focus on prepared meats, carrots, spinach, and
- recent use of medications by infant and mother

Medical History

Additional questions should be asked about the medical history including

- family history,
- known blood or enzyme disorders,
- nutritional status and growth history,
- history of recent gastroenteritis with vomiting or diarrhea,
- other episodes of cyanosis, recently or as a newborn, and
- history of tachypnea, tachycardia, or hypotension

Physical Examination

All cyanotic patients should be assessed for possible cardiac and lung disease (cardiac murmurs, gallops, arrhythmias, rales, rhonchi, wheezes, dullness, or hyperresonance in the chest). A central chocolate-brown or slate-gray cyanosis that does not respond to administration of 100% oxygen is suggestive of methemoglobinemia (40, 63). In addition, two clinical observations may help

1. the victim is often less ill than one would expect from the severity of 'cyanosis'

2. the 'cyanosis' is unresponsive to oxygen therapy (48).

Physical examination should include special attention to the color of the skin and mucous membranes. In young infants, look for labored breathing, respiratory exhaustion, hypotension, below-average weight gain, and failure to meet developmental indices. Gastroenteritis can increase the rates of production and absorption of nitrites in young infants and aggravate methemoglobinemia. If gastroenteritis is present—especially in infants—evaluate the patient for the possible presence of dehydration (i.e., poor skin turgor, sunken fontanel, dry mucous membranes) (40, 64).

Table 1. Reported Inducers of Methemoglobinemia

Agent	Source/Use
Inorganic nitrates/nitrites	Contaminated well water
	Meat preservatives
	Vegetables: carrot juice, spinach
	Silver nitrate burn therapy
	Industrial salts
	Contaminants of nitrous oxide canisters for anesthesia
Organic nitrites	Room deodorizer propellants
Butyl/isobutyl nitrite	Inhalant in cyanide antidote kit
Amyl/sodium nitrite	Oral, sublingual, or transdermal pharmaceuticals for treatment of angina
Nitroglycerine	Laundry ink
Others	Industrial solvents, gun-cleaning products
Aniline/aminophenols	Benzocaine, lidocaine, propitocaine, prilocaine
Nitrobenzene	Antibacterial drugs
Local anesthetics	Pyridium
Sulfonamides	Chloroquin, primaquine
Phenazopyridine	Dapsone

Antimalarials	Bactericide (tuberculostatic)
Sulfones	Mothballs
p-Aminosalicylic acid	Fungicide for plants, seed treatments
Naphthalene copper sulfate	Antiseborrheic, antipruritic, antiseptic
Resorcinol	Matches, explosives, pyrotechnics
Chlorates	Fires
Combustion products	

Adapted from Dabney (62).

Correlation of Signs and Symptoms with MHg Levels

Signs and symptoms of methemoglobinemia can be roughly correlated with the percentage of total hemoglobin in the oxidized form (see Table 2). Unfortunately, because methemoglobin (MHg) is generally expressed as a percent of total hemoglobin, levels may not correspond with symptoms in some patients. For example, a patient with a MHg level of 20% and total hemoglobin of 15 g/dL still has 12 g/dL of functioning hemoglobin, whereas a patient with a MHg level of 20% and total hemoglobin of 8 g/dL has only 6.4 g/dL of functioning hemoglobin. Anemia, acidosis, respiratory compromise, and cardiac disease may make patients more symptomatic than expected for a given MHg level (40).

Due to the large excess capacity of the blood to carry oxygen, levels of MHg up to 10% typically do not cause significant clinical signs in an otherwise healthy individual. Levels above 10% may result in cyanosis, weakness, and rapid pulse (22). A chocolate-brown or slate-gray central cyanosis—involving the trunk and proximal portions of the limbs, as well as the distal extremities, mucous membranes, and lips—is one of the hallmarks of methemoglobinemia and can become noticeable at a concentration of 10%–15% of total hemoglobin (65–67). Dyspnea and nausea occur at MHg levels of above 30%, while lethargy and decreased consciousness occur as levels approach 55%. Higher levels may cause cardiac arrhythmias, circulatory failure, and neurological depression. Levels above 70% are often fatal (20). Features of toxicity may develop over hours or even days (48).

Table 2. Signs and Symptoms of Methemoglobinemia	
Methemoglobin Concentration (%)	**Clinical Findings**
10–20	Central cyanosis of limbs/trunk; often asymptomatic but may have weakness, tachycardia
20–35	Central nervous system depression (headache, dizziness, fatigue), dyspnea, nausea
35–55	Lethargy, syncope, coma, arrhythmias, shock, convulsions
>70	High risk of mortality
Adapted from Dabney (62)	

Key Points	• The evaluation of nitrate/nitrite-related health effects most often presents as a clinical evaluation of an infant with cyanosis. • Exposure history for infants should focus on formula preparation and the source of formula dilution water. • Signs and symptoms of methemoglobinemia are roughly correlated with the percentage of oxidized hemoglobin in the blood.
Progress Check	12. What key areas should be addressed in the exposure history? A. recent use of medications by infant and mother B. type of formula, feeding regimen, and source of dilution water C. drinking water source and supply D. all of the above. *To review relevant content, see "Exposure History" and Table 1 in this section.* 13. What level of MHg creates a high mortality risk? A. 20% B. 40% C. 70% D. none of the above. *To review relevant content, see "Correlation of Signs and Symptoms with MHg Levels" in this section.* 14. Which of the following is/are true regarding the clinical assessment? A. All cyanotic patients should be assessed for possible cardiac and lung disease (cardiac murmurs, gallops, arrhythmias, rales, rhonchi, wheezes, dullness, or hyperresonance in the chest). B. A central chocolate-brown or slate-gray cyanosis that does not respond to administration of 100% oxygen is suggestive of methemoglobinemia C. The victim is often less ill than one would expect from the severity of 'cyanosis' D. all of the above. *To review relevant content, see "Physical Examination" in this section.*

What Laboratory Tests Can Help Diagnose Nitrate / Nitrite Toxicity?

Learning Objectives	Upon completion of this section, you will be able to • identify the laboratory test results that indicate methemoglobinemia.
Introduction	Methemoglobinemia results in distinct changes in blood color and oxygen-carrying capacity.
Bedside Testing Instructions	Place 1 or 2 drops of the patient's blood on white filter paper. The chocolate-brown appearance of methemoglobin does not change with time. In contrast, deoxyhemoglobin appears dark red/violet initially and then brightens after exposure to atmospheric oxygen. Gently blowing supplemental oxygen onto the filter paper hastens the reaction with deoxyhemoglobin, but does not affect methemoglobin (40, 67). A tube of methemoglobin-containing blood will not turn red when shaken in air or when oxygen is bubbled through it, whereas blood that is dark because of normal deoxyhemoglobin will turn red (68).
Pulse Oximetry and Arterial Blood Gases	Pulse-oximetry measurement of the oxygen saturation of hemoglobin does not provide accurate results in the presence of methemoglobinemia (69). Pulse oximetry underestimates oxygen saturation at low levels of methemoglobinemia and overestimates oxygen saturation when methemoglobinemia is severe. Arterial blood gas analysis will typically reveal a normal arterial oxygen tension (PO2) and may reveal a metabolic acidosis proportional to the severity and duration of tissue hypoxia. The profound and disproportionate metabolic acidosis seen in young infants with diarrheal illness and methemoglobinemia suggests that the acidosis is a cause or coexisting finding rather than a result of methemoglobinemia (48, 70).
Co-Oximetry and MHg Levels	Methemoglobin percentages can only be used to estimate oxygen-carrying capacity when interpreted with the total hemoglobin (49). Many hospital laboratories do not measure oxygen saturation directly on blood gas analysis. Instead, they derive it from a nomogram that is based on the measured PO2 and the presence of normal hemoglobin. In this case, the calculated oxygen saturation would be falsely elevated in the presence of methemoglobinemia. A "saturation gap" exists when the measured oxygen saturation of blood differs from the oxygen saturation calculated by routine blood gas analysis. A saturation gap of more than 5% suggests the presence of methemoglobin, carboxyhemoglobin, or sulfhemoglobin (20, 71). Co-oximetry is an accurate method of measuring methemoglobin. A co-oximeter is a simplified spectrophotometer, but unlike a pulse oximeter, it measures light absorbance at four different wavelengths. These wavelengths correspond to specific absorbance characteristics of deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, and hemoglobin. Interpreting the results from a blood gas analyzer without co-oximetry may lead to misdiagnosis because the oxygen saturation will have been calculated but not measured (72, 73).

Table 3. Suggested Lab Tests for Methemoglobinemia	
Screening Tests	• Examination of blood color • Determination of methemoglobin level • Determination of the calculated versus measured arterial saturation gap using co-oximetry • Hemoglobin and hematocrit • Serum-free hemoglobin (for hemolysis detection) • Serum haptoglobin (for hemolysis detection) • Heinz bodies on peripheral blood smear • Urinalysis
Specialized Tests	• Tests for causes of congenital methemoglobinemia • Hemoglobin electrophoresis • Activity of NADH-dependent methemoglobin reductase • Activity of glucose-6-phosphate dehydrogenase (G6PD) • Activity of NADPH-dependent methemoglobin reductase
Direct Biologic Indicators	Measurements of nitrates or nitrites in blood, urine, or saliva are not clinically useful.
Indirect Biologic Indicators	The most useful diagnostic test for nitrate toxicity is a blood methemoglobin level.

Key Points

- Methemoglobinemia results in distinct changes in blood color and oxygen-carrying capacity.
- Pulse-oximetry measurement of the oxygen saturation of hemoglobin does not provide accurate results in the setting of methemoglobinemia (69).
- Co-oximetry is an accurate method of measuring methemoglobin.

Progress Check

15. A drop of blood with methemoglobin appears what color on filter paper?

    A. chocolate-brown
    B. red
    C. violet
    D. clear yellow

    To review relevant content, see "Bedside Testing Instructions" in this section.

16. The best method for measuring methemoglobin levels is

    A. standard ABGs
    B. co-oximetry
    C. CBC
    D. pulse oximetry

    To review relevant content, see "Co-Oximetry and MHg Levels" in this section.

17. Useful diagnostic test(s) for nitrate toxicity include which of the following?

    A. measurements of nitrates in blood, urine, or saliva
    B. measurements of nitrites in blood, urine, or saliva
    C. blood methemoglobin level
    D. all of the above

    To review relevant content, see Table 3 in this section.

How Should Patients Exposed to Nitrates/Nitrites Be Treated and Managed?

Learning Objectives

Upon completion of this section, you will be able to

- describe two treatments for methemoglobinemia caused by nitrate/nitrite toxicity

Introduction

General principles of supportive care, with attention to removal of the cause, will suffice for most identified cases of methemoglobinemia resulting from nitrates and nitrites. Not all patients require specific antidotal therapy.

For infants, well water used in preparing formula is a primary etiologic suspect. Patients with chronic congenital methemoglobinemia may have adapted to the chronic cyanosis, such that very high levels of methemoglobin are tolerated without any overt symptoms (40). Proper fluid, electrolyte, and pH balance is vital, especially in infant methemoglobinemia complicated or caused by serious illness (74).

Comatose patients may require intravenous naloxone and glucose. Activated charcoal may be used, especially for ingested substances known to cause methemoglobinemia (see Table 1) (75). Monitor clinical and laboratory parameters for evidence of escalating or rebound methemoglobinemia, worsening oxygen delivery, or possible concomitant hemolysis (48, 49).

Once methemoglobinemia is recognized and confirmed, a decision to treat must be made immediately. Patients who are symptomatic or have significant concurrent problems that compromise oxygen delivery (heart disease, lung disease, carbon monoxide poisoning, or anemia) may need antidotal treatment at methemoglobin levels as low 10%. Because methemoglobin levels are typically reported as a percentage of hemoglobin, symptoms may vary depending on the total hemoglobin level. As an easy to remember guideline, the treatment action level is often considered to be 20% methemoglobin in symptomatic patients and 30% in asymptomatic patients (49, 76).

Methylene Blue

Methylene blue is an effective antidote for most patients with methemoglobinemia. Methylene blue is provided as a 1% solution (10 mg/mL). The dose is 1 to 2 mg/kg (0.2 mL/kg of a 1% solution) infused intravenously over 3 to 5 minutes. The dose may be repeated at 1 mg/kg if methemoglobin does not resolve within 30 minutes. Methylene blue should reduce methemoglobin levels significantly in less than an hour. It does this by acting as a cofactor to increase the activity of NADPH-methemoglobin reductase. Infants with methemoglobinemia resulting from diarrhea and acidosis may improve with aggressive hydration and bicarbonate to correct the acidosis. However, methemoglobin levels greater than 20% should be treated with methylene blue (40).

A second dose of methylene blue will be required in only very severe cases or if there is evidence of ongoing methemoglobin formation (48). The total dose should not exceed 7 mg/kg because the drug by itself is an oxidating agent. Certain drugs, such as dapsone, create methemoglobin

	over a long biologic half-life. In these situations, some clinicians prefer continuous infusions of methylene blue titrated from a starting rate of 0.1 mg/kg/hour, rather than intermittent bolus therapy (77). Methylene blue may discolor skin and mucous membranes, making visual interpretation of cyanosis inaccurate. It may also interfere further with pulse oximetry readings. After administration of methylene blue, it is prudent to reassess the patient's clinical status and current methemoglobin levels before proceeding with repeat doses (49). Methylene blue is excreted primarily by the kidneys. Although side effects are uncommon, large rapidly administered doses have been associated with nausea, retrosternal chest pain, tachycardia, hypertension, and anxiety. Urine will subsequently develop a blue-green discoloration (78). Because glucose is necessary for the effectiveness of methylene blue, normoglycemic patients should receive maintenance amounts of dextrose and hypoglycemic patients should receive standard dextrose therapy (40).
G6PD Deficiency	Known or suspected G6PD deficiency is a relative contraindication to the use of methylene blue (18, 40). G6PD is a key enzyme in the formation of NADPH. G6PD-deficient individuals generate insufficient NADPH to efficiently reduce methylene blue to leukomethylene blue, which is necessary for the activation of the NADPH-dependent methemoglobin reductase system. G6PD-deficient individuals are also prone to methylene blue-induced hemolysis. Methylene blue may also add to oxidative hemolysis. Young infants without G6PD deficiency have developed Heinz body hemolytic anemia at doses as low as 4 mg/kg (79, 80). Moreover, in the presence of hemolysis, high dose methylene blue can itself initiate methemoglobin formation (48, 81). Perinatal administration of higher doses of methylene blue (4 mg/kg), given amniotically, has been reported to induce hemolysis and methemoglobinemia in infants without G6PD deficiency (40).
Treatment Alternatives	For severe, life-threatening methemoglobinemia, when the patient responds poorly to methylene blue therapy or when the patient has G6PD deficiency, clinicians have tried various treatment alternatives. These treatment options include exchange transfusion and hyperbaric oxygen therapy (82, 83). During treatment in the hyperbaric chamber, sufficient oxygen can be dissolved directly in the blood to support life; reversible binding to hemoglobin is not required (84). Ascorbic acid and vitamin E (alpha-tocopherol) have been investigated, but do not seem promising as treatments for acute poisoning (48). Wright has demonstrated in vitro efficacy of N-actetylcysteine in reducing methemoglobinemia (84); however, this approach requires more study. Be aware that many G6PD-deficient patients have only a partial enzyme deficiency. Methylene blue may still lower methemoglobin levels, and the resultant hemolysis may be mild. Therefore, methylene blue is still the first-line treatment in G6PD-deficient patients with life-threatening methemoglobin. Exchange transfusion is reserved only for patients in whom methylene blue treatment is ineffective. A lower starting dose of methylene blue (0.3 to 0.5 mg/kg) is recommended. The dose may be titrated upward to reduce methemoglobin, as necessary. If the patient's condition worsens, methylene blue treatment should be stopped and exchange transfusion considered (40).

Key Points

- Many patients with methemoglobinemia require only supportive care.
- Methylene blue is an effective antidote for most patients with methemoglobinemia.
- For severe methemoglobinemia, or when the patient responds poorly to methylene blue therapy, treatment options include exchange transfusion and hyperbaric oxygen therapy.

Progress Check

18. The best course of action after giving the first dose of methylene blue is to

    A. discharge the patient
    B. discontinue oxygen therapy
    C. double the second dose
    D. reassess the patient's clinical status and methemoglobin levels

    To review relevant content, see "Methylene Blue" in this section.

19. A known contraindication to methylene blue therapy is

    A. G6PD deficiency
    B. age < 4 months
    C. leukopenia
    D. fever

    To review relevant content, see "G6PD Deficiency" in this section.

20. Which of the following is *not* an effective treatment for methemobinemia?

    A. exchange transfusion
    B. hyperbaric oxygen
    C. methylene blue
    D. dapsone

    To review relevant content, see "Methylene Blue" and "Treatment Alternatives" in *this section.*

Where Can I Find More Information?

For More Information

You can find more information about the adverse effects of nitrate/nitrite and the management of cases of human exposure from

- CDC-INFO

  800-CDC-INFO
  800-232-4636
  TTY 888-232-6348
  24 Hours/Day
  E-mail: cdcinfo@cdc.gov

- CDC Emergency Response: 770-488-7100
- your state and local health departments

Suggested Reading

Further information on nitrate/nitrite toxicity can be found in the following reports:

1. Avery AA. Infantile methemoglobinemia: reexamining the role of drinking water nitrates. Environ Health Perspect 1999; 107(7):583–6.
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Other CSEMs

Case Studies in Environmental Medicine: Nitrate/Nitrite Toxicity is one monograph in a series. For other publications in this series, go to:

http://www.atsdr.cdc.gov/csem/

Posttest Instructions

Introduction	ATSDR seeks feedback on this course so we can assess its usefulness and effectiveness. We ask you to complete the assessment questionnaire online for this purpose. In addition, if you complete the assessment and posttest online, you can receive continuing education credits as follows:

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Instructions:	To complete the assessment and posttest, go to http://www2a.cdc.gov/atsdrce/ and follow the instructions on that page. You can immediately print your continuing education certificate from your personal transcript online. No fees are charged.

Posttest

Choose all correct answers.

1. Nitrites and nitrates are

   A. Organic ions occurring naturally.
   B. Relatively insoluble in water.
   C. Ions that readily migrate in ground water.
   D. All of the above.

2. Which of the following subpopulations are most at risk of adverse effects from nitrate exposure?

   A. Girls age 13-18 years old.
   B. Telephone line workers.
   C. The elderly.
   D. Infants younger than 4 months of age.
   E. Individuals with anemia.

3. Which of the following are possible sources of nitrate exposure?

   A. Certain topical burn medications.
   B. Shallow domestic wells in rural areas.
   C. Meat preservatives.
   D. Seepage from septic tanks.
   E. All of the above.

4. Which statement about nitrates is true?

   A. Nitrates can be converted into more toxic nitrites in the gut.
   B. The higher alkalinity of an infant's gut protects it from nitrate toxicity.
   C. Vomiting and diarrhea do not affect the absorption of nitrates or nitrites.
   D. No case of nitrate poisoning has been reported since 1950.
   E. Adults are immune from nitrate toxicity if they drink water from public water systems.

5. The present maximum contaminant level appears to protect adequately even sensitive populations from nitrate-induced toxicity.

   A. True.
   B. False.

6. The mean intake of nitrate per person in the United States is about

   A. 40-100 mg/day.
   B. 1 cup/year.
   C. 5 grams/day.
   D. 1 pound/year.

7. The toxicity of nitrates is enhanced by in vivo conversion to

   A. Urea.
   B. CO_2.
   C. Protein.
   D. Nitrites.

8. Effects of methemoglobinemia include which of the following?

   A. Cyanosis.
   B. Coma or convulsions.
   C. Dysrhythmias.
   D. All of the above.

9. Methemoglobinemia can be induced by which of the following?

   A. Chloroquine.
   B. Lidocaine.
   C. Nitroglycerine.
   D. Dapsone.
   E. All of the above.

10. Which of the following systems is most directly affected by nitrates?

    A. Cardiovascular system.
    B. Pulmonary system.
    C. Hematologic system.
    D. Neurological system.
    E. Immune system.

11. Which statement is true?

    A. Signs and symptoms of methemoglobinemia are precisely correlated with percent total oxidized hemoglobin.
    B. Fetal hemoglobin is less readily oxidized by nitrites to methemoglobin than is adult hemoglobin.
    C. Methemoglobin causes arterial blood to be bright red in color.
    D. Pulse oximetry is the most useful diagnostic test for nitrate toxicity.
    E. None of the above.

12. What key areas should be addressed in the exposure history?

    A. Recent use of medications by infant and mother.
    B. Type of formula, feeding regimen, and source of dilution water.
    C. Drinking water source and supply.
    D. All of the above.

13. Which of the following is/are true regarding the clinical assessment?

    A. All cyanotic patients should be assessed for possible cardiac and lung disease (cardiac murmurs, gallops, arrhythmias, rales, rhonchi, wheezes, dullness, or hyperresonance in the chest).
    B. A central chocolate brown or slate gray cyanosis that does not respond to administration of 100% oxygen is suggestive of methemoglobinemia.
    C. The victim is often less ill than one would expect from the severity of 'cyanosis'.
    D. All of the above.

14. Useful diagnostic test(s) for nitrate toxicity include which of the following?

    A. Measurements of nitrates in blood, urine, or saliva.
    B. Measurements of nitrites in blood, urine, or saliva.
    C. Blood methemoglobin level.
    D. All of the above.

15. Which of the following treatments can be used for patients with nitrate toxicity?

    A. Hyperbaric oxygen therapy.
    B. Methylene blue.
    C. 100% oxygen.
    D. Exchange transfusion.
    E. All of the above.

16. What condition is a relative contraindication to methylene blue treatment?

    A. Psoriasis.
    B. G6PD deficiency.
    C. Methemoglobinemia.
    D. Diarrhea and vomiting.
    E. None of the above.

Relevant Content To review content relevant to the posttest questions, see

Question	Location of Relevant Content
1	What are nitrates/nitrites?
2	Who is at risk?
3	What are nitrates/nitrites?
4	What is the biologic fate of nitrates/nitrites?
5	What are U.S. standards for nitrate/nitrite levels?
6	What is the biologic fate of nitrates/nitrites?
7	What is the biologic fate of nitrates/nitrites?
8	What are the physiologic effects of exposure to nitrates/nitrites?
9	What are the physiologic effects of exposure to nitrates/nitrites?
10	What are the physiologic effects of exposure to nitrates/nitrites?
11	How should patients exposed to nitrates/nitrites be evaluated? What laboratory tests can assist with diagnosis of nitrate/nitrite toxicity?
12	How should patients exposed to nitrates/nitrites be evaluated?
13	How should patients exposed to nitrates/nitrites be evaluated?
14	What laboratory tests can assist with diagnosis of nitrate/nitrite toxicity?
15	How should patients exposed to nitrates/nitrites be treated?
16	How should patients exposed to nitrates/nitrites be treated?

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Answers to Progress Check Questions

1. Answer C. Nitrates and nitrites are naturally occurring inorganic ions that are relatively soluble in water and readily migrate in ground water.
2. Answer C. Shallow, rural domestic wells are the water sources most likely to be contaminated with nitrates, especially in areas where nitrogen-based fertilizers are in widespread use.
3. Answer D. Nitrate/nitrite exposure can occur from many nitrate-containing medications.
4. Answer C. EPA estimates that approximately 1.2% of community wells and 2.4% of private wells exceed the nitrate standard.
5. Answer D. Young infants with diarrhea who are fed formula diluted with nitrate-contaminated well water at the greatest risk for toxicity.
6. Answer B. EPA's maximum contaminant level (MCL) for nitrates is 10 ppm.
7. Answer A. True.
8. Answer A. The mean intake of nitrate per person in the U.S. is about 40–100 mg/day. Intake of some amount of nitrates is a normal part of the nitrogen cycle in humans.
9. Answer D. The major metabolic pathway for nitrate is conversion to nitrite, and then to ammonia. In vivo conversion of nitrates to nitrites significantly enhances nitrates' toxic potency.
10. Answer D. The clinical picture of methemoglobinemia from nitrate/nitrite toxicity is one of oxygen deprivation with cyanosis, cardiac dysrhythmias, and circulatory failure. CNS effects can range from mild dizziness and lethargy to coma and convulsions.
11. Answer B. The iron in hemoglobin is normally found in the Fe^{2+} state. The iron moiety of hemoglobin can be oxidized to the Fe^{3+} state to form methemoglobin. Once it is formed, the molecule loses its ability to carry molecular oxygen.
12. Answer D. Additional questions should focus on

    - location of the home (urban, suburban, or rural)
    - nearby activities (agricultural or industrial) and proximity to drinking-water source
    - type of sewer system (municipal or septic) and proximity to drinking-water source
    - recent flooding
    - occupations, avocations, and hobbies of family members
    - types of food eaten, with a focus on prepared meats, carrots, and spinach

13. Answer C. MHg levels above 70% are often fatal.
14. Answer D. All of the above.
15. Answer A. The chocolate-brown appearance of methemoglobin does not change with time. In contrast, deoxyhemoglobin appears dark red/violet initially, but brightens after exposure to atmospheric oxygen.
16. Answer B. Co-oximetry is an accurate method of measuring methemoglobin.
17. Answer C. Measurements of nitrates or nitrites in blood, urine, or saliva are not clinically useful. The most useful diagnostic test for nitrate toxicity is a blood methemoglobin level.

18. Answer D. After administration of methylene blue, it is prudent to reassess the patient's clinical status and current methemoglobin levels before proceeding with repeat doses.

19. Answer A. Known or suspected G6PD deficiency is a relative contraindication to the use of methylene blue.

20. Answer D. Dapsone. Methylene blue, exchange transfusion, and hyperbaric oxygen are treatment modalities for methemoglobinemia. Dapsone induces methemoglobinemia.