A two-month-old female infant is brought to your office for a routine well-baby checkup. According to the child’s chart, she was delivered two weeks early because of maternal toxemia and pregnancy induced hypertension. 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. 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

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.

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.

1. What is the most likely cause of this infant’s cyanosis?

a) cyanotic congenital heart disease  
   b) pneumonia  
   c) polycythemia  
   d) methemoglobinemia  
   e) argyria

2. What laboratory tests would help confirm the diagnosis?

a) arterial blood gas  
   b) co-oximetry  
   c) toxicology screen on blood and urine  
   d) complete blood count (CBC)  
   e) a and b

Answer on page 22
A 2-Month-Old Infant has Vomiting and Diarrhea, Tachypnea, and Cyanosis (Continued)

Answers:
1: d
2: e

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.

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. 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 (MHb) 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 MHb back to normal hemoglobin, has only about half the activity in infants as in adults.

Infection and inflammatory reactions can increase endogenous synthesis of nitrate in both infants and adults. Gastroenteritis with vomiting and diarrhea can exacerbate nitrite formation in infants. It has been reported to be a major contributor to MHb risk in infants independent of nitrite/nitrite ingestion. 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.

Clinical Evaluation
Several bedside evaluations can assist in diagnosing methemoglobinemia. Persistent cyanosis and an elevated respiratory rate despite the adequate administration of supplemental oxygen are clinical clues. Arterial blood with elevated methemoglobin levels may be mistaken for venous blood. To distinguish between normal venous blood and blood with elevated methemoglobin levels, the clinician can drop a few milliliters of blood into a test tube. Normal venous blood appears dark red when exposed to room air and turns bright red when exposed to 100% oxygen (eg, from a nasal cannula at the bedside). Arterial blood with elevated levels of methemoglobin has a characteristic chocolate brown color that remains unchanged after exposure to 100% oxygen.

Diagnostic Tests
The diagnosis of acquired methemoglobinemia can be clinically challenging. First, the relationship between the onset of symptoms and exposure to the culprit drug may not be recognized. There is often a delay of 20 minutes to several hours after exposure to the inciting drug before symptoms become severe. Second, in patients with multiple medical problems, distinguishing the cause of the symptoms may be difficult. For instance, shortness of breath in a patient with a known history of chronic obstructive pulmonary disease may be attributed to the underlying lung disease, a pulmonary embolism, or myocardial infarction, rather than to methemoglobinemia.

Three tests traditionally used to evaluate blood oxygenation are arterial blood gas (ABG) measurement, co-oximetry, and pulse oximetry. A certain wavelength of light is used to determine the partial pressure of oxygen and parameters of hemoglobin binding and peripheral oxygen saturation. ABG and co-oximetry require an arterial blood sample, which is usually taken from the radial artery. ABG measures the pH, partial pressure of oxygen, and partial pressure of CO2 in arterial blood. Co-oximetry measures oxygen saturation of the blood and quantifies abnormal forms of hemoglobin, such as methemoglobin and carboxyhemoglobin from carbon monoxide poisoning. Pulse oximetry noninvasively measures peripheral oxygen saturation with a probe placed on the fingertip, earlobe, or forehead. When the methemoglobin concentration is higher than 10%, the ABG and pulse oximetry readings become inaccurate. Until recently, only co-oximetry could accurately measure oxygen saturation of the blood in the presence of abnormal forms of hemoglobin, such as methemoglobin, because these cause changes in the absorption spectra of arterial blood. The ABG partial pressure of oxygen (PO2) and calculated oxygen saturation percent (SaO2) are falsely elevated in the presence of methemoglobin and carboxyhemoglobin. The pulse oximetry oxygen saturation percent (SpO2) decreases as the methemoglobin concentration increases up to 40%, after which the SpO2 value plateaus at 85%. The discrepancy between pulse oximetry and ABG data is of clinical use because an oxygen saturation gap of more than 5% is an important clue to severe methemoglobinemia. The oxygen saturation gap is the difference between the oxyhemoglobin calculated from the ABG and the oxyhemoglobin measured by pulse oximetry (SaO2 - SpO2). Co-oximetry has several limitations. First, it must be requested by the physician, and therefore methemoglobinemia must be in the differential diagnosis. Second, radial artery sticks are painful for the patient and technically difficult in infants. As many as 50% of hospitals in the United States do not offer co-oximetry because of a lack of access to the device. Recently, the ABG and co-oximetry functions have been combined into a single machine. Many laboratories with this technology automatically perform ABG and co-oximetry simultaneously.

However, the co-oximetry data are not routinely reported unless the physician ordered the test, and the diagnosis of methemoglobinemia may be missed.

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