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An Infant with Methemoglobinemia

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CASE PRESENTATION

History

A 22-day-old male infant was brought to the emergency department (ED) for evaluation of dehydration. He had been ill for 3 days with minimal interest in oral feeding. His pediatrician had examined him on the second day of illness, noted a 1-lb weight loss compared with birth weight, and instructed the mother to increase the quantity and frequency of feeds. On the following day, the infant developed nonbloody, non-mucoid diarrhea and increasing lethargy. On this third day of symptoms, he was reexamined by his pediatrician and was found to be more ill appearing, with further weight loss and dehydration, prompting referral to the ED. He had no fever, vomiting, or rash.

Key Point

True lethargy is a cause for extreme concern and requires prompt evaluation. Decreased oral intake and diarrhea may indicate hypovolemic dehydration; however, other life-threatening causes of lethargy should be considered (eg, sepsis, meningitis, toxic ingestion, nonaccidental trauma, metabolic disorder, congenital heart defects).

The infant was born at 35 weeks' gestation weighing 6 lb (approximately 10th percentile), and both the pregnancy and delivery were uncomplicated. In the first 2 weeks of life, his formula was changed from an iron-fortified cow's milk-based formula to a soy-based formula because of vomiting and loose stools. He was living with his parents in an urban area and had no known infectious contacts. There was no family history of endocrine or metabolic abnormalities.

Key Point

Most infants normally lose weight during the first week of life but recover to birth weight by age 10 to 14 days. Weight loss of 1 lb is significant in this age group, because it corresponds to more than 15% of body weight.

In addition to the infant's other signs and symptoms, this degree of weight loss suggests severe dehydration. Dehydration must be carefully and vigilantly treated in this age group; because of the lack of reserve energy stores, hypoglycemia should always be considered and rapidly assessed.

Physical Examination

When he arrived in the ED, the infant appeared toxic and cyanotic (gray-colored) with a high-pitched cry. He was lethargic with generalized weakness and decreased muscle tone, lying supine in a flaccid "frog-leg" position. His vital signs were as follows: tympanic temperature, 34.7°C (94.5°F); pulse, 170 bpm; respiratory rate, 60 breaths/min; and blood pressure, 82/34 mm Hg. His weight was 2.3 kg (5 lb, 1 oz), which is below the 5th percentile for his age. Oxygen saturation while the infant was breathing room air was 85% by pulse oximetry. Length and head circumference were not measured but appeared to be below the 50th percentile. The infant had a depressed anterior fontanelle with overlapping sutures, and his eyes were sunken. Although irritable on painful stimulation, he made no tears. His respiratory effort was labored with nasal flaring and retractions. Air entry to the lung bases was somewhat diminished, but breath sounds were clear bilaterally. Cardiovascular examination revealed a regular heart rhythm without murmur, symmetric but weak peripheral pulses, and a capillary refill time of 3 to 4 seconds. His abdomen was slightly distended with normal bowel sounds and no palpable hepatosplenomegaly or masses. His extremities were thin and appeared wasted without much subcutaneous tissue. He had no rashes, petechiae, or

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Table 1. Differential Diagnosis of Neonatal Diarrhea

Gastrointestinal causes

- Allergic colitis
- Antibiotic-associated colitis
- Gastroenteritis
- Hirschsprung's disease
- Intussusception
- Malabsorption/protein intolerance
- Necrotizing enterocolitis
- Overfeeding
- Partial bowel obstruction

Systemic causes

- Congenital adrenal hyperplasia
- Hemolytic uremic syndrome
- Hyperthyroidism
- Immunodeficiency
- Methemoglobinemia
- Sepsis

purpura. Results of a neurologic examination revealed generalized weakness with slightly decreased deep tendon reflexes but were otherwise nonfocal.

Key Point

Toxic-appearing infants require immediate evaluation and therapeutic intervention. The initial approach to critically ill patients of all ages includes primary stabilization of the airway, breathing, and circulation.

INITIAL MANAGEMENT CONSIDERATIONS

This child appeared quite tachypneic and ill out of proportion to the history of diarrhea described by his mother. He was in shock and appeared wasted with severe dehydration. Appropriate interventions include both diagnostic and therapeutic maneuvers while constantly reevaluating for response to therapy. Once the patient's airway and breathing have been stabilized, intravenous or intraosseous access must be obtained and crystalloid fluid boluses given.

Appropriate immediate laboratory studies to be obtained include rapid blood glucose measurement, basic serum electrolyte levels, complete blood count, and blood culture. In toxic-appearing infants, a septic work-up—including the analysis and culture of blood, urine, and cerebrospinal fluid—should be completed.

Broad-spectrum antibiotics should be promptly ad-

ministered. Reasonable considerations include ampicillin with gentamicin or ampicillin with cefotaxime. Common bacteria cultured in septic neonates include group B streptococci, *Escherichia coli*, and *Listeria monocytogenes*. Ampicillin will provide gram-positive coverage, and gentamicin or cefotaxime will add gram-negative coverage. *Streptococcus pneumoniae* is another pathogen to be considered, and vancomycin is indicated if there is concern about penicillinase-resistant streptococcus.

- **What is the differential diagnosis for a toxic-appearing infant with cyanosis and diarrhea?**

DIFFERENTIAL DIAGNOSES

Diarrhea is common during childhood, and although it is most commonly associated with a relatively benign infectious (viral) gastroenteritis, it also can be associated with a wide variety of other causes (Table 1). In addition, it is important to note that viral gastroenteritis is uncommon during the neonatal period and that the case patient was clearly ill beyond what would normally be expected after 1 to 2 days of gastroenteritis. The broad differential considerations for any toxic-appearing infant include infectious causes, fluid or electrolyte abnormalities, cardiovascular conditions, metabolic conditions, structural gastrointestinal disorders, and central nervous system conditions (Table 2).

Overwhelming sepsis is the prime concern in the neonatal age group, because infants at this age are relatively immunosuppressed and unable to partition off localized infection, given their impaired cell-mediated immunity. Sepsis may occur in association with meningitis, pneumonia, gastroenteritis, pyelonephritis, or osteomyelitis. The most common bacterial organisms include group B streptococci, *E. coli*, *L. monocytogenes*, and *S. pneumoniae*. Congenitally acquired infections are also a concern and include herpes, cytomegalovirus, toxoplasmosis, rubella, and syphilis. However, none of these congenital infections is usually associated with significant diarrhea. As previously discussed, toxic-appearing infants require admission to the hospital and intravenous antibiotic coverage after investigation for systemic infections, with a full sepsis evaluation (including cultures of blood, urine, and cerebrospinal fluid).

Respiratory distress may occur as a result of primary pulmonary involvement (pneumonic disease) or as a result of metabolic acidemia and an attempt to compensate with a respiratory alkalosis (Table 3). From a pulmonary standpoint, pneumonia and bronchiolitis should be considered. Respiratory syncytial virus infections are often epidemic during the winter months. Any

Table 2. Differential Diagnosis for a Toxic-Appearing Neonate

Infectious diseases
Meningitis
Pneumonia
Sepsis
Fluid/electrolyte abnormality
Dehydration (severe)
Hyponatremia/hypernatremia
Cardiovascular conditions
Bradycardia
Congestive heart failure
Shock
Tachycardia
Metabolic conditions
Adrenogenital syndrome
Hypoglycemia/hyperglycemia
Inborn error of metabolism
Methemoglobinemia
Structural gastrointestinal conditions
Hirschsprung's disease with toxic megacolon
Intussusception
Malrotation with midgut volvulus
Other bowel obstruction (eg, adhesions, hernia)
Central nervous system conditions
Increased intracranial pressure
Intracranial hemorrhage
Mass lesion

condition that results in metabolic acidosis can cause tachypnea and respiratory distress. Common entities include shock, sepsis, and inborn errors of metabolism (Table 3). Hyperpnea can also be seen with increased intracranial pressure.

Cyanosis is defined as an abnormal bluish discoloration to the skin and mucous membranes. In infants, cyanosis may be associated with congenital pulmonary abnormalities, acquired pulmonary infections, congenital heart defects, and hemoglobinopathies. In infants with cyanosis and diarrhea, methemoglobinemia must be considered.

In addition, this child was in shock. Shock occurs as a result of inadequate delivery of substrates to the tissues. It may occur either because the delivery system is impaired or as a result of tissue demands exceeding the capability of the delivery system. Septic shock

Table 3. Differential Diagnosis of Neonatal Tachypnea and Respiratory Distress

Pulmonary causes
Acquired pulmonary infections
Congenital pulmonary defects
Pneumothorax
Cardiac causes
Cardiogenic shock (myocarditis)
Congenital heart defects
Acidemia causes
Inborn errors of metabolism
Iron toxicity
Ketoacidosis
Lactic acidosis, idiopathic
Methemoglobinemia
Renal disease
Sepsis
Shock
Uremia
Other causes
Congenital diaphragmatic hernia
Gastrointestinal infection, obstruction, or perforation
Hyperthyroidism
Increased intracranial pressure

results from peripheral vasodilation in conjunction with direct toxic effects on the myocardium by toxic metabolites, and it is a major concern during the neonatal period. Hypovolemic shock occurs as a result of volume loss caused by diarrhea, vomiting, or bleeding. Severe diarrhea may result in shock, particularly when combined with poor oral intake. This child's ill appearance, however, was out of proportion to the relatively short course of diarrhea as described in his history. Cardiogenic shock is a possibility but is uncommon during the neonatal period. In such cases, pump failure occurs as a result of a variety of acquired conditions such as arrhythmia, infection (myocarditis), or toxin exposure (alcohol, cocaine, or other sympathomimetic agents).

CLINICAL COURSE

The infant was placed on a monitor, and high-flow oxygen was administered through a facemask while intravenous access was obtained and blood was drawn for laboratory studies. Despite supplemental oxygen,

Table 4. Laboratory Values of Case Patient

Variable	Result
Leukocyte count	26.0 × 10 ³ /mm ³
Differential count	
Segmented neutrophils	18%
Bands	31%
Lymphocytes	38%
Monocytes	6%
Platelet count	Clumped
Hemoglobin	16.2 g/dL
Serum electrolytes	
Sodium	121 mEq/L
Potassium	5.7 mEq/L
Chloride	107 mEq/L
Bicarbonate	6 mEq/L
Blood urea nitrogen	12 mg/dL
Serum creatinine	0.9 mg/dL
Serum glucose	387 mg/dL
Arterial blood gases	
pH	6.96
PCO ₂	15 mm Hg
PO ₂	226 mm Hg
Total CO ₂	< 5 mmol/L
Co-oximetry	
Methemoglobin	31.6% (normal, 0%–1.9%)
Oxyhemoglobin	68.2%
Carboxyhemoglobin	0.2%
Cerebrospinal fluid	
Color	Bloody (traumatic)
Xanthochromia	Absent
Cell count	
Leukocyte count	20 × 10 ³ /mm ³
Differential count	
Segmented neutrophils	15%
Bands	2%
Lymphocytes	74%
Monocytes	9%
Erythrocyte count	420,000 × 10 ³ /mm ³
Gram stain	No organisms, few leukocytes, abundant erythrocytes
Protein	300 mg/dL
Glucose	168 mg/dL
Cultures	
Blood	No growth of organisms
Urine	No growth of organisms
Cerebrospinal fluid	No growth of organisms
Stool (routine)	No growth of organisms

his pulse-oximetry reading remained at 85%, and he continued to have respiratory distress. He was urgently intubated, and his pulse-oximetry reading increased to 95% with delivery of 100% oxygen. Chest radiography showed the endotracheal tube to be in good position, with clear bilateral lung fields and normal cardiac silhouette and pulmonary vascular markings. After intravenous access was obtained, the infant was given two 20-mL/kg body weight fluid boluses of normal saline, intravenously. An arterial blood sample was obtained, and in retrospect was noted to be darker than expected. He was admitted to the pediatric intensive care unit (PICU) for continued mechanical ventilation, treatment of shock, and further diagnostic work-up.

The diagnostic work-up focused on the evaluation of the infant's respiratory distress, possible sepsis, severe acidosis, and electrolyte abnormalities (Table 4). A sepsis work-up, which had been initiated in the ED, was completed, including urinalysis, urine culture, and cerebrospinal fluid analysis and culture. His antibiotic coverage consisted of ampicillin, cefotaxime, and acyclovir. Laboratory studies revealed metabolic acidosis, hyponatremia, hyperkalemia, and an elevated serum creatinine level (Table 4). Because of concerns of a possible adrenal crisis, the infant's cortisol and 17-hydroxyprogesterone levels were measured, and he was given a stress dose of hydrocortisone pending those results (which were found to be within normal limits). While in the PICU, he continued to receive multiple isotonic fluid boluses for correction of shock and dehydration. However, based upon this child's initial degree of shock and metabolic acidosis out of proportion to the history of diarrhea, as well as his darker than normal appearing blood, methemoglobinemia was strongly suspected. His methemoglobin level as measured by co-oximetry was 31% (normal, < 2%), and he was promptly treated with methylene blue (1 mg/kg). Within a few minutes, his pulse-oximetry reading increased to 100%.

During the next few days, his status generally improved. A repeat methemoglobin level was 1% on hospital day 2, and his respiratory status had improved sufficiently such that he was extubated. Because of the initial severe acidosis and electrolyte abnormalities, the hospital's endocrinology service was consulted. An extensive laboratory work-up revealed no abnormalities, and his acid-base status and electrolytes improved with isotonic fluid administration. Antibiotics were discontinued after the results of his cultures (Table 4) and herpes simplex virus polymerase chain reaction assay were confirmed to be negative. After extubation, he remained generally hypotonic. Magnetic resonance imaging of the brain showed infarcts in the right thalamus, left brain stem,

and left cerebellum. He was restarted on oral feeding consisting of a hypoallergenic, lactose-free, sucrose-free, casein protein hydrolysate formula (Pregestimil) but had subsequent emesis and persistent loose, watery, and occasionally bloody diarrhea. He was diagnosed with intractable diarrhea of infancy. Because of continued weight loss, an indwelling central venous catheter was placed, and he was maintained on total parenteral nutrition for 4 weeks, after which he tolerated Pregestimil feedings, which were gradually increased in volume over the next 2 weeks. During his hospital course, he received both physical and occupational therapy. He was discharged to home tolerating Pregestimil 16 oz per day. For a brief period, he received daily visits from a home-health nurse for evaluation of his weight and hydration status, as well as supervision of his feeding. He was scheduled for follow-up appointments with his pediatrician, neurologist, and gastroenterologist. Although there are concerns of mild developmental delay, he is currently doing well on Pregestimil formula without emesis or diarrhea, and feedings with a cow's milk-based formula will be attempted at 1 year of age.

- What aspects of the diagnosis and clinical course of methemoglobinemia are most important to know?
- What are the most important components in the management of methemoglobinemia?

METHEMOGLOBINEMIA

Definition

Methemoglobinemia is a condition in which the iron within the hemoglobin molecule is oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. This oxidized (ie, ferric) hemoglobin has impaired ability to transport oxygen and carbon dioxide. Under normal conditions, a constant balance occurs in the relative rates of oxidation and reduction within the hemoglobin molecule. Oxidation results from electron transfer from oxygen normally dissolved in the blood, whereas reduction occurs by simultaneous endogenous enzymatic activity. This results in a "physiologic" methemoglobin level of approximately 1% in most normal individuals.¹ In persons with methemoglobinemia, the tetrameric hemoglobin molecule may not have all 4 parts of the molecule oxidized at the same time, resulting in a partially oxidized hemoglobin molecule and an interaction between the oxidized and nonoxidized portions that causes a greater oxygen affinity for the nonoxidized portions to be able to carry oxygen. As a result, the oxygen dissociation curve is shifted to the left, and less oxygen can be released in the tissues.¹

Table 5. Causes of Methemoglobinemia in a Neonate

Endogenous sources

Increased production of:

Diarrhea-related causes (protein intolerance?)

Nitrite-forming bacteria

Higher intestinal pH

Impaired reduction of:

Hemoglobin F

Immature cytochrome- b_5 reductase activity

Methemoglobin reductase activity reduced by acidosis

Exogenous sources

Antibiotics (chloroquine, sulfonamides)

Industrial compounds (aniline dyes, copper, naphthalene, phenols)

Local anesthetics (benzocaine, cetacaine, lidocaine, prilocaine, lidocaine plus prilocaine [EMLA])

Nitrates/nitrites (nitroglycerin, silver nitrate, well water)

Other medicines (dapson, phenacetin, phenytoin, sulfapyridine)

Rare

NADH methemoglobin reductase deficiency (congenital methemoglobinemia)

Factitious causes (pseudomethemoglobinemia/sulfhemoglobinemia)

Methemoglobin is reduced primarily through an enzyme system that involves cytochrome b_5 and NADH cytochrome- b_5 reductase. This system is also known as NADH methemoglobin reductase and is found in both erythrocytes and somatic cells.^{1,2} The body has other less prominent and more indirect mechanisms to protect against oxidative stress and help to reduce methemoglobin (eg, glutathione, superoxide dismutase, catalase, glutathione peroxidase).³

Other forms of abnormal hemoglobin (dyshemoglobin) are carboxyhemoglobin and sulfhemoglobin, both of which also have impaired ability to transport oxygen and carbon dioxide.

Etiology

Methemoglobinemia occurs whenever there is excess oxidized hemoglobin and the systems that reduce it to its ferrous state are overwhelmed, impaired, or lacking. The 3 common causes of methemoglobinemia are exogenous (toxin-induced), endogenous (related to diarrhea, infection, or systemic acidosis), and genetic.³ **Table 5** lists the most common conditions and agents known to cause methemoglobinemia.

Table 6. Methemoglobinemia-Related Symptoms

Methemoglobin Level	Symptoms
< 10%	None
10%–20%	Cyanosis
20%–30%	Irritability, tachypnea, tachycardia
30%–50%	Marked tachypnea, tachycardia
> 50%	Lethargy, coma, seizures, dysrhythmias
> 70%	Death

These conditions and agents may cause methemoglobinemia by either directly oxidizing the iron within hemoglobin or indirectly causing oxidation through the release of free radicals.³ In addition to drug exposure, some children develop methemoglobinemia after exposure to nitrate-containing foods or nitrates in well water. Intestinal flora convert the nitrates into nitrites that are absorbed systemically and act as oxidizing agents.^{4,5}

Although the disorder can occur at any age, small infants may be predisposed to developing methemoglobinemia. The level of cytochrome-b₅ reductase at birth is approximately half the level in adulthood⁶ and does not reach adult levels until at least 4 months of age.⁷ In addition, fetal hemoglobin is more easily oxidized, compared with adult hemoglobin.⁸ Bacterial growth in the infant intestinal tract also is enhanced by a relatively higher gastric pH, and these bacteria may convert nitrates to nitrites, which act as potent oxidizing agents.⁹

Methemoglobinemia can develop in young infants who have systemic metabolic acidosis. In these infants, the acidosis is often caused by dehydration associated with diarrhea or sepsis, but it may occur with renal disorders.^{10–12} During sepsis, it is suspected that increased nitric oxide is released and oxidizes hemoglobin as it is reduced to nitrate.¹¹ During acidosis, the NADH methemoglobin reductase enzyme system is impaired, and methemoglobin reduction can be decreased by as much as 50%.¹³

Methemoglobinemia associated with diarrhea is likely caused by a combination of factors, and the patient may not have systemic acidosis.¹⁰ In patients with infectious diarrhea, gram-negative intestinal bacteria convert nitrates to nitrites.¹⁰ Methemoglobinemia occurring in association with diarrhea may also be related to an idiopathic hypersensitivity reaction occurring in response to the particular protein contained within the formula and

subsequent increased nitrite formation caused by colonocyte inflammation.¹⁴

Hereditary methemoglobinemia is a rare genetic condition that occurs when there is a gene mutation of chromosome 22q13 on which the enzyme cytochrome b₅-reductase is found.^{15,16} The disorder is inherited in an autosomal recessive pattern, and affected infants have cyanosis and elevated methemoglobin levels shortly after birth. Because the enzyme is in both a soluble form and a membrane-bound form (ie, in the outer mitochondrial membrane and endoplasmic reticulum), 2 types of hereditary homozygous methemoglobinemia exist. In type I, the enzyme is only lacking in erythrocytes (soluble form), usually manifesting cyanosis as the only symptom.¹⁷ In type II, the rarer version, the enzyme is lacking in all cells, and the symptoms may become severe (eg, mental retardation, neurologic impairment, death).¹⁸ Heterozygotes for this gene mutation will only have clinical signs when subject to oxidative stress.⁸ Hemoglobin M is inherited in an autosomal dominant pattern, and the homozygous form is thought to be incompatible with life.³

Clinical Presentation

History. Historical symptoms vary, depending on the percentage of methemoglobin present (Table 6). A high index of suspicion should be maintained, because methemoglobinemia may occur with subtle or no symptoms. In addition, depending on the age of the patient, there may be widely divergent etiologic concerns. Infants younger than 6 months commonly have diarrhea associated with their illness; however, clinicians must also investigate for possible exposures to toxic oxidizing agents (eg, topical anesthetics or teething gels, sulfonamide antibiotics, naphthalene-containing mothballs) (Table 5).

Subclinical methemoglobinemia may be relatively common in young infants with diarrhea, particularly in those who are small for their age. In a study of 43 infants younger than 6 months who had diarrhea, 64% had elevated methemoglobin levels, and only one half of those with elevated levels were cyanotic.¹⁹ In this study, no correlation was made between methemoglobin levels and clinical assessment of dehydration; 56% of patients with elevated methemoglobin levels were below the fifth percentile for growth. Some investigators believe that diarrhea-associated methemoglobinemia is the most common etiology of methemoglobinemia occurring in infants and is related in some way to the proteins contained within feedings.^{10,14} This hypothesis is substantiated by the fact that when infants have their formulas changed, their condition has improved, and when they return to their previous formula, methemoglobinemia

has recurred.¹⁴ The physician must also investigate for other symptoms of underlying conditions that may cause systemic acidosis predisposing to methemoglobinemia or conditions that may exacerbate methemoglobinemia, if it develops.

In patients with genetic methemoglobinemia, cyanosis may occur shortly after birth, and the family history may reveal the cause. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a condition that results in intravascular hemolysis after erythrocytes are subjected to oxidative stress. It is necessary to obtain a genetic history, because it has important implications on the management of methemoglobinemia.

Physical examination. Infants with methemoglobinemia are most often ill out of proportion to their history of illness. Two other very important clues in diagnosing the disorder include cyanosis that does not resolve with administration of supplemental oxygen and blood that appears darker than normal.⁸ Although methemoglobinemia may be confused with cyanotic congenital heart defects, the cyanosis of infants with congenital heart defects usually improves at least somewhat with administration of supplemental oxygen.³ In patients with methemoglobinemia, arterial blood is frequently mistaken for being venous, and venous blood is often described as having a “chocolate brown” appearance. Cyanosis may occur when as little as 10% of the hemoglobin (1.5 g/dL) is in the methemoglobin form. In patients with severe anemia, a higher percentage of methemoglobin is required for cyanosis to occur. Signs and symptoms of methemoglobinemia vary, depending on the percentage of methemoglobin (Table 6). At higher levels of methemoglobin, patients have marked respiratory distress and altered mental status. Patients with anemia or decreased functional hemoglobin will manifest symptoms at levels of methemoglobin that are lower than expected.³ Moreover, conditions that may further impair oxygen delivery and tissue perfusion (eg, systemic acidosis, respiratory distress, cardiac conditions) may exacerbate the cyanosis and other symptoms of methemoglobinemia, regardless of the methemoglobin level.³ Hemolysis is more likely to occur in patients exposed to oxidizing drugs or in those with G6PD deficiency.¹⁰

Diagnosis

Laboratory evaluation. Although methemoglobinemia may be suspected based on history or physical examination findings, the diagnosis can only be confirmed with a serum methemoglobin level measured by co-oximetry.³ Interpretation of pulse oximetry and arterial blood gas (ABG) measurements may be misleading. In cases of methemoglobinemia, patients have

a low pulse oximetry reading but normal PaO₂ and calculated oxygen saturation (SaO₂) levels.³

Pulse oximetry detects deoxyhemoglobin and oxyhemoglobin by measuring the ratio of absorption of red and infrared light wavelengths. In the absence of dyshemoglobin (ie, methemoglobin, sulfhemoglobin, carboxyhemoglobin), deoxyhemoglobin and oxyhemoglobin are absorbed at 660 and 940 nm, respectively, with a ratio of 0.43 corresponding to 100% saturation.^{20,21} Methemoglobin is absorbed at both 660 and 940 nm. Pure methemoglobinemia results in a ratio of 1 and corresponds to a saturation reading of 85%. With methemoglobin levels greater than 30% to 35%, the pulse oximetry reading will plateau at 82% to 85%, regardless of the methemoglobin level.^{20,21}

The results of standard ABG measurements will also not diagnose methemoglobinemia. ABG analyzers measure dissolved oxygen and report an accurate PaO₂ level, but they calculate the SaO₂ level based on the pH and hemoglobin levels.²² In patients with methemoglobinemia, the calculated SaO₂ level will be falsely elevated, because of the presence of abnormal hemoglobin with impaired oxygen-carrying capacity.²²

Co-oximetry is the most accurate method to reliably measure methemoglobin. Based on differential absorption patterns of visible and infrared light, most co-oximeters will measure the percentages of 4 types of hemoglobin (ie, oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, methemoglobin).²²

A rare condition known as “pseudomethemoglobinemia” exists, in which sulfhemoglobin is erroneously detected by co-oximeters as methemoglobin, giving a falsely elevated methemoglobin level.^{23,24} Sulfhemoglobin is not measured by standard co-oximeters and requires gas chromatography as the gold standard. In sulfhemoglobinemia, a sulfur molecule is incorporated into the hemoglobin molecule, compromising its oxygen-carrying capacity, and the oxygen dissociation curve shifts to the right, resulting in easier oxygen unloading. Consequently, less severe clinical symptoms are seen than with methemoglobinemia at similar levels.²⁵ Sulfhemoglobin is associated with exposure to many of the same toxins that can produce methemoglobinemia (eg, sulfonamides, acetanilide, phenacetin, nitrates, trinitrotoluene, sulfur-containing compounds, metoclopramide, *N*-acetylcysteine).^{3,25} Sulfhemoglobin does not respond to treatment with methylene blue, and management consists predominantly of supportive care with consideration of possible exchange transfusion if the patient’s condition worsens or fails to improve.²⁵

Radiography. No pathognomonic findings of methemoglobinemia are present on chest radiography; in

fact, results are often normal. However, chest radiography may be useful in the evaluation of concurrent conditions causing respiratory distress.

Treatment

Treatment of methemoglobinemia is based on reducing the oxidized iron within the hemoglobin to its ferrous state. The treatment of choice is methylene blue 1 to 2 mg/kg given intravenously over 3 to 5 minutes.³ Methylene blue is recommended for symptomatic patients with methemoglobin levels greater than 20% or for asymptomatic patients with levels greater than 30%.³ Symptoms usually improve within 1 hour of administration.²⁶ If no improvement occurs after 30 minutes, a dose of 1 mg/kg may be repeated⁸ and is usually well tolerated. Methylene blue is itself an oxidizing agent, however, and may cause hemolytic anemia, particularly when given in higher doses (4 mg/kg) or to patients with G6PD deficiency.^{27–29} In fact, if the patient has methemoglobinemia and G6PD deficiency, methylene blue will likely be ineffective, because these patients lack the necessary cofactor NADPH. However, if the G6PD enzyme deficiency is not severe, the treatment may include a trial of methylene blue with careful evaluation for further hemolysis.³ If methylene blue is not an option, exchange transfusion is a treatment consideration for patients with G6PD deficiency. *N*-acetylcysteine is a potential alternative treatment for these patients, because it is a reducing agent as well as a precursor to glutathione, another reducing agent.³ Because glucose is a cofactor in NADPH synthesis, coadministration with methylene blue may be necessary.³⁰ Finally, in addition to treating methemoglobinemia, any underlying conditions must be evaluated and treated appropriately.

CONCLUSION

Methemoglobinemia should be included in the differential diagnosis of toxic-appearing infants presenting with cyanosis, shock, and respiratory distress. Clinicians should be particularly suspicious when evaluating infants with a history of diarrhea and an ill appearance that is out of proportion to their medical history. Important additional clues to the diagnosis include cyanosis that does not resolve with administration of supplemental oxygen and blood that appears darker than normal. The diagnosis is confirmed by co-oximetry. Methemoglobinemia can be life threatening; however, outcomes are good when patients are treated with methylene blue in an intensive care environment. For infants in whom the methemoglobinemia has occurred in association with diarrhea and failure to thrive, consideration may be given toward changing the formula. **HP**

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