CME

A Cyanotic Infant: True Blue or Otherwise?

Joseph J. Zorc, MD; and Zlatka Kanic, MD

CASE PRESENTATION

A 3-week-old male neonate was brought to the hospital for progressive cyanosis. He had been well until several hours prior to presentation, when his mother noticed a darkening in the color of his face, trunk, and extremities. On the way to the hospital, he had become irritable and increasingly tachypneic.

There was no history of fever, vomiting, diarrhea, or rash. The prenatal history was unremarkable for infections or maternal drug, alcohol, or tobacco use. He had been born by spontaneous vaginal delivery without complications. His birth weight was 6 pounds, 3 ounces, and he had been feeding well on a cow's milk formula with good weight gain since birth. Family history included one older sister with psoriasis; there was no history of congenital heart disease. The family lived in a rural town and no one else at home was currently ill. No medications or home remedies had been given to the neonate prior to presentation.

On physical examination, the neonate was irritable and dyspneic with intercostal and suprasternal retractions. His color was deeply cyanotic over all parts of his body. His axillary temperature was 36.8°C, his heart rate was 180 beats per minute, his respiratory rate was 50 breaths per minute, and the blood pressure in his right arm was 87/53 mm Hg. He weighed 7 pounds, 8 ounces. Results of an examination of the head and neck were normal, the chest was clear, and the abdomen was soft and nontender without hepatosplenomegaly. Heart sounds were normal without a murmur, rub, or gallop; pulses were palpable in both upper and lower extremities, and capillary refill was less than 2 seconds.

INITIAL DIAGNOSIS

For this neonate presenting with cyanosis and respiratory distress, congenital cardiac disease was at the top of the differential diagnosis. A face mask provided 100% oxygen, and pulse oximetry showed a saturation of 91%. There appeared to be minimal improvement in the neonate's color with oxygen. A chest x-ray showed a normal cardiac silhouette without an infiltrate.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cyanosis can be divided into two major groups: disorders involving deoxygenated hemoglobin and disorders of abnormal hemoglobin (Table 1). The first and most common group can be further categorized based on anatomy: disorders of the central nervous system and muscles, the upper airway, the lungs, the heart, and the circulatory system. Within the central nervous system, apnea due to a variety of mechanisms may result in cyanosis. These cyanotic episodes will generally resolve rapidly after the return of spontaneous breathing or resuscitation with positive-pressure oxygen.

Dr. Zorc is Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine, and Attending Physician, Division of Emergency Medicine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. Dr. Kanic is Director of Intensive Care, Hospital for Sick Children, Maribor, Slovenia. Address reprint requests to Joseph J. Zorc, MD, Division of Emergency Medicine, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104.

TABLE 1

Important Causes of Cyanosis in Infancy*

- Increase in deoxygenated hemoglobin
  - Impaired respiration
    - Central causes
      - Congenital
      - Hemorrhage
      - Infection: meningoencephalitis, respiratory syncytial virus
      - Seizure
      - Metabolic abnormalities
      - Medications: narcotics and sedatives
      - Breath-holding spells
    - Neuromuscular disorders: myasthenia and botulism
  - Upper airway obstruction
    - Choanal atresia
    - Macroglossia
    - Airway hypoplasia
    - Laryngeal web or cyst
    - Tumor
    - Tonsillar hypertrophy
    - Foreign body
    - Congenital vascular ring
  - Intrapulmonary shunt
    - Pneumonia
    - Atelectasis
    - Pneumothorax
    - Diaphragmatic hernia
    - Edema
    - Hemorrhage
    - Arteriovenous fistula
    - Pulmonary embolism
    - Pulmonary hypoplasia or malformation
    - Persistent pulmonary hypertension of the newborn
  - Cyanotic congenital cardiac disease
    - Tetralogy of Fallot and related lesions
    - Transposition of the great arteries
    - Tricuspid atresia
    - Truncus arteriosus
    - Total anomalous pulmonary venous return
    - Hypoplastic left heart
    - Ebstein's anomaly
  - Capillary stasis—decreased venous oxygenation
    - Peripheral
      - Acrocyanosis of the newborn
      - Raynaud disease
    - Generalized
      - Hypotension
      - Hyperviscosity syndromes
  - Increased hematocrit, polycythemia
- Abnormal hemoglobin
  - Methemoglobinemia
  - Carboxyhemoglobinemia

Data from Green[1] and Tunnessen et al.[2]

Cyanotic breath-holding spells are a specific type of apneic episode occurring in infants or toddlers that may have a pathophysiology similar to that of vasodepressor syncope.[3] A history of intermittent cyanosis associated with stridor or noisy breathing would indicate the need to investigate an anatomic abnormality of the upper airway, such as choanal atresia, foreign body, cyst, or vascular ring.

Shunting of deoxygenated blood within the lungs to pulmonary veins and on to the systemic circulation can occur with infection, collapse, edema, hemorrhage, or congenital malformations. Cyanosis due to these causes of hypoxemia will be accompanied by a lowered oxygen saturation and partial pressure of oxygen (pO_2). Signs and symptoms such as cough and fever or physical findings such as rales on auscultation may suggest the appropriate diagnosis. Also, abnormalities on chest x-ray would be expected for most of these etiologies of cyanosis.

Congenital cardiac disease is an important cause of cyanosis in a young infant that requires immediate recognition and treatment. Many of these lesions present in the days to weeks after birth when the ductus arteriosus closes. Therapy for these lesions requires initiation of prostaglandins by intravenous infusion to maintain patency of the ductus. Examples of lesions that may worsen with closure of the ductus include tricuspid atresia, Ebstein's anomaly, hypoplastic left heart syndrome, and transposition of the great arteries.[4] Tetralogy of Fallot and similar lesions may also be ductal dependent; cyanosis results from blood intermittently shunting across a ventricular septal defect away from an obstructed pulmonary outlet tract and into the systemic circulation. These "tet" spells require treatment with oxygen and morphine and physical maneuvers such as the knee–chest position to increase pulmonary circulation. Truncus arteriosus involves complete mixing of blood from the left and the right sides of the heart. Finally, total anomalous pulmonary veins without venous obstruction can present with cyanosis well beyond the newborn period.

Clues to the diagnosis of cyanotic congenital heart disease will vary with the lesion. Many, although not all, infants will present with physical

findings (eg, a heart murmur) or evidence of congestive heart failure (eg, rales or hepatomegaly). A chest radiograph may show cardiomegaly along with either increased or decreased pulmonary blood flow depending on the lesion.

The most helpful initial diagnostic maneuver is the hyperoxia test in which oxygenation is measured in room air and 100% oxygen; infants with a pO_2 of less than 150 mm Hg and saturations of less than 85% with 100% oxygen are likely to have congenital heart disease. Once the diagnosis has been made, oxygen should be used sparingly to keep saturations between 80% and 85%, because high concentrations of oxygen can increase pulmonary blood flow and may hasten closure of the ductus. Prostaglandins should be administered intravenously to maintain the patency of the ductus, and a pediatric cardiologist should be consulted to make a definitive diagnosis.

Other causes of cyanosis and hypoxemia include mechanisms that produce capillary stasis, resulting in further extraction of oxygen from hemoglobin and decreased venous oxygenation. The acrocyanosis frequently seen in newborns after delivery may be related to this mechanism. Generally, newborns are more likely to demonstrate cyanosis due to their high level of hemoglobin. Cyanosis typically becomes visible centrally when the level of deoxygenated hemoglobin in capillaries reaches 3 to 5 g/dL. Because the range of normal hemoglobin at birth extends to 20 g/dL, cyanosis is more likely to be present at a given oxygen saturation in a newborn than it is in older children. Conversely, cyanosis may not occur at all in severely anemic patients.

Finally, abnormal forms of hemoglobin such as methemoglobin can result in cyanosis. These differ from the other causes because the oxygen tension (pO_2) on a blood gas is normal but the total oxygen content is reduced due to the inability of the altered hemoglobin molecules to bind oxygen. Carbon monoxide poisoning also results in impaired binding of oxygen to hemoglobin, although clinical cyanosis may not be present because carboxyhemoglobin does not discolor the blood.

FINAL DIAGNOSIS

A venous blood gas obtained at the time of intravenous line placement showed a pH of 7.31, partial pressure of carbon dioxide of 30 mm Hg, and pO_2 of 79 mm Hg. Given the discrepancy between the normal venous pO_2 and the deeply cyanotic appearance of the patient, a methemoglobin level was obtained that returned at 30% (normal range 1% to 2%). The patient's methemoglobin level declined to normal during the next 48 hours with supportive care. Because an environmental exposure was suspected, public health officials tested the water from the family's well, which revealed a nitrate level of 199 mg/L (normal being less than 50 mg/L). Methemoglobin levels were normal in the other family members.

LESSONS LEARNED

The presentation of methemoglobinemia in a young infant, although uncommon in everyday practice, has been well studied.[5] Methemoglobin results from oxidation of the hemoglobin molecule from the normal ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. Low levels of methemoglobin occur in healthy individuals, but are maintained at 1% or less by enzyme systems within the red blood cell. Infants are particularly at risk for methemoglobinemia due to lower activity of these protective enzymes and the presence of fetal hemoglobin, which is more readily oxidized than the adult form. Increased levels of methemoglobin can occur due to congenital red blood cell abnormalities or, more commonly, exposure to a high concentration of an oxidant substance. Oxidant agents most frequently implicated include topical anesthetics such as benzocaine, antibiotics such as dapsone or sulfonamides, and products containing nitrite and nitrate (eg, fertilizers) that may contaminate drinking water (Table 2).[7]

Cases of methemoglobinemia have also been described in infants with diarrhea without an exogenous toxic exposure.[8] One study prospectively measured methemoglobin in 43 infants with prolonged diarrhea and found elevated levels in 27.[9] Most of these were mild elevations, but 13 of the infants had clinical cyanosis and 5 required therapy for methemoglobinemia. The etiology of methemoglobinemia in these infants remains unclear, although it may be related to the presence of nitrite-forming bacteria, acidosis, hyperchloremia, or other factors.

Symptoms associated with methemoglobine-

TABLE 2

Exogenous Causes of Methemoglobinemia*

Analgesics
Acetophenetidin
Benzocaine
Lidocaine
Phenazopyridine
Prilocaine
Aniline dyes
Antihypertensives
Hydralazine
Nitroprusside
Antimalarials and antibacterials
Dapsone
Sulfonamides
Nitrites and nitrates
Amyl nitrite
Bismuth subnitrate
Nitric oxide
Nitroglycerin
Sodium nitrite
Well water (nitrate contamination)
Other
Chlorates
Naphthalene
Phenytoin
Primaquine

Data from Wright et al.[5] and Henretig.[6]

mia are due to the inability of the altered heme molecule to bind oxygen within red blood cells, resulting in impaired oxygen-transporting capacity. Methemoglobin also increases the affinity of remaining normal hemoglobin molecules for oxygen, resulting in decreased oxygen release within tissue capillaries. The clinical effects of methemoglobinemia are due to hypoxemia of the major organ systems: irritability or lethargy (brain), tachycardia (heart), and metabolic acidosis (muscle and other tissues). If more than 1.5 g/dL of hemoglobin has been converted to methemoglobin and is not bound to oxygen, the patient will appear cyanotic; this typically occurs at a methemoglobin level of 15%, although the level may be lower in young infants. Blood containing methemoglobin has a distinctive chocolate–brown color that may be a clue to the diagnosis.

Pulse oximetry typically reads higher than the true level of oxyhemoglobin.[10] This occurs because methemoglobin alters the absorption of red light at the two wavelengths that pulse oximetry uses to predict oxygen saturation. Arterial blood gases will show a metabolic acidosis and a normal pO_2 reflecting normal pulmonary function. A definitive diagnosis is made by co-oximetry, which assesses absorption at four wavelengths to accurately predict levels of oxyhemoglobin, methemoglobin, and carboxyhemoglobin.

The treatment of methemoglobinemia varies with the degree of symptoms and the level of methemoglobin.[5] Levels less than 20% will generally resolve spontaneously, and supportive care alone will suffice. Depending on the degree of symptoms, patients with levels greater than 20% may require treatment with methylene blue. Methylene blue acts by reducing the methemoglobin molecule to its normal state. A dose of 1 to 2 mg/kg (in a 1% solution in saline) should be given intravenously during 3 to 5 minutes. If there is no response within 30 to 60 minutes, a second dose may be given. Methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because it may cause a severe hemolytic anemia. For ill patients with poor response or contraindication to methylene blue, exchange transfusion or hyperbaric oxygen therapy may be considered.

With recognition and appropriate treatment, most infants with methemoglobinemia will have a good outcome. Methemoglobinemia due to a known exogenous cause or diarrhea will generally resolve as the inciting factor is removed. If the etiology is not clear, an investigation for an exogenous cause should be undertaken. Unraveling the "twist" in this case eventually led to the discovery of an environmental hazard that might have led to reexposure for this patient or cases in other infants.

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EDUCATIONAL OBJECTIVES

1. Review the differential diagnosis of cyanosis in infancy.
2. Discuss the pathophysiology, clinical presentation, and treatment of methemoglobinemia.

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So here we see an inverse relationship between job satisfaction and the amount of complex and inpatient patients. General pediatricians spent much less time with these more challenging medical problems and were fairly satisfied with their careers. Pediatric subspecialists were the reverse. This suggests we would rather have fewer than more of these patients. For both pediatric groups (with the exception of annual income), lifestyle seems more directly related to job satisfaction. It looks like general pediatrics is doing just fine, whereas subspecialty pediatrics is in trouble. Consistent with this is that the proportion of pediatric residents who went on to take subspecialty fellowships decreased from 33% in 1990 to 23% in 2000.[3]

LOOKING AHEAD

How can general pediatricians, who seem to be experiencing a drop in medical, especially complex medical, cases plus growing competition from other professionals for less complex medical cases, well-child care, and counseling services—and with no end to these trends in sight—be so happy, whereas subspecialists, with more challenging patients and almost certainly drifting toward a more favorable supply and demand ratio, be so dissatisfied? One possibility is that our perception that these pressures on generalists are adverse is too pessimistic and they reflect change rather than predict a bleak future. Another is that, in the short term, the generalists are happy because they are getting improvements in lifestyle, but in the longer term, subspecialty pediatric practice will have more opportunity and challenge. We are afraid the latter is the more likely scenario. Stated in another way, the general pediatricians of the future may need to redefine their roles in the care of children, lest they become victims of their own success. Next month's editorial will look at ways the general pediatrician who wants to keep more challenge in his or her practice might do so.

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**Assistant Professor*
General Pediatrics
University of Missouri–Columbia
Columbia, Missouri