Cyanosis is a blue or purple appearance of the skin or mucous membranes. This clinical finding is caused by inadequately oxygenated blood perfusing peripheral tissues or the presence of abnormal hemoglobin forms unable to bind oxygen or to supply adequate oxygen to end organs and tissues. Cyanosis is a relatively rare presenting chief complaint in the emergency department (ED) and is most commonly noted in patients with a hypoperfused state or known cardiopulmonary disease, including congenital heart disease. Although carbon monoxide poisoning and cyanide toxicity result in inadequate hemoglobin oxygenation and tissue hypoxia, these entities typically do not manifest with the clinical finding of cyanosis and are discussed in other chapters.

Pathophysiology
Cyanosis is evident on physical examination when the absolute amount of desaturated (unoxgenated) hemoglobin in the circulating capillary blood is elevated to approximately 5 g/dL.\(^1,2\) It is not a percent of desaturated total hemoglobin mass or a decreased amount of oxyhemoglobin. For this reason, patients with a relatively low hemoglobin level exhibit cyanosis at a much lower partial pressure of oxygen (Pa\(\text{O}_2\)) and arterial oxygen saturation (Sa\(\text{O}_2\)) than those with normal hemoglobin levels. Cyanosis is an insensitive indicator of tissue oxygenation.\(^3\) Its presence suggests hypoxia, but its absence does not exclude it.

Abnormal hemoglobin forms contribute significantly to cyanotic disease. Under normal conditions, red blood cells (RBCs) contain hemoglobin with iron in the reduced ferrous state (Fe\(^{2+}\)). The iron molecule may be oxidized to the ferric state (Fe\(^{3+}\)) to produce methemoglobin. This reaction impairs the ability of hemoglobin to transport oxygen to and carbon dioxide from the tissues. The oxygen dissociation curve is shifted to the left, resulting in tissue hypoxia and lactic acid production (Fig. 14-1). Methemoglobin normally accounts for less than 1% of total hemoglobin.\(^4\) Cyanosis normally accounts for less than 1% of total hemoglobin.\(^5\) Cyanosis results when greater than 10 to 25% of the total hemoglobin is methemoglobin (approximately 1.5 g/dL), which has a dark purple-brown or chocolate brown color even when exposed to room air. Methemoglobin is reduced to ferrous hemoglobin primarily by nicotinamide adenine dinucleotide (NADH) cytochrome-b\(_5\) reductase, an enzyme system present within RBCs. A secondary system dependent on nicotinamide adenine dinucleotide phosphate (NADPH)-reductase uses glutathione production and glucose-6-phosphate dehydrogenase (G6PD) to reduce methemoglobin to hemoglobin. This secondary pathway normally plays a minor role but is accelerated by methylene blue.\(^6\)

Primary methemoglobinemia is the result of a congenital error in enzyme metabolism, with either diminished levels of NADH reductase or an abnormally functioning enzyme. Patients may have cyanosis in a stable compensated state. Acquired methemoglobinemia occurs when methemoglobin production (hemoglobin oxidation) is accelerated beyond the capacity of NADH reductase activity. This usually occurs as a drug reaction. (See Box 14-1 for common causes.) Newborns are at risk for methemoglobinemia because their NADH reductase activity is relatively low.\(^5\)

Pivotal Findings
Symptoms
The onset, duration, and time of day of symptoms and any previous episodes should be noted. Precipitating factors may include exposure to cold air or water, high altitude, or exercise in patients with a history of cardiopulmonary disease. Additional history should include known congenital heart disease or cardiopulmonary disease, hypercoagulable states, and any family history of cyanotic disease or hematologic illness. A history of home or occupational exposures to fumes or chemicals should be obtained, including aniline, azo dyes (phenazopyridine [Pyridium]), phenacetin, and nitrates.\(^7\) A drug history should be reviewed, including use of prescription and over-the-counter medications, health food supplements, and herbal or alternative preparations.\(^7\) The potential of pseudocyanosis resulting from exposure to dyes, heavy metals, or topically absorbed pigments should be explored.\(^8\)

In infants, congenital heart disease is suggested by difficulty feeding, sweating, lethargy, poor weight gain, or respiratory distress. Episodic cyanotic events, or “tet spells,” may be seen in children with tetralogy of Fallot (ventricular septal defect, overriding aorta, pulmonic stenosis or atresia, and right ventricular hypertrophy with outlet obstruction). These patients have cyanosis, tachypnea, and anxiety owing to decreased pulmonary blood flow with shunting of unoxygenated blood into the peripheral circulation.\(^9,10\)

Signs
There is significant interobserver variability in detecting cyanosis on physical examination. Room lighting and temperature may affect examination of the skin and mucous membranes. A patient’s
Central cyanosis is often secondary to the shunting of venous unsaturated hemoglobin into the arterial circulation or the presence of abnormal hemoglobin. A bluish discoloration of the skin and mucous membranes is best seen on perioral skin, oral mucosa, and conjunctivae.

Peripheral cyanosis is secondary to vasoconstriction and slow flow of normally oxygenated hemoglobin in arterial blood, allowing for greater oxygen extraction by the tissues. Peripheral cyanosis affects capillary beds and typically is seen in the extremities and nail beds. Differential cyanosis may occur in either the upper or lower (or the right or the left) half of the body, with the remainder appearing well oxygenated. This form of cyanosis is usually seen in patients with cyanotic heart disease with multiple anomalies.

Vital signs should be obtained from all patients. Temperature is typically normal. Blood pressure and heart rate may vary unpredictably. Upper airway obstruction and other signs of respiratory insufficiency should be sought. Intermittent apnea in infants suggests central nervous system immaturity or a central lesion. Infants with cyanosis, increased respiratory depth, periodic apnea episodes, or diaphoresis with feeding may have congenital heart disease. Tachypnea (>60 breaths/min) in a newborn may indicate a pulmonary disorder, congenital heart disease, infection, metabolic disorder, or gastrointestinal or central nervous system pathology.

General appearance and mental status should be evaluated. The head, eyes, ears, nose, and throat examination may reveal central cyanosis. Funduscopic examination may detect dilated tortuous veins and papilledema in patients with cyanotic congenital heart disease. Jugular venous distention may be seen on the neck examination in patients with pulmonary edema.

The chest examination may reveal crackles, wheezing, or inadequate ventilation. Heart sounds should be assessed for tachycardia, abnormal rhythm, or gallops, and the presence and quality of murmurs, especially in newborns. Central pulse strength should be noted. The abdomen should be examined for the presence of hepatosplenomegaly, a pulsatile mass, or abdominal bruit.

Extremity examination includes evaluation of nail beds for peripheral cyanosis, strength and symmetry of distal pulses, and capillary refill. Evidence of chronic vascular disease, such as hair loss and temperature difference, should be noted. Clubbing of the nails may occur because of increased soft tissue and expansion of the nail beds. Clubbing may be idiopathic or hereditary but is usually the result of chronic hypoxemic states, such as cyanotic heart disease, infective endocarditis, pulmonary disease (chronic obstructive pulmonary disease, cystic fibrosis), and some gastrointestinal disorders (cirrhosis, Crohn’s disease, and regional enteritis). Thrombotic events should also be considered with findings of skin and nail bed hemorrhages or end-organ damage (eye, kidney).

**Box 14-1 Common Causes of Methemoglobinemia**

**Hereditary**
- Hemoglobin M
- NADH methemoglobin reductase deficiency (homozygote and heterozygote)
- G6PD deficiency

**Acquired**

**Medications**
- Amyl nitrite
- Antineoplastic (cyclophosphamide, ifosfamide, flutamide)
- Dapsone
- Local anesthetics (benzocaine, lidocaine, prilocaine)
- Nitroglycerin
- Nitropresside
- Phenacetin
- Phenazopyridine (Pyridium)
- Quinones (chloroquine, primaquine)
- Sulfonamides (sulfanilamide, sulfathiazole, sulfapyridine, sulfamethoxazole)

**Chemical Agents**
- Aniline dye derivatives (shoe dyes, marking inks)
- Butyl nitrite
- Chlorobenzene
- Fires (heat-induced denaturation)
- Food adulterated with nitrates
- Food high in nitrates
- Isobutyl nitrite
- Naphthalene (mothballs)
- Nitrophenol
- Nitrous gases (seen in arc welders)
- Paraquat
- Silver nitrate
- Trinitrotoluene
- Well water (nitrates)

**Pediatric**
- Reduced NADH methemoglobin reductase activity in infants (<4 mo)
- Seen in association with low birth weight, prematurity, dehydration, acidosis, diarrhea, and hyperchloremia
Box 14-2  Differential Diagnosis of Cyanosis

I. Peripheral cyanosis
   A. Low cardiac output states
      1. Shock
      2. Left ventricular failure
      3. Hypovolemia
   B. Environmental exposure (cold)
      1. Air or water
   C. Arterial occlusion
      1. Thrombosis
      2. Embolism
      3. Vasospasm (Raynaud’s phenomenon)
      4. Peripheral vascular disease
   D. Venous obstruction
   E. Redistribution of blood flow from extremities

II. Central cyanosis
   A. Decreased arterial oxygen saturation
      1. High altitude (>8000 ft)
      2. Impaired pulmonary function
         a. Hypoventilation
         b. Impaired oxygen diffusion
         c. Ventilation-perfusion mismatching
            (1) Pulmonary embolism
            (2) Acute respiratory distress syndrome
            (3) Pulmonary hypertension
      d. Respiratory compromise
         (1) Upper airway obstruction
         (2) Pneumonia
         (3) Diaphragmatic hernia
         (4) Tension pneumothorax
         (5) Polycythemia
   B. Anatomic shunts
      1. Pulmonary arteriovenous fistulae and intrapulmonary shunts
      2. Cerebral, hepatic, peripheral arteriovenous fistulae
      3. Cyanotic congenital heart disease
         a. Endocardial cushion defects
         b. Ventricular septal defects
         c. Coarctation of aorta
         d. Tetralogy of Fallot
         e. Total anomalous pulmonary venous drainage
         f. Hypoplastic left ventricle
         g. Pulmonary vein stenosis
         h. Tricuspid atresia and anomalies
         i. Premature closure of foramen ovale
         j. Dextrocardia
         k. Pulmonary stenosis of atrial septal defect
         l. Patent ductus arteriosus with reversed shunt
   C. Abnormal hemoglobin
      1. Methemoglobinemia
         a. Hereditary
         b. Acquired
      2. Sulfhemoglobinemia
      3. Mutant hemoglobin with low oxygen affinity
         (e.g., hemoglobin Kansas)

A neurologic examination should be performed focusing on mental status, symmetry of motor and sensory function, and any gross deficit.

Laboratory and Ancillary Testing

The complete blood count should be checked to assess for erythrocytosis, polycythemia, or anemia. Peripheral smear assesses RBC morphology and fragments, as well as white blood cell differential count. A D-dimer level may be obtained if pulmonary embolism (PE) is suspected. A normal D-dimer is useful in ruling out PE in patients with a low pretest probability for the disease.

Figure 14-2. Symmetrical clubbing. Equal cyanosis and clubbing of hands and feet resulting from transposition of great vessels and a ventricular septal defect without patent ductus arteriosus.

The peripheral blood classically appears chocolate brown in color. Normally a small drop of blood placed on a white sheet or filter paper will turn bright red in color when exposed to 100% oxygen. No change in color is highly suggestive of methemoglobinemia.

Interpretation of pulse oximetry is problematic in the setting of cyanosis (see Chapter 5). Assessment of distal perfusion usually determines if poor circulation is a cause of low pulse oximetry. Pulse oximetry measures light absorbance of tissue at 660 nm (red, reduced hemoglobin) and 940 nm (infrared, oxyhemoglobin). The ratio of these two readings is the basis of the pulse oximetry calculation. Methemoglobin absorbs well at both wavelengths, resulting in a saturation approximation of 85%, regardless of the actual PaO₂ and SaO₂.

Arterial blood gas testing assesses SaO₂, often sampled when the patient is breathing room air (see Fig. 14-1). CO-oximetry measurements should be specifically ordered if carbon monoxide exposure or methemoglobinemia is suspected. Sulfhemoglobin is reported as methemoglobin on CO-oximetry, so if sulfhemoglobinemia is possible, measured oxygen saturation should be specifically requested. Newer devices designed to measure methemoglobin levels noninvasively (pulse CO-oximetry) may be useful but have decreasing accuracy at lower SaO₂ levels (<95%) and higher methemoglobin levels (>14%).

Imaging

A chest radiograph should be ordered to evaluate lung fields for consolidation, infiltrates, and increased vasculature or pulmonary edema. The cardiac silhouette and mediastinum may suggest congenital heart disease. In patients thought to have PE, an elevated D-dimer level may indicate the need for lower extremity venous Doppler ultrasound, computerized tomography pulmonary angiogram, or rarely ventilation-perfusion scanning.

Electrocardiogram and Echocardiogram

An electrocardiogram should be performed on all patients with cyanosis to assess for arrhythmias and acute ischemic changes. Right-axis deviation or right ventricular hypertrophy may be seen...
with significant cardiopulmonary disease (e.g., cor pulmonale, acute pulmonary hypertension). An echocardiogram may be helpful in detecting septal defects in infants or valvular disease in infants and adults.

DIFFERENTIAL ALGORITHMS

Figures 14-3 and 14-4 outline an approach to the differential diagnosis and treatment for peripheral and central cyanosis, respectively. During the initial assessment, as the distribution of cyanosis is noted, the clinician should initiate oxygen therapy and follow steps to determine the cause of cyanosis. Clinical improvement with oxygen suggests diffusion impairment. Patients who do not respond to high-concentration oxygen are more likely to have ventilation-perfusion ratio abnormalities, such as shunting from a consolidated pulmonary lobule or congenital heart disease with right-to-left shunting. Cardiac size and silhouette on a chest radiograph may provide a clue to the presence of congenital cardiac disease. If heart size is normal, impaired pulmonary function, pulmonary embolus, or other noncardiac causes should be considered. If no improvement occurs with 100% oxygen therapy, the patient's respiratory status should be reassessed, and tension pneumothorax or upper airway obstruction considered. Pulmonary embolus should be considered and a computed tomography pulmonary angiogram performed. If a patient exhibits no respiratory distress and remains resistant to oxygen therapy, cardiac shunting or abnormal hemoglobin forms should be considered and treated accordingly. Superior vena cava (SVC) syndrome should be suspected in patients with central cyanosis with facial, neck, and upper extremity swelling with venous distention and plethora.19

Critical Diagnoses

Acute cardiovascular and respiratory compromise is considered in a patient with cyanosis and symptoms or signs of shock. The differential diagnosis for these critical presentations includes acute heart failure, acute coronary syndrome, and hypovolemic or cardiogenic shock. In addition, consider acute respiratory insufficiency or failure, massive PE, an exacerbation or decompensation in a patient with known congenital heart disease, or the first presentation of pediatric congenital heart disease.

Emergent Diagnoses

Methemoglobinemia is an infrequent cause of cyanosis but should be considered in patients without a history or physical findings suggestive of cardiovascular or pulmonary disease. Sulphhemoglobinemia is a rare cause of cyanosis most commonly occurring after exposure to hydrogen sulfide from organic sources,
Figure 14-4. An algorithmic approach to central cyanosis. ABCs, airway, breathing, circulation; ABG, arterial blood gas; AV, arteriovenous; CHF, congestive heart failure; CN, cyanide; CO, carbon monoxide; CTPA, computed tomography pulmonary angiography; CXR, chest radiograph; ECG, electrocardiogram; Echo, echocardiogram; G6PD, glucose-6-phosphate dehydrogenase; Hct, hematocrit; ICU, intensive care unit; IV, intravenous; LMWH, low-molecular-weight heparin; MetHgb, methemoglobin; O₂, molecular oxygen; PaO₂, partial pressure of arterial oxygen; PE, pulmonary embolus; prn, as needed; RA, room air; SaO₂, arterial oxygen saturation; SulHg, sulfhemoglobin; V/Q, ventilation-perfusion scan.

¹Patients with chronic cyanotic heart disease may not require ICU care or even hospital admission. Disposition should be discussed with patient’s cardiologist.

²V/Q may be performed when CTPA is unavailable or contraindicated.
medications that are sulfonamide derivatives, or gastrointestinal sources (bacterial overgrowth). Strong consideration should be given to sulfhemoglobin toxicity in patients with cyanotic findings and methemoglobin on CO-oximetry but who do not improve with methylene blue treatment.

Polycythemia is defined as an elevated RBC mass from one of three causes. Polycythemia vera is a disorder of bone marrow stem cells with increased RBC mass, cyanosis, and splenomegaly. Patients may demonstrate hyperviscosity syndrome. Secondary polycythemia occurs with either an appropriate or inappropriate increase of erythropoietin, a physiologic response to chronic hypoxemia (<92% oxygen saturation), cyanotic congenital heart disease, cigarette smoking, or high altitude exposures. Relative polycythemia is an increased RBC mass, often resulting from dehydration or reduced plasma volume.

Finally, vascular disease, such as Raynaud’s phenomenon, may cause a cyanotic appearance. Raynaud’s phenomenon occurs in 15% of the population and has a female predominance. Patients have an abnormal response to excessive cold or emotional stress and report vasoconstriction, profound cold sensitivity, and recurrent events of sharply demarcated pallor or cyanosis of the digits. Most commonly the cutaneous arterial capillary beds of the fingers and toes are affected, but tongue, ear, and other distal areas may also be affected.

EMPIRICAL MANAGEMENT

Administration of high-flow oxygen is the first therapy for patients with cyanosis. Any clinical improvement, or lack thereof, should be noted. Thereafter, consideration of abnormal hemoglobin and toxin-induced cyanosis is crucial because the administration of appropriate antidotes and systemic therapies may decrease morbidity.

Intravenous fluid resuscitation should be initiated in patients with hypovolemia. Treatment of congestive heart failure, arrhythmias, or poor cardiac output should occur as clinical conditions indicate. Cardiology consultation is recommended in patients thought to have congenital or ischemic heart disease. Although several specific treatments are discussed here, the cause of the cyanosis may be elusive, and hospitalization is required in all but chronic stable cases.

Specific Strategies

Methemoglobinemia and Sulfhemoglobinemia

If cutaneous exposure to an inciting agent (i.e., aniline dyes) occurred, complete decontamination with soap and water is recommended. The staff should use appropriate protective equipment. Urgent treatment with oxygen and methylene blue (1-2 mg/kg intravenously [IV] over 5 minutes) is indicated for patients with symptomatic hypoxia (dysrhythmias, angina, respiratory distress, seizures, or coma) or methemoglobin levels greater than 30%. Sulfhemoglobinemia is suggested when the laboratory reports an elevated methemoglobin level and the patient does not respond to methylene blue. Treatment of sulfhemoglobinemia is supportive in addition to removing the causative agent.

Other Causes of Cyanosis

Acute therapy for patients with symptomatic hyperviscosity syndrome and secondary polycythemia includes phlebotomy and volume expansion with isotonic crystalloid. The goal of therapy is a normal hematocrit (45%). Long-term therapy is focused on the underlying cause, and patients require referral to a hematologist.

Patients with SVC syndrome require further evaluation for mediastinal mass or vascular abnormality. Conservative management with oxygen and elevation of the head of the bed often provide significant symptomatic relief. Vascular stenting may be necessary, and radiation or chemotherapy may be indicated in cases caused by malignancy.

Raynaud’s phenomenon is treated by warming the affected digits and extremities. Systemic vasodilating agents (e.g., calcium channel blockers [nifedipine] or nitrates, endothelin antagonists, statins, phosphodiesterase inhibitors, and botulinum toxin) may be useful in the acute setting. If there is no improvement of peripheral cyanosis with warming and administration of 100% oxygen, arterial insufficiency or occlusion may be present. In cases of critical limb ischemia, intravenous heparin should be considered in consultation with a vascular surgeon. Embolic sources, such as endocarditis and abdominal aortic aneurysms, should be considered. Vascular bypass, intra-arterial thrombolysis, or stenting may be indicated.

Carbon monoxide and cyanide poisoning do not typically cause cyanosis and are covered elsewhere.

PATIENT DISPOSITION

Admission

All patients with a first episode of cyanosis or an uncertain cause require hospital admission. Cardiology consultation and referral are recommended for children with a first episode of congestive heart failure and newly diagnosed or suggested congenital heart disease. Surgical consultation and intervention are indicated for acute arterial occlusion from embolic or thrombotic sources. Multiple consultations may be appropriate in patients with SVC syndrome, including a vascular surgeon, interventional radiologist, oncologist, and radiation oncologist.

Discharge

Patients with peripheral cyanosis from vasospasm, those with asymptomatic methemoglobinemia less than 15%, and stable patients with primary pulmonary disease may be treated as outpatients after several hours of monitoring in the ED. Follow-up should occur within 24 hours unless the patient has a previous diagnosis of chronic cyanosis. Instructions should clearly state that if the cyanosis worsens, or if dyspnea, altered mentation, or chest pain occurs after discharge, the patient should return immediately to the ED.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.
References


