Epidemiology
Cyanosis is a blue or purple appearance of the skin or mucous membranes. This clinical finding is secondary to 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 difficulty with hemoglobin oxygenation or tissue hypoxia, these entities typically do not present 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 (unoxygenated) hemoglobin in the circulating capillary blood (>4–5 g/dL in whole blood) is elevated. 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 exhibit cyanosis at a much lower partial pressure of oxygen (PaO₂) and arterial oxygen saturation (SaO₂) than those with normal hemoglobin levels. Cyanosis is an insensitive indicator of tissue oxygenation. 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 (Fe²⁺). The iron molecule may be oxidized to the ferric state (Fe³⁺) 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. 29-1). Methemoglobin normally accounts for less than 1% of total hemoglobin. Cyanosis results when greater than 10 to 15% of the total hemoglobin is methemoglobin (≥1.5 g/dL) that has a dark purple-brown color, even when exposed to room air. Methemoglobin is reduced to ferrous hemoglobin primarily by nicotinamide adenine dinucleotide (NADH) cytochrome-b₅ reductase, an enzyme system present within RBCs. A secondary NADPH-dependant system uses glutathione-6-phosphate dehydrogenase (G6PD) to reduce methemoglobin to hemoglobin. This secondary pathway normally plays a minor role, but is accelerated by methylene blue.

Primary methemoglobinemia is a congenital error of enzyme metabolism, with either diminished levels of NADH reductase or an abnormally functioning enzyme. Patients may present with 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 29-1 for common causes.) Newborns are at risk for methemoglobinemia because their NADH reductase activity is relatively low.

Differential Considerations for patients presenting with cyanosis are listed in Box 29-2.

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 (pyridium), phenacetin, and nitrates. A drug history should be reviewed, including use of prescription and over-the-counter medications, health food supplements, and herbal or alternative preparations. The potential of pseudocyanosis resulting from exposure to dyes, heavy metals, or topically absorbed pigments should be explored.

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, pulmonary stenosis or atresia, and right ventricular hypertrophy with outlet obstruction). These patients present with cyanosis, tachypnea, and anxiety due to
Common Causes of Methemoglobinemia

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

**Acquired**

**Medications**
- Amyl nitrite
- Antineoplastics (cyclophosphamide, ifosfamide, flutamide)
- Celecoxib
- Dapsone
- Local anesthetics (benzocaine, lidocaine, prilocaine)
- Nitroglycerin
- Nitroprusside
- Phenacetin
- Phenazopyridine (pyridium)
- Quinones (chloroquine, primaquine)
- Sulfonamides (sulfanilamide, sulfathiazide, 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

NADH, reduced nicotinamide adenine dinucleotide.


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decreased pulmonary blood flow with shunting of unoxygenated blood into the peripheral circulation.6,7

**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 natural skin tone, thickness, and pigmentation also may alter findings.

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, or 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 usually is seen in cases of cyanotic heart disease with multiple anomalies.

Vital signs should be obtained on all patients. Temperature is typically normal. Blood pressure and heart rate may be high, normal, or low depending on the underlying cause. 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 epi-

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![Figure 29-1. Hemoglobin-oxygen dissociation curve. Deoxygenhemoglobin does not bind oxygen efficiently. Methemoglobin has a high affinity for oxygen molecules and does not readily release oxygen to the peripheral tissues. This shifts the normal oxygen dissociation curve to the left, resulting in hypoxia and lactic acid production. Typically, when acid is produced in the tissues, the dissociation curve shifts back to the right, facilitating oxygen release; however, the high affinity of methemoglobin prevents this normal process. (Redrawn from Benz EJ Jr: Hemoglobinoanitides, in Harrison's online:)](image)
### Differential Diagnosis of Cyanosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Peripheral cyanosis</td>
<td>Low cardiac output states, Environmental exposure (cold), Arterial occlusion</td>
</tr>
<tr>
<td></td>
<td>1. Shock, Left ventricular failure, Air or water</td>
</tr>
<tr>
<td></td>
<td>2. Hypovolemia, Thrombosis, Vasospasm</td>
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<tr>
<td></td>
<td>3. Hypoplastic lung, Peripheral vascular disease, Venous obstruction</td>
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<tr>
<td></td>
<td>Redistribution of blood flow from extremities</td>
</tr>
<tr>
<td>II. Central cyanosis</td>
<td>Decreased arterial oxygen saturation, Anatomic shunts, Cyanotic congenital heart disease, Abnormal hemoglobin</td>
</tr>
<tr>
<td></td>
<td>1. High altitude (&gt;8000 ft), Pulmonary arteriovenous fistulae and intrapulmonary shunts, Endocardial cushion defects</td>
</tr>
<tr>
<td></td>
<td>2. Impaired oxygen diffusion, Ventricular septal defects, Hypoplastic left ventricle</td>
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<tr>
<td></td>
<td>3. Pulmonary embolism, Coarctation of aorta, Pulmonary vein stenosis</td>
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<tr>
<td></td>
<td>4. Ventilation-perfusion mismatching, Tetralogy of Fallot, Total anomalous pulmonary venous drainage</td>
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<tr>
<td></td>
<td>5. Diaphragmatic hernia, Premature closure of foramen ovale, Pulmonary stenosis</td>
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<tr>
<td></td>
<td>6. Respiratory compromise, Tricuspid atresia and anomalies, Dextrocardia</td>
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<tr>
<td></td>
<td>7. Upper airway obstruction, Patent ductus arteriosus with reversed shunt, Pulmonary stenosis of atrial septal defect</td>
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<tr>
<td></td>
<td>8. Pneumonia, Premature closure of the ductus arteriosus, Patent ductus arteriosus</td>
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<tr>
<td></td>
<td>9. Tension pneumothorax, Patent ductus arteriosus</td>
</tr>
<tr>
<td></td>
<td>10. Polycythemia, Patent ductus arteriosus</td>
</tr>
</tbody>
</table>

- **Laboratory and Ancillary Testing**: The complete blood count should be checked to assess for polycythemia or anemia. Peripheral smear assesses RBC morphology and fragments, as well as white blood cell differential count. Interpretation of pulse oximetry is problematic in the setting of cyanosis (see Chapter 3). 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. 29-1). 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.

- **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 pulmonary embolism, imaging may include lower extremity venous Doppler ultrasound (if deep venous thrombosis...
symptoms are present), ventilation-perfusion scanning or computerized tomography pulmonary angiogram.

**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 29-3 and 29-4 outline the differential diagnosis and treatment for peripheral and central cyanosis, respectively. After the initial assessment is completed, and the distribution of cyanosis is noted, the clinician should begin 100% oxygen therapy and follow steps to determine the cause of cyanosis. Clinical improvement with oxygen suggests diffusion impairment. Patients who do not respond to 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 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 ventilation-perfusion scan or spiral 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.

**Critical Diagnoses**

Acute cardiovascular and respiratory compromise must be considered in a patient presenting with cyanosis and symptoms or signs of shock. The differential diagnosis for these critical presentations includes acute congestive heart failure, acute coronary syndromes, hypovolemic or cardiogenic shock, acute respiratory insufficiency or failure, massive pulmonary embolism, an exacerbation or decompensation in a patient with known congenital heart disease, or the first presentation of pediatric congenital heart disease. These patients require emergent treatment, critical therapeutic intervention, and admission to the intensive care unit.

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**Figure 29-3.** An algorithmic approach to peripheral cyanosis. ABCs, airway, breathing, circulation; ABI, ankle brachial index; IV, intravenous.
Figure 29-4. 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; PaO₂, partial pressure of arterial oxygen; PE, pulmonary embolus; prn, as needed; RA, room air; SaO₂, arterial oxygen saturation; SulHgb, sulfhemoglobin; V/Q, ventilation-perfusion scan.

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

2 Cyanide and carbon monoxide toxicity do not present with cyanosis. If either of these is present, consider coexisting diagnosis.
Emergent Diagnoses

Methemoglobinemia is an infrequent cause of cyanosis, but should be considered in patients presenting without a history or physical findings suggestive of cardiovascular or pulmonary disease.

Sulfhemoglobinemia is a rare cause of cyanosis, most commonly occurring after exposure to hydrogen sulfide from organic sources, 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 cooximetry, but who do not improve with methylene blue treatment.

Polycythemia is defined as an elevated RBC mass due to one of three causes. Polycythemia vera is a disorder of bone marrow stem cells with increased RBC mass, cyanosis, and splenomegaly. Patients may present with 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 due to dehydration or reduced plasma volumes.

Finally, vascular disease, such as Raynaud’s phenomenon, may present with 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 are sometimes also affected.13

EMPIRICAL MANAGEMENT

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

Intravenous fluid resuscitation should be initiated in patients with hypovolemia. Treatment of congestive heart failure, arrhythmia, 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 to determine it.

Specific Strategies

Methemoglobinemia and Sulfhemoglobinemia

If cutaneous exposure with an inciting agent occurred (i.e., aniline dyes), 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 IV over 5 minutes)14 is indicated for patients with symptomatic hypoxia (dysrhythmias, angina, respiratory distress, seizures, or coma) and 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% in men and 42% in women). Long-term therapy is focused on the underlying cause, and patients may require referral to a hematologist.10,15

Raynaud’s phenomena is treated with warming the affected digits and extremities. Systemic vasodilating agents (e.g., calcium channel blockers [nifedipine] or nitrates) may be useful in the acute setting.16 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 present with cyanosis and are covered elsewhere.

PATIENT DISPOSITION

Admission

All patients with a first episode of cyanosis or an uncertain cause require admission. Cardiology consultation and referral is 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.

Discharge

Patients with peripheral cyanosis from vasospasm, 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. Unless the patient has a previous diagnosis of chronic cyanosis, follow-up must be arranged within 24 hours. Instructions should clearly state that if the cyanosis worsens, or if dyspnea, altered mentation, or chest pain occur after discharge, the patient must return immediately to the ED.

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