Chapter 11 – Cyanosis

NOTE: CONTENT CONTAINED IN THIS DOCUMENT IS TAKEN FROM ROSEN'S EMERGENCY MEDICINE 9th Ed.

Italicized text is quoted directly from Rosen's.

Key Concepts:

1. *Cyanosis occurs as a result of the absolute amount of desaturated hemoglobin rather than a percentage; anemic patients exhibit cyanosis at lower PaO2 than those with normal hemoglobin levels*
2. *Central cyanosis is due to a shunting of unsaturated (enous) hemoglobin to the arterial circulation, whereas peripheral cyanosis is due to vasoconstriction or slow flow of normally oxygenated hemoglobin to the peripheral tissues*
3. *Methemoglobin has a chocolate brown color, even when exposed to room air*
4. *The pulse oximeter for patients with methemoglobinemia typically reads 85%, regardless of the PaO2 or SaO2*
5. *Congenital heart disease is a prime diagnostic consideration in all infants presenting with cyanosis*
6. *Toxic exposures, particularly to aniline dyes and local anesthetics, are considered in acute cyanosis*
7. *Sulfhemoglobin is reported as methemoglobin on CO-oximetry; patients with methemoglobinemia on CO-oximetry who do not respond to methylene blue treatment will likely have sulfhemoglobinemia*
8. *Clinical improvement of the cyanotic patient with supplemental oxygen suggests a diffusion impairment as the cause*
9. *All patients with a first episode of cyanosis or an uncertain cause require hospitalization*

Rosen's in Perspective

Alright, here is the scenario for today's podcast:

It is 0350h on what has been one of the more draining shifts of your career. You have been asked by one of your colleagues in Orthopedic Surgery to run procedural sedation for a 65-year-old female with Colle's Fracture. They have put in a hematoma block and want you to give her some silly serum to make their pull-and-crack procedure a little more simple. You go to see the patient and she is increasingly short of breath, is complaining of dull substernal chest pain, and has circumoral cyanosis. What is wrong and what are you going to do?

Answer: Take a breath (because the patient might not be, haha) and rely on the information we are giving you today.

On this episode of CRACKCast, we will investigate what superficially can appear to be a frightening topic - cyanosis. Today's podcast will allow you to dig a bit deeper into the presentation of cyanosis and may give you the capacity to better conceptualize the pathophysiological mechanisms that have made your patient blue under the tongue. Along with this, we will further dive into specific causes of cyanosis, including methemoglobinemia, sulfhemoglobinemia, polycythemia, and a whole shwack of others. We will present a differential diagnosis for the cyanotic patient and give you an intervention-based algorithm to both investigate and treat that member of the Blue Man Group.

This episode is a bit on the heavy side, so do not be afraid to pause, reflect, and re-listen to our sweet sweet voices. Additionally, make sure you read through the corresponding Rosen's chapter and using the flashcard available on the CandiEM website. Now that we are through the less complex chapters, it will be more important than ever to take the time to use the CRACKCast curriculum as something to compliment as opposed to replace your Rosen's readings. We out here trying to help you succeed - so listen to our recommendations, ya heard.

Core Questions:

1. Define cyanosis and explain what causes it?
2. What is central cyanosis and what typically causes it?
3. What is peripheral cyanosis and what typically causes it?
4. At what concentration of deoxyhemoglobin does cyanosis present?
5. List 10 differential diagnoses for cyanosis - Box 11.2?
6. Describe your initial workup for the patient with cyanosis.- Figure 11.3/11.4
7. What is the oxyhemoglobin dissociation curve and what information can be taken from it? - Figure 11.1
8. Name four factors that shift the oxyhemoglobin dissociation curve to the left and three factors that shift it to the right.
9. Differentiate between ferrous and ferric hemoglobin and describe how these forms of hemoglobin affect oxygen binding.
10. What is methemoglobinemia and how does it present?
11. What are the two biochemical pathways that are used to reduce methemoglobin?
12. List 10 causes of methemoglobinemia - See Box 11.1
13. What is sulfhemoglobinemia and when should you suspect it?
14. Differentiate between primary, secondary, and relative polycythemia and how does it cause cyanosis?

WiseCracks:

1. What is the colour of the blood in a patient with methemoglobinemia?
2. What is clubbing and what causes it?
3. What SpO2 is present on the monitor in the patient with a methemoglobinemia?
4. What is the hyperoxia test and how does it help you in your workup of the cyanotic patient?
5. What is the dose of methylene blue when prescribed to treat patients with methemoglobinemia?

Core Questions:

[1] Define cyanosis and explain what causes it?

Cyanosis is defined by Rosen's Emergency Medicine as the following:

- "...a blue or purple appearance of the skin or mucous membranes"

It is important to note that cyanosis presents because of an accumulation of deoxyhemoglobin. Cyanosis does not present as the result at some SpO2 or LACK of oxyhemoglobin.

Cyanosis is a clinical finding that is the result of the following processes:

- Inadequate oxygenated blood perfusing tissue:
    - Poor systemic perfusion
    - Regional perfusion deficits/abnormalities
    - Anatomic Shunts
    - Decreased arterial oxygen saturation
- Presence of pathologic or abnormal hemoglobin:
    - Methemoglobinemia
    - Sulfhemoglobinemia

[2] What is central cyanosis and what typically causes it?

Central cyanosis can be defined as the presence of a blue/purple hue present in the oral mucosa, lips, and conjunctivae.

Typical causes of central cyanosis:

- Presence of pathologic or abnormal hemoglobin
- Shunting of venous unsaturated hemoglobin into arterial circulation
- Decreased arterial oxygen saturation

[3] What is peripheral cyanosis and what typically causes it?

Peripheral cyanosis can be defined as the presence of a blue/purple hue present in the peripheral tissues (e.g. hands, fingers)

Typical causes of peripheral cyanosis:

- Low flow states of normally oxygenated hemoglobin in arterial blood
- Peripheral vasoconstriction

[4] At what concentration of deoxyhemoglobin does cyanosis present?

Remember, cyanosis presents because of an accumulation of deoxyhemoglobin. Cyanosis predictably presents in patients with deoxyhemoglobin of 5 g/dL. For all you non-American listeners out there, that is 50 g/L of deoxyhemoglobin to cause clinically-evident cyanosis on physical exam.

[5] List 10 differential diagnoses for cyanosis? (see Box 11.2)

The following figure has been adapted from Box 11.2 in Rosen's 9th Edition. We have added conditions of abnormal hemoglobin into this list to make it more comprehensive.

Differential Diagnosis of Cyanosis
Peripheral Cyanosis **A. Low Cardiac Output States** a. Shock b. Left Ventricular Failure c. Hypovolemia **B. Environmental Exposure** a. Air or water **C. Arterial Occlusion** a. Thrombosis b. Embolism c. Vasospasm (e.g., Raynaud's phenomenon) d. Peripheral Vascular Disease **D. Venous Obstruction** **E. Redistribution of Blood Flow From Extremities**
Central Cyanosis **A. Decreased Arterial Oxygen Saturation** a. High altitude b. Impaired oxygen diffusion c. Impaired pulmonary function i. Hypoventilation

ii. Impaired oxygen diffusion
iii. V/Q Mismatch
    1. PE
    2. ARDS
    3. PHTN
iv. Respiratory Compromise
    1. Upper airway obstruction
    2. PNA
    3. Diaphragmatic Hernia
    4. Tension PTX
    5. Polycythemia

B. Anatomic Shunts
- a. Pulmonary AVF's and intrapulmonary shunts
- b. Cerebral, hepatic, peripheral AVF's

C. Cyanotic Congestion Heart Disease
- a. Endocardial cushion defects
- b. VSD's
- c. Coarctation of the aorta
- d. Tetralogy of fallot
- e. TAPVD
- f. Hypoplastic left ventricle
- g. Pulmonary vein stenosis
- h. Tricuspid atresia and anomalies
- i. Premature closure of foramen ovale
- j. Dextrocardia

D. Disorders of Abnormal Hemoglobin
- a. Methemoglobinemia
- b. Sulfhemoglobinemia
- c. G6PD Deficiency

[6] Describe your initial workup for the patient with cyanosis. (see Figure 11.3/11.4)

Rosen's 9th Edition gives us some pretty stellar algorithms that we can fall back on when we encounter that nightmarish patient we spoke about earlier. The algorithms describe the investigation and management of peripheral and central cyanosis; we have included these below.

It is important to note that we did not include the actual images in the shownotes given copyright issues. So, go back to that textbook and peep the show.

Peripheral Cyanosis:

1. Assess ABC's, check oxygen saturation, administer supplemental oxygen
2. If the patient improves with oxygen:
    a. Consider low cardiac output states, including:
        i. Hypovolemia
        ii. Sepsis
        iii. Cardiogenic shock
    b. If one of these states is identified, treat appropriately:
        i. Hypovolemia = administer IV fluids
        ii. Sepsis = administer IV fluids, antibiotics, and find the source
3. If the patient does not improve with oxygen:
    a. Consider vascular occlusive and warm the extremity
    b. If response to warming, consider:
        i. Vasospasm from environmental exposure and refer to Rheumatology/prescribe CCB's or BB's
        ii. Peripheral vascular disease, measure ABI's and consult vascular surgery
    c. If no response to warming, consider:
        i. Arterial embolism or thrombus, measure ABI's and consult vascular surgery

Central Cyanosis:

1. Assess ABC's, check oxygen saturation, get an ABG, administer supplemental oxygen
2. If the patient improves with supplemental O2 or if the patient has a PaO2 >/100 mmHg:
    a. Get a CXR
        i. If the cardiac silhouette is normal, consider pulmonary causes like infiltrative disease (e.g, PNA), non-infiltrative disease (e.g., PE, polycythemia, AV fistula) or CHF
    b. If infiltrative disease is suspected, start antibiotics and respiratory supports
    c. If CHF, get EKG and ECHO, and treat appropriately, consult Cardiology, and admit to ICU
    d. If PE is suspected, get CT PE or V/Q scan
        i. If V/Q Scan or CT PE (+), treat with LMWH or heparin and consider admission
        ii. If V/Q Scan or CT PE (-), consider Hct:
            1. If Hct >65 - consider polycythemia, nd give IV fluids, give phlebotomy, consult hematology
            2. If Hct <65, give IV fluids and consider further evaluation
3. If the patient does not improves with supplemental O2 or if the patient has a PaO2 </100 mmHg or SaO2 </70:
    a. Get a CXR, consider co-oximetry, CO, MetHgB, and CN levels
    b. If in respiratory distress:

        i. Consider PTx, PE, upper airway obstruction, or bronchospasm and treat appropriately (e.g., decompress chest, beta agonists for bronchospasm, and intubation for airway obstruction)
    c. If not in respiratory distress:
        i. Consider methemoglobinemia, G6PD deficiency, SulfHgb, or chronic cyanotic heart disease
    d. If MetHgb >30% or >15% and symptoms of end organ dysfunction exist:
        i. Give methylene blue
            1. If no response, consider SulfHgB

[7] What is the oxyhemoglobin dissociation curve and what information can be taken from it? (See Figure 11.1)

Alrighty, folks. Time to strap on your Anesthesia cap for the next two minutes. Let's talk physiology.

The oxyhemoglobin dissociation curve is a graphic representation of the interplay between the oxygen saturation of hemoglobin and the partial pressure of oxygen at the tissue level. In essence, it gives you a better understanding of the capacity of hemoglobin to bind and shed oxygen molecules. The curve can be shifted to the left of the graph or to the right depending on several factors, representing the dynamic nature of oxygen delivery. In general terms, you can think of a shift to the left as increasing the capacity of hemoglobin to hold onto oxygen molecules. A shift in this direction will reduce oxygen delivery to peripheral tissues. A shift to the right will increase the capacity of the hemoglobin molecule to shed oxygen molecules. Shifts to the right typically do not result in tissue hypoxia.

Figure 11.1 in Rosen's 9th Edition depicts the oxyhemoglobin dissociation curve. Check it out to re-familiarize yourself with the graph.

[8] Name four factors that shift the oxyhemoglobin dissociation curve to the left and three factors that shift it to the right.

Factors that shift the oxyhemoglobin dissociation curve to the left:

- Decreased temperature
- Increased pH
- Decreased 2,3 DPG
- Increased methemoglobin
- Presence of sulfhemoglobin

Factors that shift the oxyhemoglobin dissociation curve to the right:

- Increased temperature
- Decreased pH
- Increased 2,3 DPG

[9] Differentiate between ferrous and ferric iron and describe how these forms of iron affect oxygen binding.

Ferrous iron (often written as Fe2+) is the typical form of iron contained within hemoglobin molecules in normal adult patients. This form of iron is easily reduced when exposed to oxygen, forming oxyhemoglobin and readily transporting oxygen to tissues.

Ferric iron (often written as Fe3+) is the form of iron contained within methemoglobin. Ferrous iron can be created when ferrous iron is oxidized, either spontaneously or by some physiologic stress. This form of iron is not as adept at binding with and carrying oxygen and carbon dioxide to and from tissues.

[10] What is methemoglobinemia and how does it present?

As stated above, methemoglobin is a form of hemoglobin that contains ferric iron as its central molecule. Methemoglobin normally exists in the blood, typically constituting less than 1% of total hemoglobin. Methemoglobinemia is a condition defined by levels of methemoglobin existing in the blood far above this 1% normal upper limit. When concentrations of methemoglobin reach levels higher than 1.5 g/dL (again, for our non-American listeners, this is 15 g/L).

Patients typically present with this condition in the following manner:

- Asymptomatic (most common in congenital methemoglobinemia)
- Central cyanosis
- Peripheral cyanosis
- Grey ashen lips, nailbeds, skin
- Lightheadedness
- Headache
- Shortness of breath
- Chest pain
- Headache
- Tachycardia
- Fatigue
- Lethargy
- Coma
- Shock
- Seizures
- Altered LOC

[11] What are the two biochemical pathways that are used to reduce methemoglobin?

There are two biochemical pathways that reduce methemoglobin back to hemoglobin containing ferrous iron. These are described below:

- **Nicotinamide Adenine Dinucleotide (NADH) - Cytochrome b5 Reductase**
  - Primary mechanism by which methemoglobin is converted into ferrous hemoglobin
  - This biochemical system exists in RBC's
  - Low activity in infants and those with forms of congenital methemoglobinemia

- **Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Reductase**
  - Secondary mechanism by which methemoglobin is converted into ferrous hemoglobin
  - Uses glutathione production and G6PD
  - Methylene blue acts on this pathway to treat methemoglobinemia

[12] List 10 causes of methemoglobinemia. (See Box 11)

The following figure has been adapted from Box 11.1 in Rosen's 9th Edition.

Common Causes of Methemoglobinemia	
Type of Methemoglobinemia	**Causes of Methemoglobinemia**
Hereditary	• Hemoglobin M • NADH methemoglobin reductase deficiency (homozygote and heterozygote) • G6PD Deficiency

Acquired	• Medications
	  ○ Amyl nitrate
	  ○ Antineoplastics (e.g., cyclophosphamide, ifosfamide, flutamide)
	  ○ Dapsone
	  ○ Local anesthetics
	  ○ Nitroglycerin
	  ○ Nitroprusside
	  ○ Phenacetin
	  ○ Phenazopyridine (Pyridium)
	  ○ Quinolones (e.g., chloroquine,

	primaquine) ○ Sulfonamides (e.g., sulfanilamide, sulfamethoxazole) ● Chemical Agents ○ Aniline dye derivatives (e.g., shoe dyes, marking inks) ○ Butyl nitrite ○ Chlorobenzene ○ Fire ○ Foods high in nitrates ○ Isobutyl nitrite ○ Naphthalene ○ Nitrophenol ○ Nitrous gases (seen in arc welders) ○ Paraquat ○ Silver nitrate ○ Trinitrotoluene ○ Well water (containing nitrates) ● Pediatric Cases ○ Reduced NADH Reductase in infants <4M ■ Associated with LBW ■ Prematurity ■ Dehydration ■ Aciosis ■ Diarrhea ■ Hyperchloremia

[13] What is sulfhemoglobinemia and when should you suspect it?

Sulfhemoglobinemia is a condition defined by an accumulation of sulfhemoglobin (SulfHb). Sulfhemoglobin occurs when a sulfur atom oxidizes the iron atom contained within the hemoglobin molecule. This process is permanent and cannot be reversed for the life of the erythrocyte. Unfortunately, sulfhemoglobin will be interpreted by most co-oximetry testing methods as methemoglobin, so it can cause confusion in cases of undifferentiated cyanosis.

These patients are typically exposed to sulfur-containing substances, including:

- Hydrogen sulfide gas
- Sulfonamide derivatives
- Gastrointestinal sources (seen in cases of bacterial overgrowth)

Sulfhemoglobinemia is rare, but you should always consider it in your differential in the patient with positive methemoglobin levels on co-oximetry that does not respond to methylene blue.

[14] Differentiate between primary, secondary, and relative polycythemia and how does it cause cyanosis?

Alright, before we start classifying and subdividing polycythemia, we should probably define it first. According to Rosen's 9th Edition, polycythemia is defined as "an elevated red blood cell mass." This does not equate to having an increase hematocrit or hemoglobin concentration. RBC mass is key here.

Now that we have jumped over that hurdle, let's subdivide polycythemia based on its aetiology.

Primary Polycythemia (i.e., Polycythemia Vera):

- Chronic myeloproliferative neoplasm in bone marrow
- Clonal replication of cell lineage producing red blood cells

Secondary Polycythemia:

- Occurs as a response to an appropriate or inappropriate increase in erythropoietin (EPO), normal response to chronic hypoxemia/cyanotic heart disease/cigarette smoking/high altitude exposures

Relative Polycythemia:

- Defined by an increase in red blood cell mass secondary to reduced plasma volume or dehydration

All of these forms of polycythemia can precipitate a symptomatic hyperviscosity syndrome in which flow is limited, allowing for increased oxygen removal in the periphery or thrombus formation resulting in shunting.

WiseCracks:

[1] What is the colour of the blood in a patient with methemoglobinemia?

The colour of blood in the patient with methemoglobinemia is commonly described as chocolate brown or dark purple-brown. This colour does not change, even if exposed to 100% oxygen.

[2] What is clubbing and what causes it?

Clubbing is defined as the deformation of the fingers and toes, forming enlarged and rounded distal phalangeal segments. This can be hereditary, however, clubbing is typically a sign of chronic hypoxia. The lack of oxygen causes hypertrophy of distal phalangeal tissues and capillary beds.

Conditions that have been associated with clubbing include, but are not limited to:

- Congenital heart disease
- Bacterial infectious endocarditis
- Cystic fibrosis
- Lung cancer
- Mesothelioma
- Interstitial Lung Disease
- Crohn's Disease
- Ulcerative Colitis
- COPD

It is important to note that while COPD can cause clubbing, patients with severe clubbing should be worked up for other sources of their nubby fingers (e.g., bronchogenic carcinoma). Go ahead and check out the JAMA Rational Clinical Examination article for more information, but this paper posits that COPD often only causes mild clubbing and more serious or marked deformity should prompt investigation for other more serious conditions.

Article Link: https://jamanetwork.com/journals/jama/fullarticle/1150736

[3] What SpO2 is present on the monitor in the patient with a methemoglobinemia?

The patient with methemoglobinemia will often present with an SpO2 of 85% on the monitors. This is because methemoglobin absorbs both 660 nm (red, reduced hemoglobin) and 940 nm (infrared, oxyhemoglobin) light well, resulting in this oxygen saturation.

Anecdotally, some ED providers say that it can be a number slightly higher or lower than this, but generally these patients with have sats in the mid-80's.

[4] What is the hyperoxia test and how does it help you in your workup of the cyanotic patient?

The hyperoxia test is as simple as it sounds - you through some supplemental oxygen source onto a patient with cyanosis. This helps you distinguish between two forms of cyanosis. If the patient responds to supplemental oxygen, the patient likely has a diffusion deficit causing their cyanosis. If the patient does not respond to your supplemental oxygen, the patient likely has a shunt (either caused by anatomic abnormalities and V/Q mismatching) that is preventing that blood from being oxygenated.

[5] What is the dose of methylene blue when prescribed to treat patients with methemoglobinemia?

According to Rosen's 9th Edition, the dose of methylene blue is 1-2 mg/kg IV over 5 minutes.