CYANOSIS – PART 1

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DEFINITION:

Cyanosis refers to bluish discoloration of the skin and mucous membranes as a result of increased quantity of reduced hemoglobin, or hemoglobin derivatives, in the small blood vessels of those areas. The name cyanosis literally means "the blue disease" or "the blue condition". It is derived from the color cyan, which comes from kyanós, the Greek word for "blue".

Cyanosis is commonly noted in:

1. Lips
2. Tongue
3. Oral mucus membrane
4. Nail beds
5. Malar prominences.
6. Ear lobes
7. Trunk
8. Conjunctiva
9. Circumoral

Lips are more specific for the detection of cyanosis.

Physiology of cyanosis: The normal color of flesh is thought to result from the combination of the pigments-oxyhemoglobin, deoxyhemoglobin, melanin, and carotene, and from the optical effect of scattering. Blue skin coloration would result if the quantity of reflected blue waves increased disproportionately or if the quantity of other reflected wavelengths decreased disproportionately.

However, blue skin color detected in individuals who have increased amounts of deoxyhemoglobin cannot be explained on the basis of reflection of increased quantities of high-frequency wavelengths from a "blue" pigment. Presumably, the deoxyhemoglobin is less red than oxyhemoglobin and therefore absorbs more red spectrum. By subtraction of red wavelengths, the blue spectrum is allowed to predominate in the reflected light (i.e., something that is less red is more blue).

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Cyanosis has to be distinguished from florid skin characteristic of Polycythemia Vera and a cherry-colored flush is caused by Carboxy Hb.

The degree of cyanosis is dependent on:

1. The color of the cutaneous pigment
2. The thickness of the skin
3. The state of the cutaneous capillaries.

It is the absolute, rather than the relative, quantity of reduced hemoglobin that is important in producing cyanosis. Based on Lundsgaard and Van Slyke's work [1], it is classically described as occurring if 5.0 g/dl or more of deoxyhemoglobin is present [2]. This was based on an "estimate" of capillary saturation which depends on a mean of arterial versus peripheral venous blood gas measurements [3]. Since estimation of hypoxia is usually now based either on arterial blood gas measurement or pulse oximetry, this is probably an overestimate, with evidence that levels of 2.0 g/dl of deoxyhemoglobin may reliably produce cyanosis.

Cyanosis is masked in a patient with severe anemia.

Cyanosis becomes more apparent in:

1. Polycythemia (Patients with marked Polycythemia tend to be cyanotic at higher levels of SaO2),
2. Local passive congestion
3. Presence of nonfunctional hemoglobin (methemoglobin or sulfhemoglobin)

Cyanosis can be detected reliably when the SaO2 has fallen to 85%. However, in some, particularly in dark-skinned persons, it may not be detected until it has declined to 75%.

Cyanosis may be brought about by

1. An increase in the quantity of venous blood as a result of dilation of the venules and venous ends of the capillaries
2. A reduction in the SaO2 in the capillary blood

Cyanosis can be central or peripheral. All causes of central cyanosis cause peripheral cyanosis but the vice-versa is not true. Both central and peripheral cyanosis differ in etiology and mechanism and treatment. Central cyanosis can be due to cardiac or non-cardiac causes (See

Table 1). For a details list of cardiac causes for central.
cyanosis, see Table 3

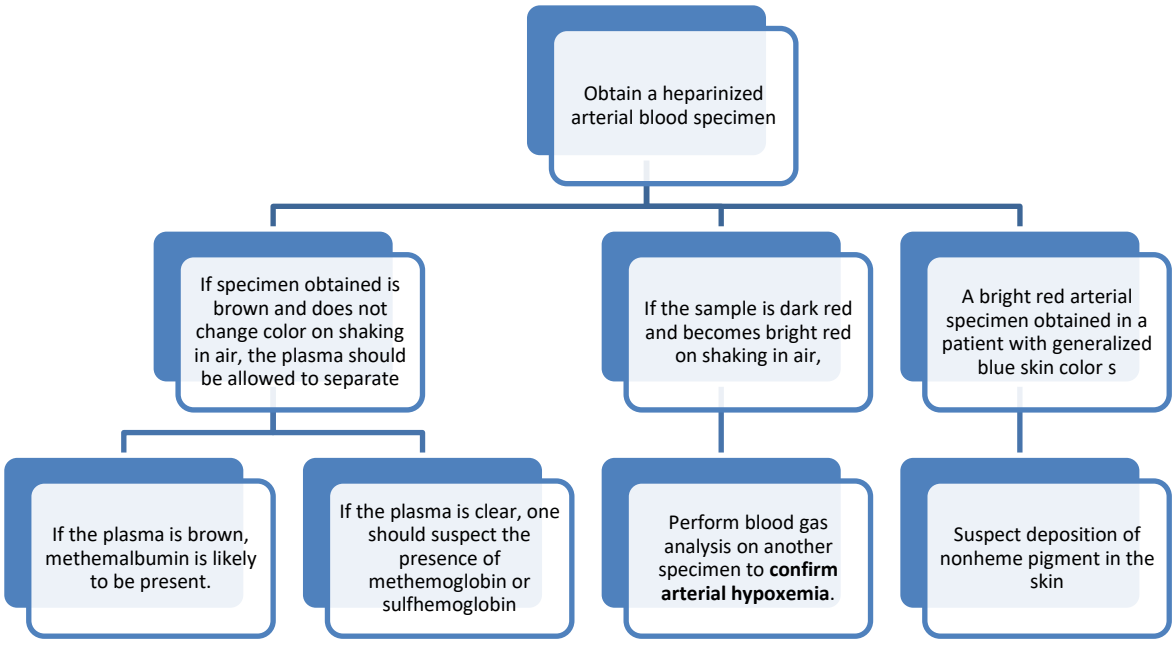
Table 1: Differences between peripheral and central cyanosis

Parameter	Peripheral cyanosis	Central cyanosis
Etiology	Slowing of blood flow and abnormally great extraction of SaO2.	Sao2 is reduced or presence of abnormal hemoglobin.
Causes	1. Reduced cardiac output -heart failure, shock. 2. Peripheral arterial disease - Thrombosis, atheroma or embolism. 3. Vasoconstriction: Cold exposure, Raynaud's phenomenon, Acrocyanosis, Erythrocyanosis and Beta-blocker drugs. 4. Venous obstruction – lower limb deep vein thrombosis (Painful blue leg -phlegmasia cerulea dolens), Superior vena cava obstruction (cyanosis, and oedema affecting the face).	1. Central nervous system involvement (impairing normal ventilation) - Intracranial hemorrhage, Drug overdose like heroin, Tonic–clonic seizure 2. Respiratory system (Impaired pulmonary function)-Pneumonia, Bronchiolitis, Bronchospasm , Pulmonary hypertension, Pulmonary embolism 3. Congenital heart diseases (E.g Tetralogy of Fallot, right to left shunts in heart or great vessels), 4. Heart failure 5. Abnormal Blood -Methemoglobinemia Polycythemia, Congenital cyanosis and 6. Others (High altitude, Hypothermia, Obstructive sleep apnea, cyanide toxicity).
Oral cavity mucus membrane	Normal	Blue discoloration
Massage or gentle warming of a cyanotic extremity	Cyanosis is abolished	Cyanosis persists
Associated with clubbing	No	Yes

Congenital cyanosis: May be due to HbM Boston which is due to a mutation in the α-codon resulting in a change of primary sequence (H → Y). Tyrosine stabilizes the Fe (III) form that is oxyhemoglobin creating a permanent T-state of Hb. HbM is inherited in an autosomal dominant pattern. It has 5 variants. Individuals in whom an alpha chain substitution has occurred are noted to be cyanotic beginning at birth. Those in whom beta chain substitution has occurred often do not become cyanotic until three to six months of age because of the normal changeover from gamma to beta chain synthesis during that time.

Low-affinity hemoglobin should be considered in patients with cyanosis and a low hematocrit when no other reason is apparent after thorough evaluation. The P50 test confirms the diagnosis. Cyanosis can be caused by small quantities of circulating methemoglobin and by even smaller quantities of sulfhemoglobin. Oxidation of deoxyhemoglobin to form methemoglobin can be caused by many drugs and toxins including nitrites, sulfonamides, and aniline derivatives. These abnormal oxyhemoglobin derivatives should be sought by spectroscopy and *digital clubbing does not occur with them.*

Approach to assessing the etiology of cyanosis: Table 2: Approach to assessing etiology of cyanosis



Drug and substance induced: Ingestion of substances containing gold or silver can produce bluish skin coloration that is most prominent in sun-exposed portions of the body. The bluish skin color associated with hemosiderin deposition is more apparent in parts of the body with less melatonin pigment. A more bronze color is seen in the presence of melanin. Polymers of the oxidation products of chlorpromazine, when deposited in the skin and other organs, can result in a blue to purple color. The antiarrhythmic agent, amiodarone, can cause lipofuscin deposition in the skin. In sun-exposed areas, a blue skin color is seen in a small percentage of patients on long-term therapy.

Cyanotic congenital heart defects: Mainly these are classified as VSD+PS physiology, Transposition physiology, Admixture physiology, Eisenmenger physiology and miscellaneous. List of the disease under this heading are mentioned in Table 3. Duct dependent pulmonary circulation like pulmonary atresia and duct dependent systemic circulation like HLHS are always produces cyanosis.

The abnormalities of position and connection of the major systemic venous channels draining to the heart are mostly rare incidental findings with not much of hemodynamic significance. In some cases it can cause cyanosis, polycythemia, paradoxical embolism and even stroke. Examples are:

1. The drainage of the SVC to LA
2. Persistent SVC with unroofed coronary sinus (Raghib syndrome)
3. Partial or complete drainage of the IVC into the LA
4. Total anomalous systemic venous drainage (TASVC) including the hepatic veins and the coronary sinus draining into the Pulmonary venous atresia also presents as TAPVC with severe pulmonary venous obstruction usually has intense cyanosis as obstructed TAPVC.

Pulmonary arteriovenous fistula (PAVF):

If right to left shunt is greater than 20 percent of systemic CO or size > 2 cm, then the patient may have obvious cyanosis. The tendency for shunting and cyanosis increases with age. In some cases of HHT (Hereditary hemorrhagic telangiectasia) even though the right to left shunt is > 20% of CO, cyanosis may be hidden by anemia or when systemic arteries rather than pulmonary arteries feed the fistulas. PAVF with cyanosis, who anticipate pregnancy need treatment.

Table 3 : Cyanotic congenital heart defects

1. VSD+PS physiology.
a. Tetralogy of Fallot (TOF).
b. D-TGA+VSD+PS
c. Doutlet right ventricle (DORV)+VSD+PS.
d. Tricuspid atresia+ VSD+PS.
e. Single ventricle +PS.
2. Transposition physiology.
a. D-transposition of great arteries (d-TGA)+VSD+PS.
b. Taussig – Bing anomaly
3. Admixture physiology.
a. Pre-tricuspid
• Total anomalous Pulmonary Venous Drainage (TAPVD)
• Hypoplastic left Heart syndrome (HLHS)
• Tricuspid atresia
• Single atrium
b. Post tricuspid
• Single ventricle
• Truncus arteriosus
4. Eisenmenger physiology – ASD, VSD, PDA
5. Near normal physiology.e.g. pulmonary arteriovenous fistula.
6. Miscellaneous
a. Ebstein's anomaly
b. PS+ASD

Table 1: Clues to diagnosis of CHD based on skeletal abnormalities

Clinical observation	Diagnosis
Bilateral prominence of the anterior chest with bulging of the upper two-thirds of the sternum is commonly present in children	Large ventricular Septal defect (VSD)
A unilateral bulge at the fourth and fifth intercostal spaces at the lower left sternal border is found in adults	VSD
Underdeveloped musculature of the lower extremities compared with the upper extremities	Coarctation of the aorta
Clubbing of the digits and cyanosis of the skin or nails	Congenital heart disease with right-to-left shunting of blood.

The time of onset of cyanosis gives a clue to aetiology of the congenital heart disease:

Table 2: Clue to CHD based on time of onset of cyanosis

Onset of cyanosis	Diagnosis
Cyanosis on day 1	d-TGA or other complex situations (see Cyanosis part-2).
Few weeks after birth	TOF (as the severity of Fallot increases, the cyanosis can appear earlier)
Characteristic biphasic pattern: cyanosis at birth, disappears as pulmonary resistance falls and reappears later as right heart failure ensues.	Ebstein's anomaly Severe valvular PS

Central cyanosis in neonates

Neonatal cyanosis is more conspicuous owing to their higher hemoglobin levels. Paradoxically, babies with higher fetal Hb level will have late visible cyanosis. In other words, infants with a high proportion of fetal hemoglobin may have a serious reduction in oxygenation before cyanosis is clinically apparent

1. Transient cyanosis after delivery: Central cyanosis should clear within a few minutes of the birth. Peripheral cyanosis clears within a few days. Increased sensitivity of the peripheral circulation to cold temperature may persist well into infancy.
2. Cardiac and circulatory causes include:
   - Transposition of the great arteries.
   - Fallot's tetralogy.
   - Stenosis or atresia of the pulmonary valve or tricuspid valve.
   - Total anomalous pulmonary venous return.
   - Atresia of the common pulmonary vein
   - Hypoplastic left heart.
   - Truncus arteriosus
   - Persistent fetal circulation Respiratory causes include:
   - Ductal dependent congenital heart diseases
   - Critical PS
3. Respiratory distress syndrome.
   - Birth asphyxia, birth injury or hemorrhage.
   - Transient tachypnea of the newborn.
   - Pneumothorax.
   - Meconium aspiration.

- Pulmonary oedema.
- Congenital diaphragmatic hernia.
- Tracheo-oesophageal fistula.
- Pleural effusion.
- Obstruction of the upper respiratory tract - for example, in Pierre Robin sequence or choanal atresia.

4. Other causes include infection, seizures and metabolic abnormalities - E.g. hypoglycemia, hypomagnesaemia.

Acknowledgements: Prof. P. Krishnum raju,
Prof. IB Vijaya Laxmi

Cyanosis –part 2 will mentioned disease specific conditions. Will be published in the next issue of this journal.

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