An approach to diagnosis and management of cyanosis and tachypnea in term infants

Ponthenkandath Sasidharan, MD

Department of Pediatrics, Division of Neonatology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA

Tachypnea and cyanosis in the newborn are frequently encountered problems in the nursery. The incidence of respiratory distress ranges from 2.9% to 7.6%, and 4.3% of newborns may require supplemental oxygen therapy [1–3]. In this article, the pathophysiology, approach to the diagnosis, and management of clinical conditions are discussed. The physiologic mechanisms involved in the pathogenesis of these problems and the clinical assessment and early stabilization of an infant before transport to a tertiary care center, if necessary, are also discussed.

Cyanosis

Cyanosis (from the Greek word meaning “dark blue”) is a blue to dusky hue in the newborn. Oxygenated hemoglobin is bright red, but the reduced hemoglobin is bluish to purple in color. This color of the reduced hemoglobin gives rise to the color seen in cyanosis. Cyanosis is sometimes difficult to detect in dark-skinned individuals. Bruising or ecchymosis may look like cyanosis and is differentiated by applying pressure over the skin, which will blanch with cyanosis but not with ecchymosis.

Cyanosis is dependent upon the absolute concentration of the reduced hemoglobin and not on the ratio of reduced hemoglobin to oxyhemoglobin. If cyanosis is present throughout the body, including the mucous membranes and tongue, it is called central cyanosis. If cyanosis is limited to the extremities, it is called peripheral cyanosis, also known as acrocyanosis.

More than three decades ago, Lees [4] reported that cyanosis would be visible if the deoxygenated hemoglobin content is greater than 3 g% (3 g per 100 mL). Because cyanosis is dependent upon the amount of deoxygenated hemoglobin level, a polycythemic infant (hemoglobin [Hb] = 25 g) who may not have respi-
ratory distress may exhibit cyanosis at 88% oxygen saturation (deoxy Hb = 3 g). In contrast, it is difficult to diagnose cyanosis in a severely anemic infant (Hb = 8 gm) unless the oxygen saturation is 63% (Fig. 1).

Capillary blood has an oxygen content that is between the venous and arterial blood oxygen contents, but in states of poor perfusion there will be large arteriovenous oxygen content difference. In such circumstances, it is possible to see

Fig. 1. The percentage arterial saturation of blood (diagonally lined portion of each column) when cyanosis will be detected at different total hemoglobin concentrations in the presence of 3 g/% of reduced hemoglobin. It is evident that central cyanosis is detectable at higher arterial saturations when the total hemoglobin concentration is high. With severe anemia, as for example 8 g of hemoglobin, central cyanosis may not be apparent until arterial saturation falls to nearly 62%. (From Lees MH. Cyanosis of the newborn infant: recognition and clinical evaluation. J Pediatr 1970;77: 484–98; with permission.)
peripheral cyanosis, because of the higher amount of deoxyhemoglobin in the capillary blood, even though the arterial blood oxygen content may be normal [5,6]. Arterial blood oxygen content will be normal in peripheral cyanosis, whereas in central cyanosis there is decreased oxygen content in the arterial blood. Peripheral cyanosis is likely to be seen with exposure to cold, polycythemia, and hypoplastic left-heart syndrome (decreased peripheral perfusion). To obviate the influence of cold temperature, infants should be examined for assessment of cyanosis while quiet in a neutral thermal environment. Although peripheral cyanosis is seen in conditions in which the infant is exposed to a cold environment, it could also be the presenting sign of serious conditions such as sepsis, hypoglycemia, or hypoplastic left-heart syndrome; hence, peripheral cyanosis should not be ignored unless other conditions have been ruled out.

Another form of cyanosis is differential cyanosis. In the common type of differential cyanosis, the upper part of the body remains pink and lower part of the body remains cyanotic. This is seen in conditions in which there is right-to-left shunt from the pulmonary artery to the descending aorta through the patent ductus arteriosus (PDA). Any condition that gives rise to right-to-left shunt through the PDA is likely to give rise to differential cyanosis, with cyanotic lower half of the body and pink upper half of the body.

In reverse differential cyanosis, the upper part of the body remains cyanotic while the lower part of the body remains pink. The conditions that give rise to this include transposition of the great vessels with pulmonary hypertension and shunt through PDA, and total anomalous pulmonary venous drainage above the diaphragm with shunt through PDA (higher oxygen content in the right ventricular blood).

Harlequin condition is a unique phenomenon in which one quadrant or one half of the body may become cyanotic or pale while the rest of the body remains pink. In this condition, the hands and feet remain warm. The exact reason for this condition is not known, but is thought to be because of vasomotor instability.

Oliver and associates have found that in serial determination of blood gases, the PO2 was 19.5 ± 12 mm Hg at 2 to 5 minutes of age, 48.7 ± 15.9 mm Hg at 6 to 10 minutes of age, 56.3 ± 12.1 mm Hg at 11 to 20 minutes of age, and 61.7 ± 13.8 mm Hg at 40 to 60 minutes of age. The calculated mean percentages of oxygen saturation were 27%, 90%, 92%, and 95% respectively [7]. Therefore, it is not unusual to see physiologic cyanosis for a few minutes after birth. During crying there may be a decrease in oxygen saturation in the infant. Prec and Cassels demonstrated that at 1.5 to 3 days of age there are variable responses to crying. Sixty-six percent of the infants had a decrease in oxygen saturation, 27% had an increase, and 6.8% had no change, whereas infants more than 4 days of age showed significant increase in oxygen saturation with crying. [8]

In theory, any of the following mechanisms can give rise to arterial oxygen desaturation:

- Hypoventilation
- Significant right-to-left intracardiac or intrapulmonary shunting
Ventilation perfusion unevenness
Diffusion impairment
Inadequate transport of oxygen by the hemoglobin.

Among these conditions, diffusion abnormality is very rare during the newborn period, and is therefore not discussed in this article.

A brief description of the physiology of oxygen transport will be helpful for further understanding the conditions that give rise to cyanosis and their management.

The physiology of oxygen transport

Oxygen is found in three states in the body: (1) as gas found in the airway of respiratory tract, (2) dissolved in the plasma, and (3) bound to the hemoglobin. The dissolved oxygen in the plasma is dependent upon the solubility coefficient of oxygen and has a value of 0.003 mL dissolved per 100 mL of plasma at a partial pressure of oxygen (PO2) of 1 mm Hg at a temperature of 38°C (ie, 0.3 mL oxygen per 100 mL plasma per 100 mm Hg PO2) [9]. The dissolved amount of oxygen in plasma is clinically insignificant compared with the amount bound to the hemoglobin. Each gram of hemoglobin can combine with 1.34 mL of oxygen at 38°C. (This value would be up to 1.39 mL of oxygen per 1 g of hemoglobin if all of the hemoglobin is available, but under physiologic conditions, some of the hemoglobin is in the form as methemoglobin, which cannot combine with oxygen [10]). The capacity of hemoglobin to carry the maximal amount of oxygen is the oxygen carrying capacity (1.34 ml/Gm Hb). The amount of oxygen actually combined with the hemoglobin is the oxygen content. The saturation of oxygen is the percentage of oxygen content to oxygen capacity. At any given oxygen saturation, the blood containing higher hemoglobin levels has higher oxygen content, and hence can carry more oxygen than blood containing a lower amount of hemoglobin. The binding of oxygen to hemoglobin is dependent on various factors. The conditions that decrease the oxygen affinity of the hemoglobin include: acidosis; increased temperature; and organic phosphates, particularly 2,3 Diphosphoglycerate (2,3 DPG). Oxygen affinity of the hemoglobin is also dependent on the type of hemoglobin, with fetal hemoglobin having a higher affinity for oxygen than adult hemoglobin. Fetal hemoglobin’s lower amount of 2–3 DPG contributes to its higher affinity to oxygen.

When the degree of oxygenation or percentage of saturation of hemoglobin with oxygen is plotted against the partial pressure of oxygen, it is referred to as oxyhemoglobin dissociation curve. The changing oxygen affinity of hemoglobin with oxygenation results in a sigmoid curve. The shape of its midportion is the midportion of the saturation (ie, 50% saturation of the hemoglobin) and its corresponding PO2 is called the P50. The adult hemoglobin has a P50 value of 27, which means that at 50% saturation the PO2 is 27 mm Hg. The P50 in the
newborn is 22; that is, at 50% oxygen saturation the PO2 is 22 mm Hg. Thus, if an infant is cyanotic, he or she may have a significantly lower PO2 value and requires immediate attention compared with an older child. Because PO2 is the driving force in oxygen exchange, a low PO2 will adversely affect the oxygen delivery to the tissues. Oxygen delivery is also dependent upon the amount of hemoglobin available to carry oxygen and the blood flow.

Hypoxia may result in a low rate of oxygen use by the tissues caused by inadequate delivery. This could be caused by low oxygen content in the blood or by poor perfusion of the tissues. Hypoxia may be present in extreme anemia caused by low oxygen content (low hemoglobin), although the PO2 may be normal. Hypoxemia is caused by low PO2, and its relationship to hypoxia is dependent on blood flow, amount of hemoglobin, and the affinity of hemoglobin to oxygen. We should be more concerned about hypoxia in the evaluation and assessment of infants. Thus, an infant could be normoxemic but could still be hypoxic because of severe anemia, poor perfusion, or conditions in which the hemoglobin is tightly bound to oxygen (increased affinity of hemoglobin to oxygen) [11,12]. Because cyanosis is dependent upon the absolute amount of deoxyhemoglobin, hypoxemia may or may not correlate with the degree of cyanosis.

The optimal PO2, or what constitutes adequate oxygenation in a newborn who has mild cyanosis or respiratory distress, is difficult to define [13]. Normally, oxygen delivery is four to five times the oxygen consumption. In the neonate, the resting oxygen consumption is around 7 mL/min/kg and the oxygen delivery (also called oxygen transport) is approximately 30 mL/min/kg [14,15]. Therefore, 20% to 25% of the oxygen delivery is used, and the rest remains in the venous blood. If the arterial blood is 100% saturated, normal venous blood will be 75% to 80% saturated. Decreased venous saturation may be caused by a decrease in the delivery of oxygen, or by an increase in O2 consumption. Delivery of oxygen may be affected by the changes in cardiac output, or by oxygen content in arterial blood [16]. The net result of an inadequate oxygen delivery to the tissues leading to hypoxia is increased production of hydrogen ions and lactic acid, giving rise to metabolic acidosis. The detection of metabolic acidosis along with cyanosis in an infant usually indicates a compromised state and requires immediate attention.

In the normal lung, the average ventilation-to-perfusion ratio is in the range of 0.8 to 1.0. The concentration of oxygen in the gas entering the alveolus, the concentration of oxygen in the mixed venous blood entering the capillaries, and the respective quantities of the gas flow and blood flow are the main variables for gas exchange at the alveolar level [9]. Although diffusion abnormalities exist in adults, they are not commonly seen in the newborn. In the normal physiologic state, the pulmonary blood flow (QP) should be equal to systemic blood flow (QS). In other words, the volume of blood entering the lungs should be equal to the volume of blood leaving the left ventricle. This is given in the equation QP = QS. The volume of blood that participates in gas exchange, however, may not be equal to the volume of blood entering the pulmonary circulation. The volume of blood that participates in actual gas exchange is called effective...
pulmonary blood flow (QeP). In an ideal circumstance, the QP should be equal to QeP; the total volume of blood that enters the lungs participates in gas exchange. This does not take place normally, however. When there is a shunt between the systemic venous return to the pulmonary veins, or the left ventricle, it is called right-to-left shunt. In this case QP (QeP) is less than QS. This gives rise to decreased oxygen content in arterial blood (Fig. 2) [17]. Conversely, with a shunt from the left ventricle or aorta to the right ventricle or pulmonary artery (left-to-right shunt), there is increase in pulmonary blood flow, and hence QP is greater than QS. In this condition, the infant will not develop cyanosis until the formation of pulmonary congestion and pulmonary edema. Intrapulmonary shunting takes place when nonventilated portions of the lungs are perfused, because the blood return from those areas does not take part in gas exchange. Intrapulmonary shunting or low ventilation to perfusion (V < Q) is seen in pulmonary edema, atelectasis, or pneumonia. During the newborn period, the total percentage of shunting from right to left is approximately 2% to 5%, but this does not give rise to hypoxia.

One condition in which the PO2 may be normal but the subject may look cyanotic is methemoglobinemia. Normal methemoglobin level is less than 1%. Methemoglobin results from the oxidation of hemoglobin molecules from the normal ferrous to ferric state. This is maintained at the low level by the enzyme systems (methemoglobin reductase) within the red blood cells; however, the

### Tissue Oxygenation and Blood Oxygen Content

1. Tissue oxygenation = systemic arterial blood oxygen content × cardiac tissue.
2. Systemic arterial blood oxygen content = \( \frac{(\text{Hb in gm/dL} \times 1.36 \text{ in ml O}_2/\text{gm per Hb} \times \text{Hb O}_2 \text{ saturation in per cent})}{\text{ (PaO}_2 \text{ in mm Hg} \times 0.003 \text{ ml O}_2/\text{dL per mm Hg})} \)

The second term, \( \text{PaO}_2 \times 0.003 \), represents oxygen dissolved in the blood, unattached to hemoglobin.

\[
\frac{V_{ao}}{[(\text{Hb} \times 1.36 \times \text{Sao}_2) - (\text{PaO}_2 \times 0.003)]} - [(\text{Hb} \times 1.36 \times \text{SmvO}_2) + (\text{PmvO}_2 \times 0.003)]
\]

\[
\frac{V_{ao}}{[(\text{Hb} \times 1.36 \times \text{SpvO}_2) - (\text{PpvO}_2 \times 0.003)]} - [(\text{Hb} \times 1.36 \times \text{SpaO}_2) + (\text{PpaO}_2 \times 0.003)]
\]

\[
\frac{V_{ao}}{[(\text{Hb} \times 1.36 \times \text{SpvO}_2) + (\text{PpvO}_2 \times 0.003)]} - [(\text{Hb} \times 1.36 \times \text{SmvO}_2) + (\text{PmvO}_2 \times 0.003)]
\]

Where:
- \( V_{ao} \) = oxygen uptake, liter/min
- \( \text{Hb} \) = hemoglobin, gm/dL
- \( \text{PmvO}_2 \) = mixed venous
- \( \text{Pa} \) = pulmonary artery
- \( 1.36 \) = ml O\(_2\)/gm Hb
- \( \text{PpvO}_2 \) = pulmonary vein
- \( 0.003 \) = ml O\(_2\)/dL per mm Hg
- \( \text{SaO}_2 \) = O\(_2\) saturation in aorta

Fig. 2. Tissue oxygenation and blood oxygen content. (From Driscoll DJ. Evaluation of the cyanotic newborn. Pediatr Clin N Am 1990;37:1–23; with permission.)
activities of these enzymes are low in infants. Fetal hemoglobin, which is more easily oxidized than the adult hemoglobin, makes infants more susceptible to methemoglobinemia [18,19]. The risk factors for methemoglobinemia are exposure to oxygen stress, topical anesthetics (prilocaine), antibiotics (sulfonamides), metoclopropamide, products that contain nitrites and nitrates, inhaled nitric oxide, presence of low levels of enzymes required for reduction of methemoglobin to hemoglobin, or the presence of abnormal hemoglobin resistant to reduction (hemoglobin-M) [20–22] This type of hemoglobin cannot be oxygenated or deoxygenated as normal hemoglobin. Mutant hemoglobins with altered oxygen affinity give rise to cyanosis without respiratory distress in the newborn [23–25]. Methemoglobinemia has also been described in infants who have diarrhea, probably from the nitrite-forming bacteria in the gut. The essential problem with methemoglobinemia is caused by the altered heme molecule, which is unable to bind oxygen within the red blood cells, and with the increased affinity of the remaining hemoglobin molecules for oxygen, resulting in decreased oxygen release to the tissues. Infants have a slate-gray cyanotic appearance with no respiratory distress. Arterial blood appears chocolate brown with a normal PO2. The severity of hypoxia is quite out of proportion to the cyanosis. The pulse oximetry may be higher than the true level of oxyhemoglobin [26,27]. The higher reading of pulse oximetry might be related to differences in the absorption characteristics of the methemoglobin of the two wave lengths that pulse oximetry employs. Generally, methemoglobin levels less than 20% resolve spontaneously [28].

During the assessment of cyanotic the newborn, it is important to identify the cause of cyanosis on a physiologic basis. It will be helpful to ask whether the cyanosis is caused by: (1) cardiac or (2) pulmonary conditions, because these are the most common causes for cyanosis in the newborn; (3) abnormality in the oxygen carrying states of the hemoglobin; or (4) miscellaneous causes. Causes for newborn cyanosis are listed in Box 1.

**Tachypnea**

Tachypnea is one of the manifestations of neonatal respiratory distress, and is defined as a respiratory rate greater than 60 breaths per minute. Tachypnea may be present with or without cyanosis in an infant; similarly, cyanosis may be present with or without respiratory distress in the newborn.

The etiology of tachypnea can be broadly classified into pulmonary and nonpulmonary causes. Pulmonary causes are listed in Box 2. The nonpulmonary causes of tachypnea may be due to cardiac, infectious, metabolic, CNS, or miscellaneous conditions. These are listed in Box 3.

Tachypnea is commonly caused by decreased lung compliance from delayed resorption of fetal lung fluid or surfactant deficiency. In conditions with decreased lung compliance, low tidal volume with increased frequency of breathing is an efficient strategy by the infant to maintain FRC (functional
Box 1. Causes for cyanosis in the full-term newborn in the nursery

**Pulmonary**

**Parenchymal**
- Transient tachypnea of newborn (TTN)
- Hyaline membrane disease (HMD)
- Aspiration—meconium, blood, mucus, or milk
- Pneumonia
- Pulmonary hemorrhage
- Pulmonary edema
- Pulmonary hypoplasia
- Pulmonary lymphangiectasia

**Nonparenchymal**
- Tracheo esophageal fistula (TEF)
- Congenital diaphragmatic hernia (CDH)
- Congenital cystic adenomatoid malformation (CCAM)
- Pulmonary sequestration
- Pneumothorax, pneumomediastinum
- Pleural effusion
- Choanal atresia
- Laryngeal web
- Lobar emphysema

**Persistent pulmonary hypertension of newborn (PPHN)**

**Cardiac**
- The five Ts (Transportation of great arteries [TGA], tetralogy of fallot [TOF], total anomalous pulmonary venous drainage [TAPVD], truncus, tricuspid atresia)
- Pulmonary stenosis/atroresia
- Ebstein’s anomaly
- L→R shunt with pulmonary edema
- Single ventricle states
- Low cardiac output states
residual capacity) with lesser increase in work of breathing [29,30]. If tachypnea is associated with grunting beyond the first 3 to 4 hours after birth, it indicates worsening respiratory distress caused by hyaline membrane disease, pneumonia, sepsis, or a serious cardiac problem. Some infants are tachypneic, but do not seem to be in any distress (happy tachypneic infants).

Tachypnea is seen frequently in cardiac conditions that give rise to left-to-right shunt with increased pulmonary blood flow (QP > QS). It is also seen when there is an obstruction to the pulmonary venous flow (TAPVD) or when there is congestive cardiac failure with pulmonary edema.

Tachypnea can be the presenting sign in sepsis and in bacterial or viral pneumonias. Exposure to an increased environmental temperature, particularly to the face, gives rise to tachypnea. It is frequently seen in infants experiencing narcotic withdrawal and painful stimuli. Metabolic acidosis caused by mild perinatal hypoxic depression (asphyxia), delayed transition and metabolic disorders giving rise to metabolic acidosis (congenital lactic acidosis, organic acidurias, and so on) give rise to tachypnea. Other metabolic causes for tachypnea include hypocalcemia and hypoglycemia. The author and colleagues have recently seen an infant who had respiratory distress that could only be attributed to significant esophagitis at birth.

Diagnosis

In the approach to the diagnosis, it is important to recognize that many infants may be cyanotic and tachypneic within the first few minutes after birth, but they
will resolve within the first 15 to 20 minutes of age. Careful assessment is required if cyanosis and tachypnea persist beyond 20 minutes of age.

Because the majority of the causes for tachypnea and cyanosis are due to cardiopulmonary problems, it is important to differentiate the etiology between cardiac and pulmonary causes for tachypnea and cyanosis [31–35]. To begin with, a detailed clinical history should be obtained, because it may yield valuable clues to the diagnosis (Table 1). There is a higher incidence of transient tachypnea, hyaline membrane disease, and hypoglycemia in large-for-gestational-age infants born to mothers who have diabetes [36–38]. It has also been reported that

**Box 2. Pulmonary causes of tachypnea**

*Mechanical (restrictive)*
- Rib cage anomalies (asphyxiating thoracic dystrophy)
- Pneumothorax
- Pneumomediastinum
- Pleural effusion
- Chylothorax
- Severe abdominal distension

*Developmental abnormality*
- TEF
- CCAM
- CDH
- Sequestration
- Pulmonary hypoplasia
- Lobar emphysema
- Lung cyst

*Airway anomalies*
- Choanal stenosis, atresia
- Laryngeal web
- Laryngotracheomalacia
- Bronchomalacia
- Subglottic stenosis

*Parenchymal*
- TTN, HMD
- HMD
- Pulmonary edema
- Delayed maturation of epithelial sodium channel (ENaC)
- Aspiration syndromes—meconium, mucus, milk, blood
- Pneumonia
- Pneumatocele
- Pulmonary hemorrhage
- Interstitial pneumonitis

*PPHN*
there is a high incidence of transient tachypnea in newborns born to mothers who have asthma [39,40].

Narcotic withdrawal is a symptom usually not present at birth, but should be manifest within the first 24 to 36 hours of age. With a history of pregnancy-induced hypertension (PIH), placental insufficiency, chronic placental abruption, and prenatal diagnosis of intrauterine growth retardation, infants may be polycytemic at birth, with the risk of developing hypoglycemia. These infants may appear cyanotic because of the polycythemia. There is a higher incidence of respiratory distress from polycythemia, caused by elevated pulmonary vascular

---

**Box 3. Nonpulmonary causes for tachypnea**

*Cardiac*
- Left-to-right shunt—↑pulmonary blood flow
- Congestive cardiac failure
- PDA
- Truncus
- Coarctation/interrupted aortic arch
- Atroventricular (AV) canal
- AV malformation with high output failure

*Neurologic*
- Postasphyxial state
- Subarachnoid hemorrhage
- Infections—meningitis

*Metabolic*
- Metabolic acidosis
- Hypoglycemia
- Hypocalcemia

*Sepsis*

*Miscellaneous*
- Hyperthermia
- Hypothermia
- Narcotic withdrawal
- Pain
- Drugs—progesterone, methylxanthines
- Esophagitis
- Post-blood transfusion state
- Feeding intolerance
- Hirschsprung’s
- Volvulus
- Mesenteric thrombosis
- Large for gestational age-infant of diabetic mother (LGA–IDM)
- Trisomy-21
resistance and delayed clearance of fetal pulmonary fluid. If there is a history of polyhydramnios, it may indicate a fetus that may not be swallowing amniotic fluid because of neurologic condition or anatomic abnormality of the gastrointestinal tract. Tracheo-esophageal fistula in the newborn is usually associated with a history of polyhydramnios in the mother. Oligohydramnios, with or without chronic leakage of amniotic fluid, leads to fetal pulmonary hypoplasia. A history of previous siblings’ health at birth should be sought. There is a higher incidence of familial respiratory distress syndrome caused by surfactant protein B deficiency. There is a higher incidence of early onset group B beta streptococcus infection in infants born to mothers whose previous infant also had early onset invasive group B streptococcal (GBS) disease. The rate of occurrence of congenital heart disease in a first-degree relative is 1% to 4%, and if there are two affected first-degree relatives, the recurrence rate of congenital heart disease is 3% to 12% [41]. The incidence of congenital heart disease in infants born to diabetic mothers is 4%, which is approximately five times the incidence in the general population [42,43].

The history of the labor and delivery may yield valuable clues to the diagnosis. Prolonged rupture of membranes (>18 hours) is associated with higher incidence of sepsis or pneumonia in newborns. If there is intrapartum maternal fever suspected to be caused by chorioamnionitis, the risk for infection in the newborn is high. Epidural anesthesia is associated with a higher incidence of fever in mother and newborn, which is not related to infection [44,45]. Fever in the

<table>
<thead>
<tr>
<th>History</th>
<th>Likely diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>TTN, RDS, hypoglycemia, LGA</td>
</tr>
<tr>
<td>Asthma</td>
<td>TTN</td>
</tr>
<tr>
<td>Drugs</td>
<td>Narcotic withdrawal</td>
</tr>
<tr>
<td>Pregnancy induced hypertension (PIH)</td>
<td>Intrauterine growth retardation (IUGR), polycythemia, hypoglycemia</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>TEF</td>
</tr>
<tr>
<td>Previous sibling with respiratory distress</td>
<td>SPB deficiency, GBS pneumonia</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>Pulmonary hypoplasia</td>
</tr>
<tr>
<td>Labor and delivery</td>
<td></td>
</tr>
<tr>
<td>Prolonged rupture of membranes (PROM)</td>
<td>Sepsis, pneumonia</td>
</tr>
<tr>
<td>Epidural Anesthesia</td>
<td>Fever</td>
</tr>
<tr>
<td>Anesthesia/Analgesia</td>
<td>Depression, apnea, cyanosis</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>Cerebral edema, metabolic acidosis</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>Sepsis</td>
</tr>
<tr>
<td>C-section without labor</td>
<td>TTN, RDS, PPHN</td>
</tr>
<tr>
<td>Breech</td>
<td>Trauma, Erb’s with phrenic nerve palsy</td>
</tr>
<tr>
<td>Newborn</td>
<td></td>
</tr>
<tr>
<td>Onset at birth</td>
<td>TTN, RDS, pneumothorax or air leak, MAS, CDH, CCAM</td>
</tr>
<tr>
<td>Onset hours after birth</td>
<td>Cyanotic congenital heart disease, aspiration, TEF</td>
</tr>
</tbody>
</table>
newborn will give rise to tachypnea. Mothers who have received narcotic analgesia or anesthesia may have a higher risk for a newborn born with respiratory depression and cyanosis. With a history of nonreassuring fetal heart-rate tracings and perinatal hypoxic depression at birth, there is a risk for hypotension, metabolic acidosis, and cerebral edema in the newborn, who may develop respiratory distress and cyanosis. Cesarean section deliveries without labor are associated with a higher risk of transient tachypnea and persistent pulmonary hypertension in newborns [46,47]. A difficult vaginal breech delivery can give rise to Erb’s palsy associated with phrenic nerve paralysis, giving rise to respiratory distress. After the infant is born, the time course of the respiratory distress and cyanosis may give some clues to the diagnosis. Infants who become symptomatic at birth may have transient tachypnea of the newborn, respiratory distress syndrome (RDS), pneumothorax, meconium aspiration syndrome, CDH, or CCAM. If an infant develops respiratory distress and cyanosis several hours after birth, it may be related to cyanotic congenital heart disease, postnatal aspiration syndromes, or tracheo-esophageal fistula. A few cases of CDH and congenital lobar emphysema may not be symptomatic for several hours to days after birth [48,49].

Physical examination

Infants should be examined in a neutral thermal environment, and if cyanosis is present, it should be determined whether it is central or peripheral (acrocyanosis). Perfusion may be assessed by capillary refill time, which is normally less than 2 seconds. It may be prolonged soon after birth, exposure of skin to cold environmental temperature, and polycythemia. Significant pallor may indicate peripheral vasoconstriction from acidosis, hypovolemia, or severe anemia from fetomaternal hemorrhage or hemolysis. Both brachial and femoral pulses should be palpated, and the quality and volume of the pulses should be noted. It is important to obtain the blood pressure on all four extremities.

Barrel-shaped chest is frequently seen in postterm infants who have meconium aspiration syndrome. The thorax may look small and narrow in infants who have (Jeune’s) asphyxiating thoracic dystrophy, who will be tachypneic and cyanotic. Respiratory rate should be recorded, along with signs of nasal flaring, retractions, and grunting. Two types of retractions may be noted in infants. If there is primarily upper airway obstruction, the retractions will be noted in the supraventricular, submandibular, and suprasternal areas, whereas the respiratory distress caused by diminished compliance of the lungs reveals intercostal and subcostal retractions. During auscultation, a few rales and rhonchi may be heard before the clearance of fetal pulmonary fluid soon after birth. It is important to note whether air entry is equal bilaterally. The breath sounds may not be very well heard, or may be heard distantly in cases of pneumothorax, atelectasis, or pleural effusion. Holding the bell of the stethoscope over the nostrils will help in identifying nasal obstruction from choanal atresia.
Normal heart rates in the full-term newborn are around 120 per minute, with a range of 100 to 140. During quiet states, it may be as low as 90. Heart rates greater than 160 during quiet state are abnormal, and in supraventricular tachycardia the rate is higher than 200. The variability of the heart rate is also important, because in severe sepsis and asphyxia, the beat-to-beat variability will be lost. The second heart sound might be loud and narrowly split in pulmonary hypertension. A single second heart sound is generally indicative of severe pulmonic stenosis or atresia, or abnormal single-valve position (transposition of the great arteries), or the presence of one large semilunar valve, as seen in truncus arteriosus. It is important to record the type and quality of murmurs. The location of apical impulse should be noted to rule out dextrocardia. Precordial thrill indicates significant murmur of grade >3/6. Precordial hyperactivity is generally caused by increased ventricular activity. It is important to remember that all heart murmurs are not pathologic, and that not all pathologic conditions have murmurs.

The abdomen may appear scaphoid in CDH. Abdominal distension caused by bowel obstruction or ascites can give rise to respiratory distress. Significant hepatosplenomegaly, as seen in cases of severe hemolytic disease of the newborn, associated with ascites and hydrops, gives rise to respiratory distress. Absence of bowel sounds indicates ileus, which may be seen in sepsis, gangrenous bowel, or peritonitis.

Hypotonia is one of the earliest signs caused by sepsis, asphyxia, or metabolic disorders in a newborn, whereas hypertonia is frequently seen in infants undergoing narcotic withdrawal. Phrenic nerve paresis or paralysis that gives rise to respiratory distress is frequently associated with Erb’s palsy after difficult vaginal delivery with traction on the neck or vaginal breech extraction.

Stridulous breathing will be seen in laryngotracheomalacia, subglottic stenosis, vocal cord paralysis, or glossoptosis with micrognathia (Pierre-Robin syndrome). Bilateral choanal atresia generally gives rise to significant retractions at birth, and the symptoms are relieved with an oral airway.

Chest radiograph

A chest radiograph is an integral part of the initial assessment of the newborn who has respiratory distress [50,51]. The locations of stomach, liver, and heart should be determined to rule out dextrocardia and situs inversus. The size and shape of the heart may yield some clues to the diagnosis. A small heart may be caused by hypovolemia, adrenal insufficiency from asphyxia or adrenal hemorrhage, significant pulmonary interstitial emphysema, or congenital lobar emphysema. The commonly described cardiac silhouette in congenital heart disease includes the following: egg-on-end appearance of transposition of the great vessels, snowman sign of total anomalous pulmonary venous return, and boot-shaped heart of tetralogy of Fallot. Severe cardiomegaly is seen in Ebstein’s anomaly, and moderate cardiomegaly is seen in infants of diabetic
mothers (hyperinsulinemia), those with cardiomyopathy (caused by infections, metabolic disorders or asphyxia), and those with congestive cardiac failure. Increased pulmonary vascular markings and pulmonary congestion are indicative of a left-to-right shunt, and decreased pulmonary vascular markings (oligemic lung fields) are generally indicative of pulmonary stenosis or pulmonary atresia with inadequate ductal shunting and occasionally persistent pulmonary hypertension of the newborn (PHN). The expansion of lungs (lung volume) on both sides should be checked. Normal inspiratory films should have eight intercostal spaces of lung fields on both sides. Diaphragmatic paralysis, more commonly seen on the right side, is manifest by elevation of the right hemidiaphragm by more than two intercostal spaces compared with the left side. This may simulate right lower-lobe atelectasis. Hyperinflated lung fields are seen occasionally in lobar emphysema or cystic lesions of lungs. The incidence of spontaneous air leaks giving rise to pneumothorax and pneumomediastinum in full-term newborns is approximately 1% to 2%. In transient tachypnea of the newborn, lung fields may appear hazy, with normal lung volume and increased parahilar markings, and frequently with fluid in the horizontal fissure. In mild hyaline membrane disease, the radiograph may not be very characteristic initially. Within a few hours, as hyaline membrane disease (HMD) gets progressively worse, the characteristic reticular granular pattern and air bronchograms will be visible. In severe cases of HMD, there will be less lung volume. In meconium aspiration syndrome, fluffy infiltrates may be visible; it may also manifest as patchy areas of atelectasis and areas of hyperinflation caused by air trapping. Pulmonary interstitial emphysema may appear as honeycomb appearance of the lung fields. Pleural effusion or chylothorax are generally visible on the lateral aspect of the lung fields as linear opacity. In large effusions, the whole area of one lobe of the lung may look opaque, with mediastinal shift to the contralateral side. In lobar atelectasis, there will be mediastinal shift toward the ipsilateral side. In pneumonic consolidation, which may simulate atelectasis, there will be no mediastinal shift. Soon after birth, a large area of opacity may sometimes be the only finding in CDH, instead of the classical finding of bowel gas in the thorax. This should be differentiated from CCAM. It is important to check the bony thoracic cage. In asphyxiating thoracic dystrophy, the thoracic cage will be small and narrow. In severely hypotonic neurologic conditions, the thorax may have a bell-shaped appearance. Fractures of the ribs, humerus, or clavicles should be looked for in difficult vaginal deliveries, because infants may develop respiratory distress from the pain and splinting of the chest.

Ultrasound examination of the diaphragmatic motion during spontaneous breathing is useful to detect paradoxical motion of the diaphragm in diaphragmatic paralysis. Ultrasound is also useful to detect pleural effusion, eventration of diaphragm, and the size and location of liver and spleen. CT scan of chest is done if diagnosis is not clear, and is helpful in detecting congenital abnormalities and tumors of the mediastinum, lungs, and heart.

Feeding-associated cyanosis may be caused by incoordination of sucking and swallowing, vocal cord paralysis, laryngeal cleft, or severe birth asphyxia. Upper
gastrointestinal (GI) contrast study should be obtained to rule out severe gastroesophageal reflux and esophagitis.

**Pulse oximetry**

It is currently the standard of care to have pulse oximetry monitoring on all infants who have respiratory distress and cyanosis. It is an accurate and reliable method of monitoring oxygen saturation noninvasively in infants [52–55]. If there is severe cyanosis with respiratory distress, both preductal and postductal oxygen saturations should be monitored to detect the gradient across the ductus arteriosus. For this purpose, the pulse oximeter probes should be placed over the right hand and a lower extremity. Pulse oximetry screening has been found to be helpful in early detection of congenital cardiovascular malformations in the newborn nursery [56].

**Hyperoxia test**

A hyperoxia test is another clinical tool to differentiate between cardiac and pulmonary etiology in infants who have cyanosis. If the infant’s pulse oximeter

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Interpretation of oxygen challenge test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$F_{1}O_2 = .21 , \text{PaO}_2$ ($%$ saturation)</td>
</tr>
<tr>
<td>Normal</td>
<td>70 (95)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>50 (85)</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>50 (85)</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>70 (95)</td>
</tr>
</tbody>
</table>

- **Cardiac disease**
  - Separate circulation<sup>a</sup> <40 (<75) <50 (<85) 35
  - Restricted PBF<sup>b</sup> <40 (<75) <50 (<85) 35
  - Complete mixing without restricted PBF<sup>c</sup> <50 (<85) <150 (<100) 35

- **Persistent pulmonary hypertension**
  - Preductal 70 (95) <40 (<75) Variable 35–50
  - Post ductal <40 (<75) Variable 35–50

- **PFO (no R to L shunt)** 70 (95) <40 (<75) Variable 35–50
- **PFO (with R to L shunt)** <40 (<75) <40 (<75) Variable 35–50

*Abbreviations:* PBF, pulmonary blood flow.

<sup>a</sup> D-transposition of the great arteries (D-TGA) with intact ventricular septum.

<sup>b</sup> Tricuspid atresia with pulmonary stenosis or atresia: pulmonary atresia or critical pulmonary stenosis with intact ventricular septum: or tetralogy of Fallot.

<sup>c</sup> Truncus, total anomalous pulmonary venous return, single ventricle, hypoplastic left heart, D-TGA with ventricular septal defect, tricuspid atresia without pulmonary stenosis or atresia.

reading is less than 85% in both room air and 100% oxygen, a hyperoxia test should be performed [57]. To do the hyperoxia test, arterial blood gases should be obtained. A transcutaneous oxygen tension monitor may also be used for this purpose. A hyperoxia test should not be performed with a pulse oximeter. It is advisable to obtain a right radial, arterial, blood-for-blood gas determination in room air and again in 100% oxygen. Wait approximately 15 minutes after the infant is placed in 100% oxygen before obtaining the blood gas. The assumption is that as the alveolar level of PO2 increases in 100% oxygen, it will give rise to an increase in pulmonary venous PO2 and subsequently arterial PO2, provided there is no significant right-to-left shunt. The degree of increase in the PO2 may be partly dependent upon ventilation. In cyanotic congenital heart disease, there will not be a significant rise, or no rise at all in PO2 with 100% oxygen breathing; however, this may not be true if there is significant increase in pulmonary blood flow caused by decrease in pulmonary vascular resistance [58]. The increase in pulmonary blood flow will cause an increase in QP:QS ratio and may result in an increase in PO2, although not as great as you would expect in an infant who has pulmonary parenchymal disease. In infants who have significant PPHN, a hyperoxia test may not be helpful to differentiate it from cyanotic congenital heart disease (Table 2).

**Laboratory tests**

Arterial blood gases help in determining the oxygenation, ventilation, and acid-base status of the infant. In methemoglobinemia, the PO2 will be normal even with cyanosis. The complete blood count (CBC) with differential count is important to rule out polycythemia, anemia, neutropenia, leukopenia, abnormal immature-to-total-neutrophil ratio, and thrombocytopenia as signs of sepsis. If sepsis is suspected, a blood culture should be obtained and a spinal tap performed before antibiotic therapy is started. If there is significant metabolic acidosis, it may indicate cardiac failure, sepsis, asphyxia, or metabolic disorders. Closure of the ductus arteriosus in an infant who has ductal-dependent cardiac lesion will lead to shock and severe metabolic acidosis, with cyanosis and respiratory distress. Calcium and magnesium levels should be obtained in babies in whom other causes are ruled out. Metabolic screening of urine and drug screening of urine and meconium screening should be performed as clinically indicated.

An EKG is an important test, but of limited value except in certain specific conditions [59,60]. Normally, there is right-ventricular predominance in the newborn, and many cases of cyanotic congenital heart disease (CHD) will have similar findings. Left axis deviation with left ventricular dominance is seen in tricuspid atresia or pulmonary atresia with intact ventricular septum. Left axis deviation, frequently associated with right ventricular hypertrophy, is seen in AV canal malformation. EKG is important in the diagnosis of arrhythmias. Echocardiogram is the gold standard in the diagnosis of congenital cardiac lesions and pulmonary hypertension, but a technician trained in performing
Management of any infant who has respiratory distress and cyanosis depends upon the diagnosis, the severity, and the time of presentation. Furthermore, management after the initial stabilization varies based on the level of care in the nursery, the expertise of the staff in the nursery, and the availability of a cardiologist and a neonatologist for consultation. Infants suspected of having cyanotic heart disease or severe respiratory distress should be transferred to a neonatal intensive care unit.

There are certain general principles that need to be observed in the management of infants who have respiratory distress and cyanosis. Infants who have respiratory distress should be NPO with intravenous fluids (10% dextrose solution during first day of life) administered at a rate of 3 to 3.5 mL/kg/h. This will provide 72 to 84 mL/kg/d. Blood glucose levels should be monitored frequently and blood glucose levels should preferably be above 50 mg/dL. Vital signs should be closely monitored with pulse oximetry and a cardiorespiratory monitor.
Infants should be observed in a neutral thermal environment under a radiant warmer or in an incubator. If perfusion seems compromised, administer 20 mL/kg of normal saline as an intravenous bolus over 15 minutes. It has been shown that term newborns who have tachypnea caused by delayed adaptation respond well to volume expansion [61]. There is significant improvement to the respiratory status in tachypneic infants when they are positioned prone with elevated head position [62]. This is likely caused by the higher FRC resulting from the reduced cephalad stress on the diaphragm from the abdomen. Infants who have respiratory distress should have an orogastric or nasogastric tube. This will rule out tracheoesophageal fistula with esophageal atresia, empty the stomach, and prevent gastric distention. Presence of more than 25 mL of fluid in the stomach soon after birth may be suggestive of gastric outlet obstruction.

Administration of oxygen can be done in several ways [63]. The most efficient way is to administer it through a nasal cannula. The disadvantage of this method is that it cannot provide 100% oxygen, because the pharyngeal concentration of

---

**Assessment of Cyanosis**

- **Abnormal**
  - Pulmonary/Cardiac Causes
  - Cardiac vs. Pulmonary Causes
  - Sepsis, Hypoglycemia, Polycythemia
  - Cardiac Causes PPHN

- **Normal**
  - Chest X-ray
  - ABG Hyperoxia Test
  - Sepsis Screen Blood Glucose
  - EKG Echocardiogram

**Fig. 4. Assessment of cyanosis in the newborn.**
oxygen is much lower than the concentration of oxygen at the cannula. The fraction of oxygen at the hypopharyngeal level is dependent on several factors, and various formulas have been published to calculate the actual concentration of oxygen inspired [64,65]. It is more efficient to monitor the pulse oximeter and adjust the flow and concentration of oxygen delivered. Another concern is the positive pressure delivered through the nasal cannula at higher flow rates. This is dependent on the size of the nasal cannula [66]. Prolonged administration of oxygen through a nasal cannula can give rise to nasal mucosal inflammation. With the use of an air/oxygen blender, the concentration of oxygen can be titrated. Most infants are given around 40% oxygen at a flow rate of 1 to 2 lpm as a starting point. It is advisable to aim for oxygen saturation of 90% to 95% (pulse oximetry). If an infant is suspected to have PPHN, higher oxygen saturation (96%–98%) should be maintained. Oxygen may also be administered through an infant oxygen hood. The disadvantage of a hood is limited access to the infant for oral suctioning. Because oxygen is administered warm and humidified, many infants become uncomfortable when their faces are exposed to the warm and humidified environment within an oxygen hood.

If a ductal-dependant congenital heart disease is suspected and echocardiogram is not available, it is advisable to start prostaglandin E-1 infusion at a rate of 0.05 mcg/kg/min, after consultation with a cardiologist or neonatologist [67]. Prostaglandin infusion may give rise to apnea, so it is important to have an intubation set up at the bedside. One condition that may become worse with prostaglandin infusion is total anomalous pulmonary venous return.

Needle aspiration of the chest followed by chest-tube insertion is done as an emergency procedure to evacuate the air in tension pneumothorax. Antibiotics therapy for sepsis is initiated with ampicillin and cefotaxime or gentamicin, and continued pending culture results. A 7- to 10-day course of antibiotics is commended for pneumonia or sepsis. Infants who have severe respiratory distress and cyanosis should be transferred to a tertiary care center. If the infant’s cry is abnormal, an ear, nose, and throat (ENT) consultation should be obtained to rule out abnormalities of the larynx and vocal cords.
Summary

Tachypnea and cyanosis are frequently seen in the newborn nursery, and a rational approach to the diagnosis, based on the physiology and pathogenesis, helps in assessment and management. Although the majority of conditions that give rise to tachypnea and cyanosis are caused by cardiopulmonary causes, there are several other conditions that may present with similar symptoms. A systematic approach to the diagnosis, starting with the history, physical examination, work-up (including chest radiograph, EKG, echocardiogram, hyperoxia test), and laboratory tests including blood glucose, calcium, CBC, and septic work-up as indicated, is required. Management is based on the clinical diagnosis and requires initial stabilization, assuring hemodynamic stability, oxygen administration, and either referral to a neonatal intensive care unit or continued care in a Level II nursery. General principles of care of an infant who has respiratory distress should be observed. Prognosis depends on the diagnosis, but is generally good with prompt recognition and intervention.

References


