Neonatal Respiratory Distress
A Practical Approach to Its Diagnosis and Management

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KEYWORDS
- Respiratory distress syndrome
- Transient tachypnea of newborn
- Meconium aspiration syndrome
- Bronchopulmonary disease
- Interstitial lung disease
- Congenital lung disorders

KEY POINTS
- Respiratory disorders are the most frequent cause of admission to the special care nursery both in term and preterm infants.
- In critically ill infants or when the diagnosis is unclear, a neonatologist, cardiologist, pulmonologist, or ear, nose, and throat (ENT) surgeon must be promptly consulted.
- The need for referral to a tertiary perinatal-neonatal center for fetal intervention or early neonatal intervention, such as congenital diaphragmatic hernia, other congenital malformations, or delivery of very low-birth-weight (BW) infants is of paramount importance.

Respiratory disorders are the most frequent cause of admission to the special care nursery both in term and preterm infants. Pediatricians and primary care providers may encounter newborn infants with respiratory distress in their office, emergency room, delivery room, or during physical assessment in the newborn nursery. Often these infants may be in distress because of the failure of transition from fetal to extraterine environment due to retained lung fluid commonly seen in neonates born by cesarean delivery, being immature with relative surfactant deficiency, or having meconium aspiration syndrome (MAS).1–4 In some instances, the cause of respiratory distress may pose a diagnostic challenge, especially in differentiating from cardiac diseases.5 Significant advances have been made in fetal diagnosis, pathophysiology,
and early management of these diseases. Therefore, referral to a tertiary perinatal-neonatal center for fetal intervention or early neonatal intervention for congenital diaphragmatic hernia, other congenital malformations, or delivery of a very low-BW infant is of paramount importance.

In this article, the authors have proposed a practical approach to diagnose and manage such infants with suggestions for consulting a neonatologist at a regional center (Box 1). For an in-depth review, the reader is encouraged to preview a text on the subject. The authors’ objective is that practicing pediatricians should be able to assess and stabilize a newborn infant with respiratory distress, and transfer to or consult a neonatologist, cardiologist, or pulmonologist after reading this article.

**PHYSIOLOGIC CHANGES AT BIRTH**

Before birth, the lung is fluid filled, receiving less than 10% to 15% of the total cardiac output, and fetal oxygenation occurs by the placenta. The transition from intrauterine to extraterine life requires establishment of effective pulmonary gas exchange. This complex process entails rapid removal of fetal lung fluid controlled by ion transport across the airway and pulmonary epithelium with varying roles of catecholamines, glucocorticosteroids, and oxygen-regulating sodium uptake in alveolar fluid clearance. During fetal life, the high pulmonary vascular resistance directs most of the blood from the right side of the heart through the ductus arteriosus into the aorta. At birth, clamping the umbilical vessels removes the low-resistance placental circuit with increase in systemic blood pressure and relaxation of the pulmonary vasculature. Adequate expansion of the lungs and increase in $\text{PaO}_2$ values results in an 8- to 10-fold increase in pulmonary blood flow and constriction of the ductus arteriosus. The cardiopulmonary transition takes approximately 6 hours, resulting in rise in $\text{PaO}_2$ values and decrease in $\text{PCO}_2$ values as the intrapulmonary shunt decreases, and the functional residual capacity (FRC) after crying establishes adequate lung volume. Initially the respiratory pattern may be irregular but soon becomes rhythmic modulated by chemoreceptors and stretch receptors, with rates of 40 to 60 breaths per minute. Respiratory distress is common in preterm infants because of poor respiratory drive, weak muscles, compliant chest wall, and surfactant deficiency.

**Clinical presentation** involves tachypnea (rate>60 breaths per minute), cyanosis, expiratory grunting with chest retractions, and nasal flaring. The underlying disease may be due to pulmonary, cardiac, infectious, metabolic, or other systemic disorders. Peripheral cyanosis or acrocyanosis is often observed in normal newborn infants or in ill infants with poor cardiac output. Central cyanosis is assessed by examining the oral mucosa and suggests inadequate gas exchange signifying more than 3 to 5 g/dL of desaturated hemoglobin. Clinical determination of central cyanosis may be unreliable.

**Box 1**

When to call a neonatologist for respiratory distress in an infant

- Inability to stabilize or ventilate infant, or requiring vasopressors
- Suspect cardiac disease
- Meconium aspiration with and without pulmonary hypertension
- Sepsis with pneumonia
- Pulmonary hemorrhage
- Pneumothorax or pneumomediastinum
(ie, not observed) in severely anemic patients despite low PaO2 values; in contrast, polycythemic infants may appear cyanotic despite normal values of PaO2. Hence, oxygen saturation measured by pulse oximetry (arterial oxygen saturation [Sao2]) is recommended by the American Academy of Pediatrics to screen infants for hypoxemia, and Sao2 values less than 90% after 15 minutes of age are considered abnormal.11 Decrease in O2 saturation, apnea, or both may be present in infants with respiratory distress.5,11–13 Irregular (seesaw) or slow respiratory rates of less than 30 breaths per minute if associated with gasping may be an ominous sign.

Chest retractions occur because the neonatal chest wall is compliant making it susceptible to alterations in lung function resulting in substernal, subcostal, or intercostal retractions. The retractions result from negative intrapleural pressure generated by the contraction of diaphragm and accessory chest wall muscles along with impaired mechanical properties of the lungs and chest wall. Retractions are observed in lung parenchymal diseases such as respiratory distress syndrome (RDS), pneumonia, airway disorders, pneumothorax, atelectasis, or bronchopulmonary dysplasia (BPD).

Nasal flaring is caused by contraction of alae nasi muscles decreasing the resistance in the nares with resultant reduced work of breathing. Neonates primarily breathe through the nose, hence nasal resistance contributes significantly to total lung resistance, which occurs in choanal atresia or obstruction due to secretions. During resuscitation, suction of mouth is followed by suctioning the nose to prevent aspiration of secretions, blood, or meconium. Occasionally, nasal flaring is observed during feeding or active sleep in normal infants.

Grunting is a compensatory effort made during expiration by closure of the glottis, increasing the airway pressure and lung volume with resultant increased ventilation perfusion (V/Q) ratio. Unlike normal breathing, wherein the vocal cords abduct to enhance inspiratory flow, expiration through partially closed vocal cords in some respiratory disorders produces a grunting sound. Depending on the severity of lung disease, grunting may be either intermittent or continuous. Grunting can maintain FRC and values of PaO2 equivalent to those during the application of 2 or 3 cm H2O of continuous distending pressure.

Accessory respiratory muscles also assist in optimizing upper airway functions. The genioglossus muscle protrudes the tongue and maintains pharyngeal patency, whereas the laryngeal muscles move the vocal cords regulating airflow during expiration.

Assessing a Neonate with Respiratory Distress

It is not surprising that incomplete cardiopulmonary transition results in respiratory distress with approximately 10% of neonates requiring respiratory support immediately after delivery and up to 1% requiring intensive resuscitation.11 Therefore, the American Heart Association and the American Academy of Pediatrics recommend that the personnel attending to the newborn in the delivery room should be Neonatal Resuscitation Program (NRP) certified.11 The cause of respiratory distress can be either pulmonary or nonpulmonary in origin.

The initial approach in assessing an infant with respiratory distress involves physical examination and rapid assessment to identify any life-threatening conditions such as tension pneumothorax, chylothorax, congenital diaphragmatic hernia, or upper airway anomalies. Infants with significant respiratory distress and hypoxia should be initially stabilized. When attending a high-risk delivery, antenatal history of oligohydramnios suggests hypoplastic lungs, whereas polyhydramnios may be present in infants with tracheoesophageal fistula (TEF). Infants of diabetic mothers are at risk for RDS, transient tachypnea of newborn (TTN), or cardiac anomalies causing respiratory distress; fetus in distress with meconium-stained amniotic fluid are at risk for developing
meconium aspiration pneumonia, pneumothorax, and persistent pulmonary hypertension (Box 2). History of chorioamnionitis may give a clue to the infant developing pneumonia or sepsis. Repeating physical examinations after initial stabilization for temperature instability with worsening clinical status suggests infection; tachycardia may indicate sepsis or hypovolemia. Stridor is often associated with upper airway obstruction. A scaphoid abdomen with bowel sounds auscultated in the left side of chest indicates congenital diaphragmatic hernia. Asymmetric breath sounds suggest tension pneumothorax or inadvertent placement of endotracheal tube in the main stem bronchus.

DIFFERENTIAL DIAGNOSIS

Breathing occurs because of movement of air in and out of the lungs. Impairment of airflow because of disease states leads to respiratory distress (Box 3). However, it is important to remember that parenchymal lung disease may also lead to obstruction as seen in pneumonia, where the obstruction of airways can be due to increased secretions requiring suctioning. The signs and symptoms of airway obstruction in the neonates are characteristic of the site. Irrespective of the cause of the obstruction, respiratory distress results in hypoventilation with an increase in the PCO₂ value and a decrease in the PO₂ value. Differentiation from congenital cyanotic heart disease can be challenging. By placing the infant on fraction of inspired oxygen (FiO₂) equal to 1.0 (hyperoxia test), in lung diseases the PaO₂ value usually increases over 150 torr, whereas in cyanotic congenital heart disease, it is below 120 torr. If the patient has ductal-dependent cyanotic heart disease, intravenous prostaglandin may have to be administered to keep the ductus arteriosus patent and the patient has to be transferred to a tertiary center (preferably where a cardiac surgery can be performed) to confirm the diagnosis by echocardiogram and manage the cardiac diseases.

UPPER AIRWAY ANOMALIES

Some neonates diagnosed with choanal atresia may require consultation from a geneticist to rule out anomalies, such as CHARGE (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital abnormality and Ear

<table>
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<th>Box 2</th>
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<td>Maternal history giving a clue to neonatal respiratory distress</td>
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<td>Diabetes mellitus: RDS, cardiomyopathy, CHD, hypoglycemia, polycythemia</td>
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<td>Polyhydramnios: tracheoesophageal fistula</td>
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<td>Oligohydramnios: hypoplastic lungs</td>
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<td>Drug withdrawal</td>
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<td>Anesthesia causing neonatal depression</td>
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<td>Antepartum hemorrhage: anemia</td>
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<td>Meconium-stained amniotic fluid: aspiration syndrome</td>
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<tr>
<td>Hydrops fetalis: pleural effusion</td>
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<td>Premature labor: RDS</td>
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<tr>
<td>PROM and chorioamnionitis: pneumonia, sepsis</td>
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Abbreviations: CHD, congenital heart disease; PROM, prolonged rupture of membranes.
abnormality) association. Regardless of the cause of obstruction, establishing a secure airway is paramount. In the absence of underlying lung disease or laryngotra-
cheal abnormalities, placement of an oral airway may be sufficient, along with supple-
mental oxygen. Alternatively, oral endotracheal intubation with ventilator support may
be required. In any infant with airway obstruction, failure to maintain adequate ventila-
tion and/or oxygenation with an endotracheal tube in place may signify progressive
pulmonary disease, hence neonatology consultation should be obtained (see
Box 1). Although the larynx is the most common site of stridor, neonates with supra-
glottic or glottis laryngeal abnormalities often present with a combination of problems
involving respiration, phonation, and/or deglutition. The clinical presentation of the ab-
normalities is variable and includes stridor, abnormal cry, snorting during sleep, retrac-
tions and coarse inspiration. These symptoms could be due to laryngomalacia, cysts,
hemangioma, stenosis, stricture due to prolonged intubation in premature infants, or
laryngeal web. In severe cases, suprasternal and intercostal retractions may be
seen. Aspiration may occur, and feeding may be difficult in patients with a mass lesion
or severe obstruction. Laryngomalacia is the most frequent cause of stridor and often
worsens in the supine position, with feeding, or due to agitation. Rarely, laryngospasm
may occur secondary to gastroesophageal reflux disease (GERD), sometimes leading
to apnea, bradycardia, or desaturation, and it should be considered when the cause of
obstruction is obscure.3,14 In addition, GERD has been identified frequently in patients
with apnea, chronic cough, laryngomalacia, recurrent croup, and subglottic stenosis,
although 1 study did not find a temporal relationship between gastroesophageal reflux
and apnea of prematurity.14 Examination of the oropharynx may reveal macroglossia,
glossoptosis, retrognathia, cleft palate (Pierre Robin anomaly), or cyst. Flexible endos-
copy may be required to diagnose lingual thyroid, dermoid, hemangiomas, or lym-
phangioma. Computed tomography (CT) or magnetic resonance imaging has been

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**Box 3**

**Differential diagnosis of respiratory distress in the newborn**

- Upper airway obstruction: choanal atresia, nasal stenosis, nasal stuffiness (? congenital
syphilis), Pierre Robin anomaly, cleft palate, glossoptosis, laryngeal stenosis or atresia,
hemangioma, vocal cord paralysis, vascular rings, tracheobronchial stenosis, cystic hygroma.

- Pulmonary diseases
  
  a. Congenital: hypoplasia, congenital diaphragmatic hernia, chylothorax, pulmonary
  sequestration, congenital cystic adenomatous malformation of lung, arteriovenous
  malformation, congenital lobar emphysema, congenital alveolar proteinosis.
  
  b. Acquired: TTN, RDS, aspiration pneumonia, other pneumonia (bacterial, viral, fungal,
syphilis), air leak syndrome (pneumothorax, pneumomediastinum), atelectasis,
hemorrhage, BPD, PPHN, diaphragmatic paralysis.

- Chest wall deformities: asphyxiating thoracic dystrophy.

- Cardiac diseases: cyanotic and acyanotic heart diseases, congestive heart failure,
cardiomyopathies, pneumopericardium.

- Metabolic: hypoglycemia, inborn errors of metabolism.

- Hematologic: polycythemia, severe anemia, hypovolemia.

- Neuromuscular diseases: hypoxic-ischemic encephalopathy, hemorrhage, hydrocephalus,
seizure, narcotic withdrawal, muscle and spinal cord disorders.

- Miscellaneous: apoxxia, acidosis, hypothermia or hyperthermia.

*Abbreviation*: PPHN, persistent pulmonary hypertension of the newborn.
used to confirm the diagnosis of complex upper airway anomalies in some patients. If no obvious anatomic abnormality can be identified by examination, video fluoroscopy may be used to diagnose glossoptosis, pharyngeal wall collapse, or laryngomalacia. All infants should have cardiorespiratory monitoring including pulse oxymetry. Tracheobronchial abnormalities causing respiratory distress in the neonates include tracheal rings, tracheomalacia, tracheal stenosis, hemangioma, and tracheo-esophageal fistula. The clinical presentation of these abnormalities may be expiratory stridor, wheezing, or brassy cough. Anterolateral radiograph of the chest and barium esophagogram may be used for diagnosis in addition to endoscopy. Endotracheal intubation with assisted ventilation is used in severe cases to stabilize them. A pediatric ENT surgeon should be consulted if upper airway disease is suspected, and the parents should be informed that severe cases may require tracheostomy.

**Transient Tachypnea of Neonate**

This condition occurs in near-term, term, or late preterm infants, affecting 3.6 to 5.7 per 1000 term infants and up to 10 per 1000 preterm infants. Risk factors include cesarean delivery, and it may occur in mothers with diabetes, asthma, prolonged labor, and fetal distress requiring anesthesia or analgesia. Clinical presentation is rapid shallow breathing with occasional grunting and rarely respiratory failure. Arterial blood gases show varying degrees of hypoxemia with normocarbia or hypercarbia. The chest radiograph shows perihilar streaking, patchy infiltrates, increased interstitial markings, and fluid in interlobar fissures (Fig. 1). It can be difficult to differentiate TTN from neonatal pneumonia or meconium aspiration in the presence of risk factors for these disorders. There may be a wet silhouette around the heart as well as signs of alveolar edema. Treatment of TTN is supportive. However, a definitive diagnosis of TTN is usually made on retrospection once the symptoms resolve within 1 to 5 days after minimal therapeutic intervention. Hence, it takes time to differentiate TTN from other causes of neonatal respiratory distress. Until then, the overall management of the neonates with respiratory distress should cover all the diagnostic possibilities. The disorder usually responds to oxygen therapy, but maintaining appropriate oxygen saturation may require continuous positive airway pressure (CPAP), which increases the distending pressure of the alveoli and aids the absorption of the extra lung fluid. Very rarely is mechanical ventilation necessary.

![Fig. 1. Radiograph of chest showing transient tachypnea of newborn; note patchy densities and fluid in the horizontal fissure (arrow).](image)
Although TTN is a common pathologic diagnosis designated to the neonates presenting with respiratory distress due to delayed clearance of fetal lung fluid, these neonates almost invariably show complete recovery with no long-term sequelae.\textsuperscript{15} Differential diagnosis includes pneumonia and cerebral hyperventilation in patients with perinatal asphyxia. The neonates are tachypneic without changes in chest radiograph apart from mild cardiomegaly related to asphyxia.

**Pneumonia**

Pneumonia is a significant cause of respiratory distress in newborns and may be classified as either early-onset (\(\leq 7\) days of age) or late-onset pneumonia (\(>7\) days of age). The routes of acquiring infection and the pathogens commonly associated with them are listed in Table 1.

Congenital pneumonia is a severe disease that frequently results in either stillbirth or death within the first 24 hours after birth. Signs typically present in the first several hours after birth unless the pneumonia is acquired postnatally.\textsuperscript{1,9} Pneumonias that are acquired later present most often as systemic disease.\textsuperscript{9} The clinical signs in neonatal pneumonia mimic other conditions like TTN, RDS, or MAS, thus making it difficult to distinguish from them. Nonrespiratory signs and symptoms may include lethargy, poor feeding, jaundice, apnea, and temperature instability. If pneumonia is suspected, initial screening tests, including complete blood cell with differential count and blood culture, should be obtained before beginning antibiotic therapy. Ampicillin and gentamicin, or amikacin, are the antibiotics used most frequently in the neonatal period for treating infection. Findings from chest radiograph are variable, depending on the cause.\textsuperscript{17} In utero infection typically manifests as bilateral consolidation or whiteout. Other pneumonias can manifest as lobar consolidations on chest radiograph (Fig. 2). It should be borne in mind that 50% of infants who have group B beta Streptococcus pneumonia have radiographic findings indistinguishable from those of RDS or TTN.\textsuperscript{17} When present, pleural effusion or mild heart enlargement in the absence of cardiac anomalies suggests the diagnosis of pneumonia. Treatment of pneumonia focuses on supportive care of the infant and administration of antibiotic medications that target the causative organism. Oxygen therapy, mechanical ventilation, and vasopressor administration may be necessary. Oxygen should be used to maintain saturations in the normal ranges for gestational age.

<table>
<thead>
<tr>
<th>Intrauterine</th>
<th>Perinatal</th>
<th>Postnatal</th>
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<tbody>
<tr>
<td>Rubella</td>
<td>Group B streptococcus</td>
<td>Respiratory viruses (adenovirus, respiratory syncytial virus)</td>
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<tr>
<td>Herpes simplex virus</td>
<td><em>Escherichia coli</em></td>
<td>Gram-positive bacteria (Groups A, B, and G streptococci or <em>Staphylococcus aureus</em>)</td>
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<tr>
<td>Adenovirus</td>
<td><em>Syphilis</em></td>
<td></td>
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<tr>
<td>Mumps</td>
<td><em>Neisseria gonorrhoeae</em></td>
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<tr>
<td><em>Toxoplasma gondii</em></td>
<td><em>Chlamydia trachomatis</em> (usually occurs for &gt;2 wk)</td>
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<tr>
<td>Varicella zoster virus</td>
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<tr>
<td><em>Treponema pallidum</em></td>
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<tr>
<td><em>Mycobacterium tuberculosis</em></td>
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<tr>
<td><em>Listeria monocytogenes</em></td>
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<td>Human immunodeficiency virus</td>
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**Table 1**

Modes of transmission and the pathogens causing neonatal pneumonia
Respiratory Distress Syndrome

RDS is seen soon after birth and worsens over the next few hours. RDS is commonly seen in premature infants and occurs because of surfactant deficiency. The risk of RDS increases with decreasing gestational age with approximately 5% of near-term infants affected, 30% of infants of gestational age less than 30 weeks affected, and 60% of premature infants of gestational age less than 28 weeks affected. Surfactant is a complex mixture of 6 phospholipids and 4 apoproteins produced by the type II pneumocytes in the lung epithelium. Functionally, dipalmitoyl phosphocholine or lecithin is the principal phospholipid, which along with surfactant protein A and B lowers the surface tension at the air-liquid interface in vivo. With decrease in surfactant or its function, alveolar surface tension increases and collapses at the end of expiration. The disease progresses rapidly with increase in work of breathing, intrapulmonary shunting, V/Q mismatch, and hypoxia with eventual respiratory failure. Factors contributing to RDS are male sex in Caucasians, infants of mothers with diabetes, perinatal asphyxia, hypothermia and multiple gestations, born via cesarean delivery without labor, or presence of RDS in a previous sibling.

On physical examination, infants have grunting, retraction, cyanosis, and tachypnea. Radiograph of the chest shows reticulogranular appearance, air bronchogram, or ground glass appearance of the lungs because of microatelectasis and poor expansion (Fig. 3). Arterial blood gases show respiratory acidosis, hypoxia, and eventually metabolic acidosis. Mothers with extremely premature infants should be managed at a perinatal center if not in labor. Amniocentesis should be performed to assess lung maturity for elective cesarean delivery and in mothers with diabetes. Management involves antenatal corticosteroids to increase fetal lung maturity, preventing preterm labor with use of tocolytic agents, and use of antibiotics for chorioamnionitis. At birth, after resuscitation by skilled personnel, avoiding hypothermia and stabilizing the infant, intratracheal surfactant is administered. Babies that do not have significant chest retraction and require FiO₂ values less than 40% may be placed on nasal CPAP of 6 to 7 cm H₂O. If infant has labored breathing, assisted ventilation is provided. Surfactant is administered via endotracheal tube, umbilical vessels are catheterized, and the ventilator and FiO₂ values are adjusted to keep the pH between

Fig. 2. Radiograph of chest showing pneumonia of right middle lobe and left lower lobe (arrows).
7.25 and 7.40, \( P_{aO_2} \) value between 50 and 70 torr, \( P_{CO_2} \) value at 45 to 65 torr, and base deficit less than 10. \(^{3,9,18,20,21}\) Studies comparing use of various types of surfactant preparations, timing of administration, and various modalities of ventilation are discussed in several publications. \(^{3,9,17,19,20}\) Care should be taken to optimize V/Q by using minimally invasive ventilation and optimal positive end-expiratory pressure. Supportive therapy involves maintaining fluid and electrolyte balance and avoiding hypoglycemia and hypothermia. \(^{3,9,18,20}\) Blood cultures are obtained along with total white blood cell and differential count along with C-reactive protein estimation. Antibiotics (ampicillin and gentamicin or amikacin) are administered and withdrawn after 48 hours if the infant is stable. Nutrition is provided and trophic feeding commenced as soon as possible, preferably using mother’s milk. Blood gases and chest radiographs are repeated as clinically indicated. The neonatal intensive care unit (NICU) staff should encourage maternal-infant bonding and family support.

Complications seen early in the course of RDS are air leaks, apnea, intraventricular hemorrhages, anemia, hypoglycemia, hypernatremia, patent ductus arteriosus, necrotizing enterocolitis, as well as renal and growth failure. \(^{9,22,23}\) Outcome is improved by avoiding complications.

Late complications include gastroesophageal reflux, feeding intolerance, growth failure, apnea, sudden death, BPD, as well as developmental and neurologic deficits including visual and auditory handicaps. \(^{14,22}\) After discharge, they are followed up by a team composed of developmental pediatrician, nutritionists, social worker, physical therapist, and other medical and surgical consultants. \(^{9,18,24}\)

**Meconium Aspiration Syndrome**

Most infants born to mothers with meconium-stained amniotic fluid are asymptomatic. MAS occurs in term or postterm infants born through meconium-stained amniotic fluid; these infants have in utero hypoxia and are at increased risk for respiratory distress. \(^{1,4,15}\) Although meconium-stained amniotic fluid occurs in 10% to 15% of deliveries, MAS is seen in 4% to 5% of them. Passage of meconium in utero is a sign of fetal distress occurring because of relaxation of anal sphincter. The resultant hypoxia and gasping breathing leads to aspiration of meconium before birth. Maternal risk factors include preeclampsia, diabetes, chorioamnionitis, and illicit substance abuse. Evidence suggests that patients with severe MAS have chronic in utero hypoxia. Severe MAS is associated with alterations in the pulmonary vasculature,
including remodeling and thickening of the muscle walls. This process results in pulmonary vascular hyperreactivity, vasoconstriction, and high resistance and pressure. Meconium consists of desquamated cells from the gastrointestinal tract, skin, lanugo, hair, bile salts, pancreatic enzymes, lipids, mucopolysaccharides, and water. Chemical pneumonitis occurs from the bile salts and other components deactivating pulmonary surfactant. This phenomenon along with particulate matter in the meconium results in atelectasis. Meconium also activates the complement cascade, which leads to inflammation and constriction of pulmonary veins.

Infants with MAS develop respiratory distress within a few hours of birth. On clinical examination, they may have staining of nails and umbilical cord, barrel-shaped chest on inspection, and signs of respiratory distress along with crackles (rales) and rhonchi on auscultation. The chest radiographic findings are variable and are composed of patchy atelectasis due to terminal airway obstruction, areas of overinflation due to air trapping; in severe cases, widespread involvement of all lung fields are seen with whiteout lung fields (Fig. 4). There may also be evidence of air leak, such as pneumothorax, pneumomediastinum, or interstitial or subcutaneous air (Fig. 5). The last of these is uncommon because of improved resuscitation techniques at birth.

Management: Although in the past amnioinfusion and suctioning of oropharynx before delivery at birth was practiced widely, it has been abandoned because meta-analysis of randomized controlled studies did not show their benefit. At present, the Neonatal Resuscitation Textbook of the American Academy of Pediatrics recommends to suction the trachea after intubation only in apneic infants, even though no controlled studies have confirmed its benefit. It is recommended that if there is no meconium after 1 attempt to suction the trachea in apneic infants, they should be intubated, ventilated, oxygenated, and stabilized immediately. If the infant is vigorous as defined by strong respiratory effort, heart rate greater than 100 beats per minute, and good muscle tone, bulb syringe suctioning should be done, followed by standard procedures described in the NRP manual. Cord blood gases should be obtained to determine the degree of acidosis, and if the pulse oximeter shows Sao2 values less than 90% after 10 minutes, arterial blood gases should be obtained, particularly if the infant requires resuscitation. Management in most patients is supportive. Infants who develop respiratory distress should be admitted to the NICU. Oxygen therapy may be delivered via oxygen hood, and arterial blood gases are monitored after placing umbilical vessel catheters. CPAP at 5 to 6 cm of H2O should be provided if oxygen requirement exceeds 0.4 to 0.5. In patients with respiratory acidosis, assisted

Fig. 4. Radiograph of chest showing meconium aspiration syndrome; note bilateral patchy infiltrates (arrows).
ventilation may be required to maintain pH between 7.3 and 7.5, \( \text{PCO}_2 \) values at 30 to 50 torr, and \( \text{PaO}_2 \) values above 100 torr. Infants developing severe MAS should be cared for at a tertiary center with the ability to administer surfactant, high-frequency ventilation, inhaled nitric oxide (iNO), and extracorporeal membrane oxygenation (ECMO), because of their predilection to suddenly develop hypoxia due to their labile pulmonary vasculature. Surfactant therapy should be administered cautiously in infants and requires moderately high settings and oxygen on conventional ventilator because the surfactant is inactivated by the aspirated meconium, and this is considered a standard therapy. Recent studies have suggested that early use of high-frequency ventilation to optimize V/Q along with early use iNO therapy may decrease the use of ECMO and improve outcome. These infants should be followed up longitudinally, and despite appropriate interventions, they may have sequelae, such as learning disability or neurodevelopmental or hearing handicaps due to perinatal asphyxia and their NICU course, hence, should be followed up.

**Bronchopulmonary Dysplasia**

BPD develops in low-birth-weight infants weighing less than 1500 g, particularly those weighing less than 1000 g. In 2001, a National Institutes of Health workshop developed a consensus on definition of BPD based on gestational age at birth, time of assessment, and severity of disease.

In 1967, Northway and his colleagues described BPD classifying it into 4 stages in infants with RDS. The form that occurs in neonates receiving high inspired oxygen and developing ventilator-induced injury is termed old or classical BPD and is rarely seen these days. With the use of antenatal steroid, surfactant therapy, caffeine therapy, and gentler modes of ventilation as the new standard of care for RDS, smaller infants who survive develop a milder form of BPD that is termed by Jobe as new BPD, and this is associated with disruption of lung development, specifically an arrest of alveolar septation and vascular development in the distal part of the lung and impaired pulmonary function in later years of life. Some extremely preterm infants develop lung disease after an initial period without oxygen or mechanical ventilation, and this form has been labeled as chronic lung disease (CLD) of prematurity. CLD is similar to what Dr Peter Auld described as “chronic pulmonary insufficiency of prematurity,” which usually developed after the

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**Fig. 5.** (A) Radiograph of chest showing pneumomediastinum borders shown by arrows. Note thymic silhouette. (B) Radiograph of chest showing tension pneumothorax (arrows). Marked collapse of the right lung with large lucency peripherally. Depression of the right hemidiaphragm and shift of the cardiothymic silhouette to the left.
second week of life in premature infants after apnea and/or bradycardia for which the infant required oxygen and assisted ventilation. Thus it is unclear whether the new BPD represents a single different disease entity or is a group of entities with complex epigenetic, environmental (especially antenatal and postnatal infections), and inflammatory-mediated dysregulation of lung maturation or other factors.

The incidence of BPD varies with gestational age, respiratory illness severity, duration of oxygen, and ventilator support requirement, the FiO₂ value required to maintain Sao₂ value greater than 90%. In a 2007 study by Fanaroff and colleagues, the incidence of BPD when defined as oxygen requirement at 28 days was 42% (BW 501–750 g), 25% (BW 751–1000 g), and 11% (BW 1251–1500 g), respectively, with majority occurring in infants with BW less than 1250 g. Application of a definition to assess the adequacy of oxygenation and ventilation at 36 weeks postmenstrual age and the level of the infant’s need for supplemental oxygen and/or ventilator assistance reduces the incidence by 10%. BPD has a multifactorial cause. Within a few days of premature birth, inflammatory biomarkers (chemokines, adhesion molecules, proinflammatory and antiinflammatory cytokines, proteases, and growth factors) have complex interactions that alter subsequent lung maturation. An imbalance between proinflammatory and antiinflammatory cytokines released because of various factors leads to apoptosis in the lung with varying degrees of repair. This condition leads to impaired alveolarization and angiogenesis, which lead to larger, more simplified alveoli and a dysmorphic pulmonary vasculature, the pathologic hallmark of BPD. The multifactorial insults to the developing lung include intrauterine and postnatal infections, inflammation in the immature lung, effects of resuscitation techniques, patent ductus arteriosus, as well as ventilator- and oxygen-induced injury. Inadequate nutrition may also impair alveolar development and surfactant production and inhibit lung growth and repair. The uneven damage to the airways and lungs results in marked V/Q mismatch. Bronchomalacia increases airway resistance because of inflammation and partial collapse of small and large airways during expiration. Lung compliance is also reduced secondary to edema and fibrosis. As the disease progresses, atelectasis with areas of hyperinflation are seen on chest radiograph (Fig. 6).

Management includes judicious use of oxygen to maintain Sao₂ value between 90% and 94%, use of noninvasive ventilation to minimize further pressure-induced lung...
damage, and fluid restriction. Some patients may transiently respond to diuretics, bronchodilators, and inhaled steroids, hence their prolonged use is not recommended. Adequate nutrition with micronutrients and macronutrients is essential to optimize lung and somatic growth and should be monitored closely. Patients with severe BPD are at risk of developing pulmonary hypertension diagnosed by echocardiogram in consultation with cardiologist. These patients are at risk of sudden death because of pulmonary hypertension or bronchospasm. Use of iNO to prevent BPD has not been validated across clinical trials. Oral sildenafil has been used in some studies to treat pulmonary hypertension; its response is variable perhaps because of inconsistent absorption. Before discharge from the NICU, careful planning should be done. Home environment should be checked because there is an increased chance of rehospitalization (up to 50%) in them. If the infant is discharged on oxygen and receives medications or feeding via gastrostomy tube, parents should room-in and learn how to administer medications and feeds under nursing supervision. Use of home oxygen and ventilator should be coordinated by specially trained staff and home health services conversant with care of infants with BPD. All immunizations should be up to date before discharge. The respiratory syncytial virus (RSV) prophylaxis is recommended within 6 months of the RSV season for all infants younger than 2 years. Influenza vaccine is administered to all care providers, siblings, and infants with BPD older than 6 months. Parents should be counseled to avoid second-hand smoke, to keep people with cold away from the infant, and to not take these infants to day care facility. Growth and nutrition should be monitored. Some infants have gastroesophageal reflux requiring therapy. Respiratory symptoms may persist beyond infancy into childhood. Patients with BPD may have delayed development, learning disorders, and neurologic problems. Hence it is important for the pediatrician to work with subspecialist and community support agencies to help the family. Although most patients with BPD do well, patients with severe disease develop worsening respiratory failure, pulmonary hypertension, and cor pulmonale requiring repeated hospitalization in the intensive care unit, which may prolong suffering and death. Hence, end-of-life care should be discussed with parents including withdrawing assisted ventilation.

**Interstitial Lung Disease**

On rare occasions, neonates and infants have other chronic respiratory disorders. This category encompasses a group of diseases called childhood interstitial lung diseases (chILDs) or diffuse lung disease (DLD). The American Thoracic Society has published an official clinical practice guideline for classification, evaluation, and management of childhood interstitial lung disease in infancy. Causes include surfactant function abnormalities, persistent tachypnea of infancy or neuroendocrine cell hyperplasia of infancy, alveolar capillary dysplasia associated with misalignment of pulmonary veins, and pulmonary interstitial glycogenesis (Box 4, Fig. 7).

All neonates and infants (<2 years of age) with DLD should have common diseases excluded, which include GERD, cystic fibrosis, congenital or acquired immune deficiency, congenital heart disease, BPD, pulmonary infection, H-type TEF, primary ciliary dyskinesia presenting with newborn respiratory distress, and recurrent aspiration. After they have been eliminated, a neonate or infant with DLD is regarded as having chILD syndrome if at least 3 of the following are present: (1) respiratory symptoms (cough, rapid and difficult breathing, or exercise intolerance), (2) respiratory signs (tachypnea, rales, retractions, digital clubbing, failure to thrive, or respiratory failure), (3) hypoxemia, and (4) diffuse abnormalities on a chest radiograph or CT. Newborns who present with chILD syndrome and severe disease, or family history of adult or...
chILD, should be tested for genetic diseases, such as mutation in genes SFTPB, SFTPC, and ABACA3, which encode proteins SP-B, SP-C, and ABCA3. Newborns presenting with chILD syndrome, congenital hypothyroidism, and hypotonia should be tested for NKX2.1 (ie, thyroid transcription factor).

**Congenital Lung Diseases**

Various congenital malformations of the lung such as congenital diaphragmatic hernia (Fig. 8), TEF (Fig. 9), sequestration of lung, congenital cystic adenomatous

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**Box 4**

*Disorders causing severe neonatal childhood interstitial lung disease syndrome*

- Acinar dysplasia
- Pulmonary hypoplasia/alveolar simplification
- Alveolar capillary dysplasia with misalignment of the pulmonary veins (FOXF1 mutations)
- PIG
- Surfactant protein B deficiency (homozygous SFTPB mutations) ABCA3 gene mutations
- TTF-1 (NKX2.1) mutations
- Pulmonary hemorrhage syndromes
- Pulmonary lymphangiectasia

*Abbreviations: PIG, pulmonary interstitial glycogenosis; TTF, thyroid transcription factor.*


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**Fig. 7.** Genetic approach to chILD diagnosis. Possible genetic mechanisms are listed on the right, ordered depending on age of the patient at presentation (top to bottom), as well as selected phenotypic characteristics. Arrows point to initial gene or genes to be analyzed; if results of initial studies were negative, arrows on right indicate additional genetic studies to be considered. PAP, pulmonary alveolar proteinosis; PPHN, persistent pulmonary hypertension of the newborn. (*From Kurland G, Deterding RR, Hagood JS, et al. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. Am J Respir Crit Care Med 2013;188:376–94; with permission.*)

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malformation of lung, congenital lobar emphysema, lymphangiectasis, or mass in the chest may present with respiratory distress either in the newborn period or during infancy.5–8,34–36 If these are diagnosed antenatally, the patient should be transferred to a perinatal center for further management. A pediatric surgeon should be consulted.

Fig. 8. Radiograph of chest showing congenital diaphragmatic hernia (Bochdalek). Note stomach bubble in the left side of chest (arrow) and cardiothymic silhouette displaced into the right side of chest.

Fig. 9. Tracheoesophageal fistula. Note upper blind pouch (radio opaque tube) with fistula (air in stomach and intestines).
SUMMARY

Respiratory distress presents with varying degrees of tachypnea, grunting, chest retractions, nasal flaring, and/or cyanosis. After initial stabilization, followed by history taking and physical examination, chest radiograph, as well as blood gases, a diagnosis should be made in most instances, which includes TTN, RDS, MAS, pneumonia, CLD of prematurity, interstitial lung disease, or upper airway disorders. Cyanotic heart disease should be suspected if Sao2 value is less than 90% after 15 minutes of age. In critically ill infants or when the diagnosis is unclear, a neonatologist, cardiologist, pulmonologist, or ENT surgeon must be promptly consulted.

REFERENCES