

A COMPREHENSIVE REVIEW OF NEONATAL RESPIRATORY DISEASES: PATHOPHYSIOLOGY, DIAGNOSIS, MANAGEMENT, ADVANCED TECHNIQUES AND PREVENTION

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ABSTRACT

Neonatal respiratory diseases are important causes of morbidity and admission to neonatal intensive care units, particularly among preterm and low-birth-weight infants. These disorders develop when the transition from fetal fluid-filled lungs to independent air breathing is impaired or when immature pulmonary, vascular, infectious, or structural conditions interfere with normal gas exchange. Common neonatal respiratory disorders include respiratory distress syndrome, transient tachypnea of the newborn, meconium aspiration syndrome, neonatal pneumonia, persistent pulmonary hypertension of the newborn, pneumothorax, bronchopulmonary dysplasia, and apnea of prematurity. Fetal lung development progresses through embryonic, pseudoglandular, canalicular, saccular, and alveolar stages, and interruption of these processes may result in pulmonary hypoplasia and respiratory dysfunction. Clinical manifestations include tachypnea, grunting, nasal flaring, chest retractions, cyanosis, apnea, and increasing oxygen requirements. Diagnosis is based on clinical assessment supported by pulse oximetry, blood gas analysis, laboratory investigations, chest radiography, echocardiography, and lung ultrasound. Management depends on gestational age, underlying cause, disease severity, and oxygenation status. Current treatment emphasizes early recognition, controlled oxygen therapy, non-invasive respiratory support, surfactant therapy, and lung-protective ventilation while minimizing ventilator-induced lung injury. Advanced approaches include CPAP, non-invasive ventilation, lung ultrasound, volume-targeted ventilation, high-frequency ventilation, and selected use of inhaled nitric oxide. Future neonatal respiratory care is expected to become increasingly personalized through improved monitoring, ultrasound-guided treatment, and artificial intelligence-assisted prediction. Prevention includes antenatal corticosteroids, appropriate delivery-room care, infection control, and gentle respiratory support to improve neonatal outcomes.

KEYWORDS: Neonatal Respiratory Diseases; Respiratory Distress Syndrome; Fetal Lung Development; Pathophysiology; Respiratory Support; Advanced Neonatal Care.

1. INTRODUCTION

Respiratory diseases are a broad group of disorders that affect the respiratory system and interfere with normal breathing. They may involve the airways, lung tissue, or other structures responsible for the movement of air and exchange of gases. The respiratory system plays an essential role in supplying oxygen to the body and removing carbon dioxide.^[1] respiratory diseases can occur at any age and may be acute or chronic. Some conditions develop over a short period, such as respiratory tract infections and pneumonia, whereas others may continue for many years. Common respiratory diseases include asthma, chronic obstructive pulmonary disease (COPD), pneumonia, tuberculosis, bronchiectasis, respiratory allergies, occupational lung diseases, and lung cancer.^[2]

respiratory diseases may develop because of a combination of genetic, environmental, occupational, infectious, and lifestyle-related factors. Tobacco smoke, air pollution, occupational exposure to dust and chemicals, allergens, and respiratory infections are important contributing factors. Exposure to biomass fuels and other indoor pollutants may also increase the risk of respiratory disease, particularly when ventilation is inadequate.^[3]

Air pollution is an important environmental factor affecting respiratory health. Prolonged exposure to particulate matter and other pollutants can irritate the respiratory tract and may contribute to the development or worsening of respiratory conditions. Similarly, repeated occupational exposure to dust, fumes, vapors, gases, and chemicals can cause or aggravate several respiratory diseases.^[4]

The symptoms of respiratory diseases vary according to the type and severity of the condition. Common manifestations include cough, wheezing, shortness of breath, chest tightness, and sputum production. Symptoms may occur intermittently or remain persistent and can interfere with physical activity, sleep, work, and other daily activities.^[5]

Respiratory diseases can have a considerable effect on quality of life and may contribute to increased healthcare

use. Persistent respiratory symptoms can limit physical activity and make routine tasks more difficult. Severe respiratory illness may impair oxygenation and carbon dioxide removal and can progress to respiratory failure.^[6]

Prevention has an important role in maintaining respiratory health. Avoiding tobacco smoke, reducing exposure to air pollution and occupational hazards, maintaining adequate indoor ventilation, and preventing respiratory infections can help reduce respiratory health risks.^[7]

NEONATAL RESPIRATORY DISEASES

Neonatal respiratory diseases are a group of disorders that affect breathing and normal lung function during the first 28 days of life. The neonatal period is a critical stage because the newborn has to make a rapid transition from intrauterine life to independent breathing. Before birth, the lungs are filled with fluid and oxygen is supplied through the placenta.^[8]

Respiratory problems are among the common causes of illness and admission to neonatal intensive care units (NICUs). Premature infants are at greater risk because immature lungs may have insufficient surfactant and reduced ability to maintain normal alveolar function.⁹ Neonatal respiratory diseases include conditions that interfere with normal breathing, ventilation or oxygenation in newborn infants. Respiratory distress is a common clinical presentation, but it is not itself a single disease. It can occur because of problems involving the lungs, heart, infection, pulmonary circulation, airway or other body systems. Therefore, identifying the underlying cause is an important part of neonatal assessment.^[10]

Common respiratory disorders seen during the neonatal period include respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), meconium aspiration syndrome (MAS), neonatal pneumonia, persistent pulmonary hypertension of the newborn (PPHN) and pneumothorax. Congenital abnormalities of the airway, lungs and diaphragm can also cause breathing difficulties.^[11]

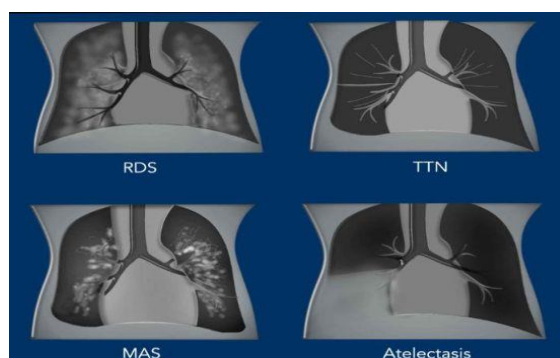


Figure 1: Schematic comparison of chest radiographic appearances in respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), meconium aspiration syndrome (MAS), and atelectasis.

Respiratory problems in newborns can develop for several reasons. Prematurity is an important risk factor because lung development and surfactant production increase with advancing gestational age. Other respiratory disorders may result from delayed clearance of fetal lung fluid, aspiration of meconium, infection, abnormal pulmonary circulation or structural abnormalities.^[12] The clinical features of neonatal respiratory disease depend on its cause and severity. Common signs include rapid breathing (tachypnea), nasal flaring, expiratory grunting and chest retractions. These findings indicate increased effort to maintain effective breathing.^[13]

Respiratory symptoms may appear immediately after birth or develop during the following hours. Persistent or increasing respiratory effort, increasing oxygen requirement or worsening oxygen saturation should therefore receive prompt attention.^[14]

Respiratory distress syndrome is mainly associated with prematurity and pulmonary surfactant deficiency. Reduced surfactant activity increases alveolar surface tension, leading to difficulty maintaining open alveoli and impaired gas exchange.^[15]

Transient tachypnea of the newborn is usually related to delayed removal of fetal lung fluid. It commonly produces rapid breathing shortly after birth and generally improves as the excess fluid is absorbed.^[16]

Meconium aspiration syndrome occurs when meconium-containing amniotic fluid enters the newborn's respiratory tract. It can cause airway obstruction, inflammation and impaired lung function and may be associated with more severe respiratory complications.^[17]

Neonatal pneumonia may develop because of infection acquired before, during or after delivery. Infection can cause inflammation of the lungs and interfere with normal oxygen exchange.^[18]

Early recognition of respiratory disease is important because newborns can deteriorate quickly. Assessment includes observation of the breathing pattern, respiratory rate, work of breathing and oxygen saturation. Depending on the clinical condition, investigations such as blood gas analysis, blood tests and chest radiography may be required to identify the underlying cause.^[19]

Treatment depends on the specific disorder and its severity. Supportive measures may include oxygen supplementation and non-invasive respiratory support such as continuous positive airway pressure (CPAP). Current neonatal care emphasizes early appropriate respiratory support while avoiding unnecessary invasive ventilation and minimizing lung injury.^[20]

Neonatal respiratory diseases are clinically important because inadequate breathing and oxygenation can rapidly affect vital organs. Early identification of abnormal respiratory signs, appropriate investigation and timely treatment can reduce the risk of progression to respiratory failure and other complications.^[21] Their causes range from developmental immaturity and delayed lung-fluid clearance to infection, aspiration, pulmonary vascular abnormalities and congenital disorders. Understanding these conditions and recognizing their early clinical features are essential for providing appropriate neonatal care and improving outcomes.^[22]

2. FETAL LUNG DEVELOPMENT IN RELATION TO NEONATAL RESPIRATORY DISEASES

Fetal lung development starts from foregut and completes after birth. Any interruption leads to respiratory disease.

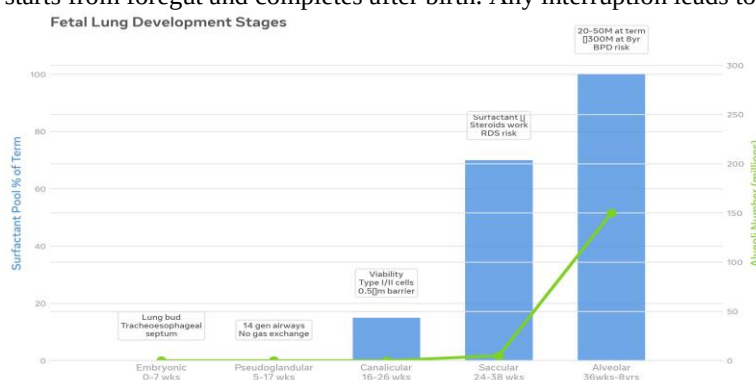


Figure 2: Stages of Fetal Lung Development and Major Developmental Changes.

2.1.1 Embryonic Stage (0-7 weeks)

Lung bud arises from ventral foregut at 26 days. Divides into right and left buds, then lobar bronchi. Tracheoesophageal septum forms. Defect → tracheoesophageal fistula, pulmonary agenesis.^[23]

2.1.2 Pseudoglandular Stage (5-17 weeks)

Repeated dichotomous branching - 14 generations of airways formed by 16 weeks. Cartilage, smooth muscle, glands develop. No gas exchange. Respiratory bronchioles formed. Oligohydramnios in this stage → pulmonary hypoplasia, lethal.^[24]

2.1.3 Canalicular Stage (16-26 weeks)

Most critical stage for viability. Acinus formation starts. Capillaries invade mesenchyme, blood-air barrier thins to 0.5 micron. Type I and Type II pneumocytes differentiate at 20-24 weeks. Surfactant synthesis starts at 20 weeks in small amount. Lamellar bodies appear at 22-24 weeks. Infants born 22-24 weeks → severe RDS, high mortality.^[25]

2.1.4 Saccular Stage (24-38 weeks)

Terminal sacs formation, surfactant pool increases exponentially. Type II cells produce surfactant - DPPC and SP-B,C. Surfactant detectable in amniotic fluid at 28-32 weeks. Alveolar fluid CI- secretion active, lung fluid 4-5 mL/kg/h produced. Maternal steroids accelerate maturation. Birth at 24-34 weeks → surfactant deficiency → RDS, air leak, BPD.^[26]

2.1.5 Alveolar stage (36 weeks-8 years)

True alveoli formation starts at 36 weeks. At term 20-50 million alveoli present, adult 300 million by 8 years. Alveolar septation by secondary crests. Microvascular maturation - double to single capillary network. Interruption → BPD with simplified alveoli - few large alveoli, arrested growth.^[27]

2.1 ETIOLOGY OF NEONATAL RESPIRATORY DISEASES

Neonatal respiratory distress is multifactorial, resulting from interaction between immature lung development, perinatal events, and maternal factors. The prevalence varies between 3-7% of live births, with higher incidence in preterm (19.7%) compared to term neonates (2.3%).

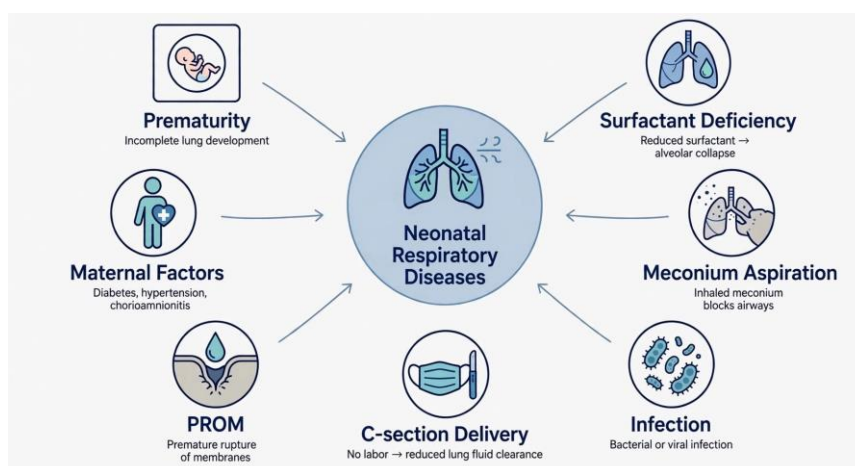


Figure 3: Schematic representation showing key etiological factors of neonatal respiratory diseases including prematurity, surfactant deficiency, meconium aspiration, infection, C-section delivery, PROM, and maternal factors. These factors can co-exist and increase risk of respiratory distress.

2.1.1 Primary pulmonary causes

a) Surfactant Deficiency (RDS/HMD): Most common in preterm <34 weeks due to immature Type II pneumocytes leading to alveolar collapse, low lung compliance and impaired gas exchange. Prematurity and low birth weight are strongest predictors.

b) Lung Fluid Disorders: Transient Tachypnea of Newborn (TTN) occurs due to delayed clearance of fetal lung fluid, especially after elective caesarean section without labor. Maternal diabetes, macrosomia and asthma are additional risk factors.

c) Aspiration Syndromes: Meconium Aspiration Syndrome (MAS) follows intrauterine hypoxia → relaxation of anal sphincter → meconium passage into amniotic fluid → aspiration causing airway obstruction, chemical pneumonitis and surfactant inactivation. Common in term and post-term infants.^[28]

Infectious Etiology

Early-onset pneumonia (within 72 hours) is acquired from maternal genital tract (Group B Streptococcus, E.

coli) while late-onset is hospital-acquired. Prolonged rupture of membranes (PROM) >18 hours, chorioamnionitis and maternal sepsis increase risk.^[29]

2.1.2 Pulmonary Vascular Cause

Persistent Pulmonary Hypertension of Newborn (PPHN) results from failure of normal postnatal fall in pulmonary vascular resistance, leading to right-to-left shunting. It often complicates MAS, RDS and pneumonia and carries highest mortality (up to 91.2%).^[30]

2.1.3 Structural and Extra pulmonary Causes

Includes congenital anomalies such as choanal atresia, tracheo-oesophageal fistula, congenital diaphragmatic hernia, pulmonary hypoplasia associated with oligohydramnios, and cystic lesions. Cardiac causes, haematological tal (polycythemia, anaemia) and metabolic acidosis also mimic respiratory distress.^[31]

2.2 Classification of neonatal respiratory disease

Neonatal respiratory diseases comprise a heterogeneous group of conditions that affect the airways, lung parenchyma, pulmonary circulation, respiratory control

mechanisms, and structural development of the respiratory system. They may occur because of prematurity, inadequate surfactant production, delayed clearance of fetal lung fluid, aspiration, infection, abnormal pulmonary vascular adaptation, chronic lung injury, neurological immaturity, or congenital

abnormalities. For a practical understanding, neonatal respiratory diseases can be classified according to their principal underlying mechanism as follows.^[32]

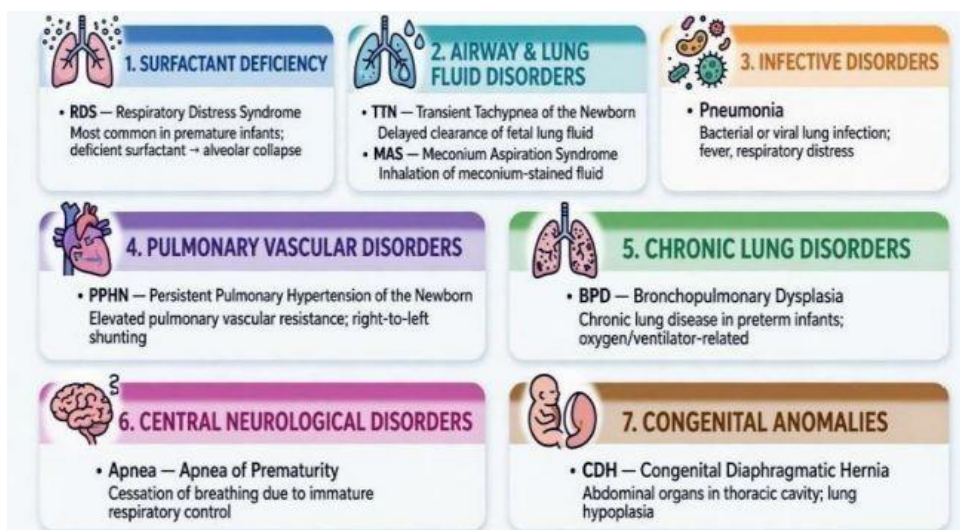


Figure 4: Major Categories of Neonatal Respiratory Disorders.

2.2.1 Surfactant Deficiency Disorders

Respiratory Distress Syndrome (RDS) is the major surfactant deficiency disorder encountered predominantly in preterm neonates. Immaturity of the lungs results in inadequate production or function of pulmonary surfactant, increasing alveolar surface tension and promoting alveolar collapse. This leads to reduced lung compliance, impaired gas exchange and progressive respiratory distress after birth. The risk is particularly high with decreasing gestational age.^[33]

Examples: Respiratory distress syndrome (RDS), surfactant dysfunction/deficiency disorders.

2.2.2 Airway and Lung Fluid Disorders

This group includes disorders in which airway obstruction, abnormal airway function, or delayed removal of fetal lung fluid interferes with normal ventilation. Transient tachypnea of the newborn (TTN) occurs when fetal lung fluid is not adequately cleared after birth, producing tachypnea and increased respiratory effort. Meconium aspiration syndrome (MAS) develops when meconium-contaminated amniotic fluid is aspirated, causing airway obstruction, chemical inflammation and surfactant inactivation.^[34]

Examples: Transient tachypnea of the newborn (TTN), meconium aspiration syndrome (MAS), pneumothorax and other air-leak disorders.

2.2.3 Infective Disorders

Respiratory infections are important causes of neonatal respiratory morbidity and may occur before, during or after birth. Neonatal pneumonia can produce inflammation of the lung tissue, impaired gas exchange and respiratory distress. Infection may occur together with neonatal sepsis, in which systemic infection can further impair respiratory function and contribute to respiratory failure. Maternal infection, prolonged rupture of membranes, prematurity and perinatal complications may increase the risk.^[35]

Examples: Neonatal pneumonia, congenital pneumonia and sepsis-associated respiratory disease.

2.2.4 Pulmonary Vascular Disorders

Persistent pulmonary hypertension of the newborn (PPHN) is a disorder of pulmonary vascular adaptation in which pulmonary vascular resistance remains abnormally high after birth. As a result, pulmonary blood flow is reduced and right-to-left shunting may occur through fetal circulatory pathways, producing hypoxemia and cyanosis. PPHN may occur as a primary vascular disorder or secondary to conditions such as RDS, MAS, pneumonia, sepsis or pulmonary hypoplasia.^[36]

Example: Persistent pulmonary hypertension of the newborn (PPHN)

2.2.5 Central and Neurological Respiratory Disorders

Respiration in newborns depends on coordinated activity of the brainstem respiratory centres, chemoreceptors and respiratory muscles. In premature infants, these regulatory mechanisms are incompletely mature, which

can result in apnea of prematurity. Episodes may involve prolonged pauses in breathing and can be accompanied by oxygen desaturation or bradycardia. The frequency and severity generally increase with greater prematurity.^[37]

Example: Apnea of prematurity.

2.3 Risk Factors of Neonatal Respiratory Diseases

Neonatal respiratory diseases are influenced by factors that affect fetal lung growth, surfactant production, pulmonary vascular development, and adaptation to breathing after birth. Important risk factors include the following:

2.3.1 Prematurity and Low Birth Weight

Prematurity is one of the strongest risk factors for neonatal respiratory disease because lung maturation and surfactant production are incomplete before term. Infants born before 37 completed weeks are at increased risk of respiratory distress syndrome, apnea, and other respiratory complications. Low birth weight is defined as a birth weight below 2500 g, irrespective of gestational age, and these infants are particularly vulnerable to respiratory problems.^[38]

2.3.2 Inadequate Lung Growth and Pulmonary Hypoplasia

Normal lung growth increases progressively with gestational age. Lung volume rises markedly during late gestation, and alveolar development continues after birth. In term neonates without respiratory pathology, reported total lung volume is approximately 39–47 mL/kg.³ The lung-volume-to-body-weight ratio is approximately 33–34 mL/kg during 16–31 weeks and decreases to about 23.4 mL/kg at term because body weight increases relatively faster near term.^[4] Reduced lung growth or pulmonary hypoplasia can therefore predispose a newborn to respiratory insufficiency.^[39]

2.3.3 Abnormally Low Lung Weight Relative to Body Weight

Lung weight should be interpreted according to gestational age rather than using one fixed normal value. Post-mortem reference studies found a mean lung-weight/body-weight ratio of approximately 2.98–3.15% at 16–27 weeks, decreasing to about 2.55% at 28–36 weeks and 1.79% at term.^[5] A lung-weight/body-weight ratio below the age-specific reference range may indicate pulmonary underdevelopment. A value $\leq 1.5\%$ has traditionally been used as a marker of marked pulmonary hypoplasia in very premature infants, although age-specific reference values are more appropriate for identifying milder abnormalities.^[40]

2.3.4 Maternal and Pregnancy-Related Factors

Maternal diabetes, hypertension, infection, multiple pregnancy, premature rupture of membranes, and conditions associated with oligohydramnios may increase the risk of neonatal respiratory complications. Prolonged rupture of membranes and conditions that

restrict fetal lung expansion can interfere with normal pulmonary development and may contribute to pulmonary hypoplasia.^[41]

2.3.5 Birth-Related and Neonatal Factors

Caesarean delivery without labour, perinatal asphyxia, low Apgar score, meconium-stained amniotic fluid, meconium aspiration, neonatal infection, and congenital abnormalities of the lungs or airway can increase the likelihood of respiratory distress. Structural conditions such as congenital diaphragmatic hernia and severe renal abnormalities can markedly impair lung development.^[42]

2.4 SIGNS AND SYMPTOMS OF NEONATAL RESPIRATORY DISEASES

Neonatal respiratory diseases present with overlapping clinical features reflecting impaired gas exchange, increased work of breathing, and altered lung mechanics. Early recognition of signs is critical for timely intervention.

2.4.1 General Respiratory Signs

Tachypnea is defined as respiratory rate $>60/\text{min}$ sustained, first sign in most disorders. Grunting results from closure of glottis during expiration to maintain FRC and prevent atelectasis. Nasal flaring indicates increased airway resistance and effort to reduce it. Chest retractions - intercostal, subcostal, and suprasternal - occur due to highly compliant chest wall and negative intrathoracic pressure generation against stiff lungs. Cyanosis appears when arterial saturation falls below 85% or $\text{PaO}_2 < 50 \text{ mmHg}$. In dark-skinned neonates, central cyanosis is assessed over tongue and mucous membranes.^[43]

2.4.2 Respiratory Distress Syndrome (RDS):

Onset within 15 minutes to 4–6 hours after birth in preterm infant. Progressive worsening over 48 hours. Signs include marked tachypnea, severe grunting, retractions, and requirement of oxygen $>40\%$. Auscultation reveals diminished air entry with fine crepitations due to atelectasis. Apnea may occur in extremely preterm due to fatigue. Untreated cases develop respiratory failure with lethargy, pallor, and mixed acidosis.^[44]

2.4.3 Transient Tachypnea of Newborn (TTN)

Occurs in term and late-preterm infants, especially after elective caesarean without labour and infants of diabetic mothers. Onset within 2 hours after birth, tachypnea is prominent 60–120/min with mild to moderate retractions, but grunting is minimal. Chest appears hyperinflated or barrel-shaped. Cyanosis is mild and responds to low $\text{FiO}_2 < 40\%$. Course is benign with resolution by 24–72 hours.^[45]

2.4.4 Meconium Aspiration Syndrome (MAS):

Presents in term or post-term infant with meconium-stained amniotic fluid. Signs include tachypnea, grunting, retractions, barrel chest due to air-trapping, and coarse

crepitations or rhonchi. Meconium staining of nails, skin, and cord may be present. Severe cases show air leak - pneumothorax - indicated by sudden desaturation and asymmetric chest expansion. Associated pulmonary hypertension manifests as labile hypoxemia with difference >10% between preductal and postductal SpO₂.^[46]

2.4.5 Neonatal Pneumonia: May present early-onset within 72 hours or late-onset after 72 hours. Signs are nonspecific - tachypnea, grunting, retractions, fever or hypothermia, lethargy, poor feeding. Purulent secretions may be present on suction. Apnea is common presentation in preterm. Features of sepsis - tachycardia, hypotension, prolonged capillary refill - may coexist.^[47]

2.4.6 Persistent Pulmonary Hypertension of Newborn (PPHN): Presents as severe cyanosis disproportionate to respiratory distress, unresponsive to high FiO₂ 100% - refractory hypoxemia. Labile desaturations with handling. Loud single second heart sound and systolic murmur of tricuspid regurgitation may be heard. PaO₂ difference between right radial (preductal) and lower limbs (postductal) >15-20 mmHg is characteristic.^[48]

2.4.7 Bronchopulmonary Dysplasia (BPD): History of prematurity with prolonged oxygen and ventilation requirement at 28 days of life. Chronic tachypnea, retractions, wheezing, and crackles. Chest is hyperinflated with increased anteroposterior diameter. Growth failure due to increased metabolic demand.^[49]

2.5 PATHOPHYSIOLOGY OF NEONATAL RESPIRATORY DISEASES

Neonatal respiratory distress results from failure of the complex transition from fetal to neonatal pulmonary physiology. At birth, lungs must convert from fluid-filled organ to air-filled organ within minutes, which requires coordinated events - absorption of fetal lung fluid, establishment of functional residual capacity (FRC), fall in pulmonary vascular resistance (PVR), and initiation of continuous breathing.^[50]

2.5.1 SURFACTANT DEFICIENCY DISORDERS (RDS)

Surfactant is a lipoprotein complex composed of 90% phospholipids and 10% surfactant proteins (SP-A, B, C, D), synthesized by Type II pneumocytes after 24 weeks, with peak production after 34 weeks. In preterm infants, deficiency leads to high surface tension at alveolar air-liquid interface.

According to Laplace law ($P = 2T/r$), small alveoli require higher pressure to remain open. Without surfactant, end-expiratory alveolar collapse occurs leading to atelectasis, reduction in FRC, ventilation-perfusion (V/Q) mismatch, and intrapulmonary shunting. Collapsed alveoli trigger hypoxia and hypercapnia which cause anaerobic metabolism, lactic acidosis, and pulmonary vasoconstriction. Pulmonary vasoconstriction

increases PVR, leading to right-to-left shunting through patent ductus arteriosus and foramen ovale, worsening hypoxemia - a vicious cycle.^[51]

2.5.2 AIRWAY AND LUNG FLUID DISORDERS

In utero, fetal lungs are filled with fluid secreted by pulmonary epithelium (4-6 mL/kg). During labor, increased catecholamines and reversal of transepithelial chloride transport via ENaC channels promote fluid absorption. In TTN, this mechanism fails, especially in elective caesarean without labor and in infants of diabetic mothers. Retained fluid occupies alveolar space, compresses airways, causes peribronchial edema, and reduces compliance leading to tachypnea and hypoxia, but without severe gas exchange abnormality.

In MAS, aspiration of meconium-stained fluid causes three-phase injury: acute ball-valve airway obstruction leading to hyperinflation and air leak; chemical pneumonitis within hours due to pro-inflammatory mediators (IL-8, TNF-alpha); and secondary surfactant inactivation because meconium displaces and inhibits surfactant function, producing RDS-like picture in term infant.^[52]

2.5.3 INFECTIVE DISORDERS

Pneumonia triggers inflammatory cascade with neutrophil infiltration, alveolar edema, and exudation. Bacterial endotoxins damage Type II pneumocytes causing secondary surfactant deficiency. Infection also increases alveolar-capillary permeability, leading to pulmonary edema and decreased compliance. Systemic sepsis impairs central respiratory drive and causes metabolic acidosis, further depressing respiration.^[53]

2.5.4 PULMONARY VASCULAR DISORDER (PPHN)

Normally at birth, PaO₂ rises and pH rises, causing fall in PVR from 8-10 Wood units in fetus to 2-3 units in neonate within 24 hours. In PPHN, factors like hypoxia, acidosis, MAS, and sepsis cause sustained vasoconstriction, muscular hypertrophy of pulmonary arterioles, and endothelial dysfunction with reduced nitric oxide and increased endothelin-1.

Elevated PVR maintains fetal circulation with right-to-left shunting, causing severe refractory hypoxemia unresponsive to oxygen. Hypoxemia causes further vasoconstriction, perpetuating cycle.^[54]

2.5.5 CHRONIC LUNG DISORDER (BPD)

BPD results from arrested alveolarization and vasculogenesis due to exposure of immature lungs to hyperoxia, volutrauma, and inflammation. Hyperoxia generates reactive oxygen species, damaging Type I pneumocytes and endothelium. Barotrauma causes alveolar rupture and interstitial emphysema. Chronic inflammation leads to fibrosis, decreased alveolar number, and enlarged simplified alveoli with reduced

surface area for gas exchange, causing chronic oxygen dependence.^[55]

2.5.6 CENTRAL NEUROLOGICAL DISORDER

Apnea of prematurity occurs due to immaturity of brainstem respiratory centers, blunted response to hypercapnia and hypoxia, and decreased upper airway muscle tone. Premature infants have paradoxical response to hypoxia - initial increase followed by depression of breathing - leading to periodic breathing and apnea.^[56]

2.5.7 CONGENITAL ANOMALIES (CDH)

In diaphragmatic hernia, abdominal contents herniate into thoracic cavity during 8-10 weeks of gestation, compressing developing lung bud. This causes pulmonary hypoplasia with reduced bronchial generations, alveoli, and pulmonary vessels, plus pulmonary hypertension due to reduced vascular cross-sectional area.^[57]

2.6 Diagnostic Evaluation of Neonatal Respiratory Disease

2.6.1 Clinical Assessment

Clinical assessment is the first step in evaluating neonatal respiratory disease. Breathing pattern,

respiratory rate, heart rate and signs such as nasal flaring, grunting, retractions, cyanosis and apnea should be assessed to determine the severity of distress. Gestational age, delivery history, meconium exposure, maternal risk factors and antenatal findings should also be considered. Persistent oxygenation problems may suggest conditions such as pulmonary hypertension or congenital heart disease.^[58]

2.6.2 Chest radiography

Chest radiography is a key investigation for identifying the cause of neonatal respiratory distress. Typical findings can help differentiate conditions such as RDS, transient tachypnea and meconium aspiration syndrome. It can also detect pneumothorax, congenital diaphragmatic hernia and other lung abnormalities. When congenital lesions require further evaluation, additional imaging such as CT may be performed to guide diagnosis and treatment.^[59]



Figure 5: Chest radiograph showing the characteristic diffuse reticulogranular (“ground-glass”) appearance with air bronchograms, consistent with neonatal respiratory distress syndrome.

2.6.3 Laboratory Investigations

Laboratory tests help assess oxygenation, ventilation, infection and the overall condition of a newborn with respiratory distress. Common investigations include FBC, CRP, blood culture and ABG analysis. ABG helps evaluate gas exchange and acid-base balance, while FBC, CRP and cultures support the assessment of suspected infection. These results should always be interpreted together with clinical findings and imaging, as normal inflammatory markers cannot completely exclude infection.^[60]

2.6.4 Other Investigations

Pulse Oximetry Pulse oximetry is an important non-invasive investigation and is included among the first-line investigations for neonatal respiratory distress. It provides continuous information about oxygen saturation and helps identify hypoxemia.^[61]

Echocardiography

Echocardiography is particularly useful when a cardiac cause of respiratory distress is suspected. It plays an important role in diagnosing persistent pulmonary hypertension of the newborn (PPHN) and differentiating it from cyanotic congenital heart disease. In PPHN,

echocardiography can demonstrate the condition and help estimate pulmonary arterial pressure.^[62]

Pre- and Post-ductal Oxygen Saturation

Comparison of pre-ductal and post-ductal oxygen saturation can provide evidence of right-to-left shunting in PPHN. A significant difference between the two measurements may support the diagnosis.^[63]

Lung Ultrasound

Lung ultrasound is another useful investigation in neonatal respiratory disease. The article notes that ultrasound findings can help differentiate conditions such as transient tachypnoea of the newborn and respiratory distress syndrome.^[64]

Transillumination

In suspected pneumothorax, chest transillumination using a fibre-optic light may be useful, particularly when the infant is critically ill and rapid assessment is required.^[65]

2.7 MANAGEMENT

Management of neonatal respiratory diseases depends on the underlying cause, gestational age, severity of respiratory distress, and oxygenation status. The main goals are to maintain adequate oxygenation and ventilation, stabilize temperature and circulation, correct

metabolic abnormalities, and treat the specific cause. Early recognition of worsening respiratory distress is important because neonates can deteriorate rapidly.^[66]

2.7.1 Respiratory Support

Respiratory support is provided according to the severity of respiratory distress and the infant's oxygenation and ventilation status. Oxygen therapy and non-invasive respiratory support are preferred whenever they are sufficient, while invasive ventilation is reserved for babies who do not respond adequately to less invasive methods.^[67]

2.7.2 Oxygen Therapy

Supplemental oxygen is commonly used when a newborn develops hypoxemia. Oxygen may be delivered through a head box, nasal cannula or other suitable respiratory interface. The oxygen concentration should be adjusted according to oxygen saturation and the clinical condition of the infant. Continuous pulse-oximetry monitoring is useful for avoiding both inadequate oxygenation and unnecessary oxygen exposure. Careful control of oxygen is especially important in premature infants because prolonged exposure to excessive oxygen may contribute to complications such as retinopathy of prematurity and lung injury.^[68]

DRUGS USED IN NEONATAL RESPIRATORY DISEASES

Table 1: Commonly Used Drugs in the Management of Neonatal Respiratory Diseases.

DRUG	AGE	DOSE	MOA
Beractant (Survanta) – Surfactant	RDS, preterm <34 wks, from birth	100 mg/kg (4 mL/kg) intratracheal, q6h up to 4 dose	Lowers alveolar surface tension, prevents collapse, increases compliance, and increases FRC
Poractant alfa (Curosurf)	RDS, preterm	200 mg/kg initial, then 100 mg/kg q12h, max 300–400 mg/kg total	Animal-derived surfactant that lowers alveolar surface tension and prevents alveolar collapse.
Caffeine Citrate	Apnea of prematurity, <34 wks	Loading 20 mg/kg IV/PO, maintenance 5–10 mg/kg/day once daily	CNS stimulant and adenosine A1/A2 antagonist that increases central respiratory drive, CO ₂ sensitivity, and diaphragmatic contractility.
Dexamethasone	BPD prevention, >7 days age, ventilator dep	DART regimen – 0.15 mg/kg/day ×3 days, then taper over 10 days	Anti-inflammatory action that decreases pulmonary edema and inflammation and promotes surfactant production.
Inhaled Nitric Oxide (iNO)	PPHN, term and near-term >34 wks	20 ppm inhaled, wean to 5 ppm.	Selective pulmonary vasodilator → ↑ cGMP → relax smooth muscle → ↓ PVR, ↓ R-L shunt
Ampicillin + Gentamicin –	Neonatal pneumonia/sepsis.	0.15 mg/kg/dose q6h nebulization.	Cell wall synthesis inhibition + protein synthesis inhibiti
Salbutamol (Neb)	TTN with wheeze, BPD.	Ampicillin 50 mg/kg q12h, Gentamicin 4 mg/kg q24h (term), 0–7 days.	Beta2 agonist → bronchodilation, ↑ lung fluid clearance

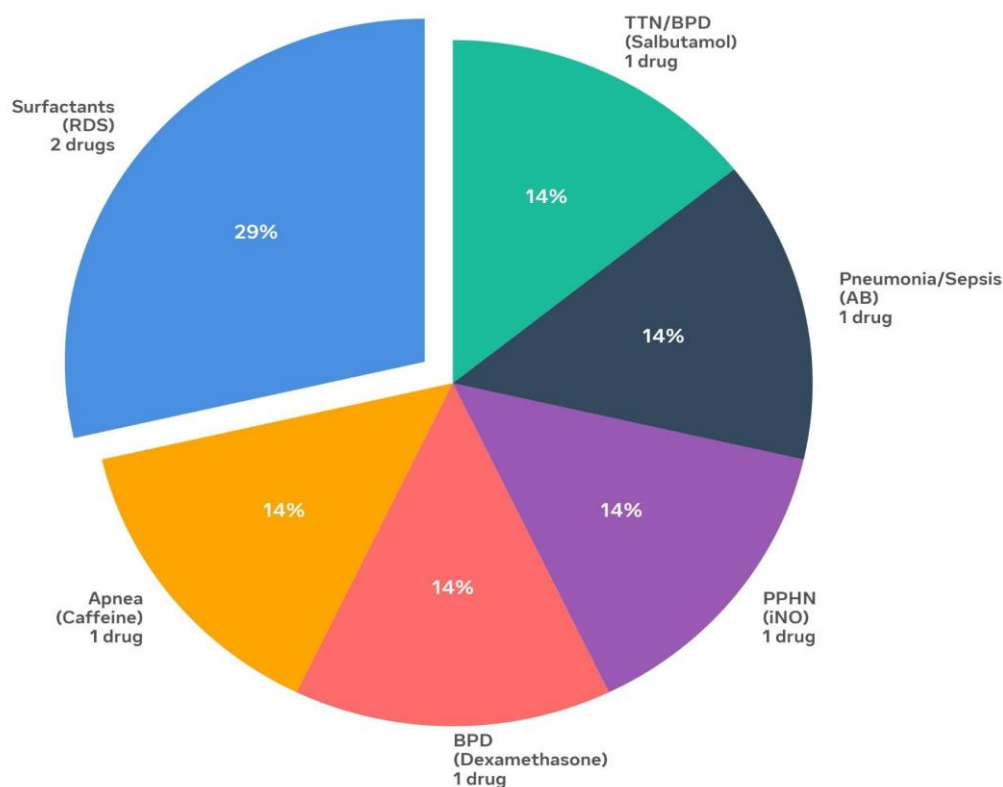


Figure 5: Pie Chart Showing Distribution of Drugs Used in Neonatal Respiratory Diseases by Indication (n=7) – Based on Table 5.

2.7.3 Advanced Techniques of Neonatal Respiratory Diseases

Neonatal respiratory care has changed considerably with the development of non-invasive ventilation, surfactant therapy, improved monitoring and bedside imaging. The main aim of modern treatment is to maintain adequate oxygenation and ventilation while avoiding unnecessary intubation and ventilator-induced lung injury. Current management is increasingly based on early identification of respiratory disease, gentle respiratory support and individualised treatment according to the condition of each newborn. CPAP, non-invasive intermittent positive-pressure ventilation, surfactant administration, lung-protective mechanical ventilation, high-frequency ventilation and lung ultrasound are now important components of advanced neonatal respiratory care.^[69]

2.7.4 Non-invasive respiratory support

Continuous positive airway pressure (CPAP) became an important method of neonatal respiratory support during the 1970s and is now widely used for premature infants with respiratory distress syndrome (RDS). CPAP keeps the alveoli open and reduces the work of breathing without requiring an endotracheal tube. It is particularly useful in spontaneously breathing preterm infants with RDS, and it may also be started immediately after birth in selected very preterm infants. The 2022 WHO

recommendations support CPAP for preterm infants with clinical signs of RDS.^[70]

2.7.5 Lung-protective mechanical ventilation

When non-invasive support is insufficient, mechanical ventilation may be required for severe RDS, recurrent apnoea, severe hypoxaemia, respiratory failure or other serious neonatal lung conditions. Modern ventilation aims to provide adequate gas exchange while limiting excessive pressure and volume exposure to the immature lung. Volume-targeted ventilation (VTV) and other lung-protective strategies are increasingly preferred when invasive ventilation is necessary. The European Consensus Guidelines recommend minimising the duration of mechanical ventilation and using lung-protective modes when ventilation is required.^[71]

2.7.6 Advanced monitoring and lung ultrasound

Lung ultrasound (LUS) has become an important bedside technique in neonatal respiratory care, particularly during the 2010s and early 2020s. Unlike chest radiography, it does not expose the newborn to ionising radiation and can be performed repeatedly at the bedside. LUS can help identify and differentiate conditions such as RDS, transient tachypnoea of the newborn, pneumonia and pneumothorax. It can also help assess disease severity and guide decisions regarding respiratory support and surfactant administration. By 2022, several reviews

described lung ultrasound as a useful tool not only for diagnosis but also for monitoring the response to treatment. However, adequate operator training and standardised interpretation remain important limitations.^[72]

Targeted treatment for pulmonary hypertension and difficult respiratory disease. Some newborns, particularly those with persistent pulmonary hypertension of the newborn (PPHN), meconium aspiration syndrome or severe hypoxic respiratory failure, require specialised management. Treatment may include optimised oxygenation and ventilation, echocardiographic assessment and, in selected cases, inhaled nitric oxide. In preterm infants, inhaled nitric oxide is generally not used routinely; current European guidance recommends restricting it to selected cases with documented pulmonary hypertension and severe respiratory distress.^[73]

2.7.7 Future perspectives

Future neonatal respiratory care is likely to become more personalised and less invasive. Artificial intelligence (AI) is already being investigated for prediction of respiratory deterioration, mechanical-ventilation requirements and bronchopulmonary dysplasia. AI-assisted analysis of chest images and lung ultrasound may eventually help clinicians recognise respiratory disease earlier and select appropriate treatment. However, a 2026 review found that current evidence is still limited by small studies, methodological differences and insufficient external validation, so these technologies are not yet ready to replace clinical assessment. Future research is also expected to focus on automated monitoring of oxygenation and ventilation, improved non-invasive interfaces, ultrasound-guided surfactant therapy, better prediction of BPD and therapies that support normal lung development. The overall direction is toward earlier diagnosis, gentler respiratory support, shorter exposure to invasive ventilation and more individualised treatment. These developments may improve survival while reducing long-term complications in very preterm and critically ill newborns.^[74]

2.8 PREVENTION

Prevention of neonatal respiratory diseases mainly focuses on reducing the risk of prematurity, improving lung maturity before birth, providing appropriate care during delivery, and preventing infection or lung injury after birth. Preventive measures can be considered at the antenatal, intrapartum and postnatal stages. Appropriate perinatal planning and early respiratory support can reduce respiratory morbidity in newborns, particularly in preterm infants.^[75]

2.8.1 Antenatal Prevention – Antenatal Steroids, MgSO₄

Antenatal prevention of neonatal respiratory problems mainly focuses on reducing complications of preterm

birth. Antenatal corticosteroids promote fetal lung maturation and surfactant production, thereby reducing the risk of respiratory distress syndrome. Magnesium sulfate is recommended before very preterm birth mainly for fetal neuroprotection. Early identification of high-risk pregnancies, treatment of maternal infections, and planned delivery in a suitable perinatal centre can further improve neonatal outcomes.^[76]

2.8.2 Intrapartum Prevention Proper Resuscitation

Intrapartum prevention focuses on providing safe care immediately after birth and reducing the risk of respiratory complications. Newborns should be assessed promptly for breathing and heart rate, with warmth maintained and resuscitation provided when needed. Apnoeic or gasping infants with significant bradycardia require prompt positive-pressure ventilation. In spontaneously breathing preterm infants, early nasal CPAP may provide respiratory support while reducing the need for invasive ventilation.^[77]

2.8.3 Postnatal Prevention – Infection Control, Gentle Ventilation

Postnatal prevention focuses on reducing infection, maintaining adequate oxygenation and preventing additional lung injury. Infection-control practices are particularly important because newborns, especially preterm infants, have immature immune systems and are vulnerable to healthcare-associated infections.^[78]

CONCLUSION

Neonatal respiratory diseases are important causes of morbidity and mortality, particularly among preterm and low-birth-weight infants. Their development is closely related to the maturity of the fetal lungs, surfactant production, clearance of fetal lung fluid, pulmonary vascular adaptation, infection, aspiration, and congenital abnormalities. Early recognition of respiratory distress through clinical signs, oxygen saturation monitoring, appropriate laboratory investigations, imaging, echocardiography, and lung ultrasound is essential for timely diagnosis and treatment.

Management should be individualized according to gestational age, underlying cause, and severity of respiratory disease. Appropriate oxygen therapy and early non-invasive respiratory support can reduce the need for invasive ventilation, while surfactant therapy and lung-protective ventilation are important in severe disease. Advanced techniques such as CPAP, lung-protective mechanical ventilation, lung ultrasound, targeted management of pulmonary hypertension, and improved bedside monitoring have strengthened modern neonatal respiratory care.

Prevention through antenatal corticosteroids, appropriate perinatal care, infection prevention, early respiratory support, and gentle ventilation can further reduce respiratory complications. Future developments, including artificial intelligence-assisted prediction,

automated monitoring, improved non-invasive interfaces, and ultrasound-guided therapies, may allow earlier diagnosis and more individualized treatment. However, these emerging technologies still require further clinical validation. Overall, early diagnosis, timely intervention, lung-protective strategies, and individualized neonatal care are essential to improve survival and reduce long-term respiratory complications.

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