How to Cite:
Al-Mutairi, N. S. A., Alotaibi, F. Z. H., Alqahtani, M. N. A., Aldossri, H. A. Z., Saleh, S., Alharthi, M. M. H., Almutairi, M. A., Alruqi, M. K., & Alotaibi, A. S. M. (2018). Neonatal respiratory distress syndrome: Current evidence and clinical management for nursing and health assistant practice. *International Journal of Health Sciences*, *2*(S1), 555–573. https://doi.org/10.53730/ijhs.v2nS1.15978

Neonatal respiratory distress syndrome: Current evidence and clinical management for nursing and health assistant practice

Nader Saad Awad Al-Mutairi
National Guard Health Affairs

Faisal Zabin Hashar Alotaibi
National Guard Health Affairs

Mohammad Naseer Ali Alqahtani
National Guard Health Affairs

Hzam Alkorbi Zid Aldossri
National Guard Health Affairs

Shaie Saleh
National Guard Health Affairs

Mashan Mashal Hubaylis Alharthi
National Guard Health Affairs

Muteb Abdullah Almutairi
Ministry of National Guard

Mohammed Khalaf Alruqi
King Abdulaziz Medical City, Al-Ahsa

Abdullah Saleh Mohammed Alotaibi
National Guard Health Affairs, Riyadh

***Abstract*---Background:** Neonatal Respiratory Distress Syndrome (RDS) remains one of the leading causes of neonatal morbidity and mortality among premature infants worldwide. The condition primarily develops because of pulmonary surfactant deficiency resulting from incomplete fetal lung maturation, leading to alveolar collapse, impaired gas exchange, respiratory failure, and prolonged neonatal intensive care admission. **Aim:** This review aimed to provide an updated evidence-based overview of the etiology, pathophysiology,

Manuscript submitted: 27 April 2018, Manuscript revised: 09 May 2018, Accepted for publication: 15 June 2018

epidemiology, clinical manifestations, diagnostic evaluation, and current management strategies of neonatal RDS, with emphasis on the clinical roles of nurses and health assistants in improving neonatal outcomes. **Methods:** A comprehensive narrative review was conducted using current evidence from published clinical guidelines, peer-reviewed literature, and recent studies addressing fetal lung development, surfactant biology, genetic susceptibility, diagnostic modalities, respiratory support, surfactant replacement therapy, supportive care, and emerging individualized treatment approaches. **Results:** Prematurity remains the strongest determinant of neonatal RDS because of insufficient surfactant production and structural pulmonary immaturity. Early recognition through clinical assessment, blood gas analysis, chest imaging, and lung ultrasound facilitates timely intervention. Current management prioritizes antenatal corticosteroid administration, early continuous positive airway pressure (CPAP), selective rescue surfactant therapy, lung-protective ventilation, and comprehensive supportive care. Less invasive surfactant administration techniques and precision medicine approaches have demonstrated promising improvements in respiratory outcomes while reducing complications associated with invasive mechanical ventilation. **Conclusion:** Neonatal RDS continues to represent a major clinical challenge despite substantial advances in neonatal intensive care. Early diagnosis, prompt respiratory stabilization, individualized surfactant therapy, and coordinated multidisciplinary management significantly improve survival and reduce both short- and long-term complications.

***Keywords*---**Neonatal respiratory distress syndrome, prematurity, pulmonary surfactant, continuous positive airway pressure, surfactant replacement therapy, neonatal intensive care, lung ultrasound, respiratory support, neonatal nursing, health assistants.

Introduction

Respiratory distress syndrome (RDS) is one of the most prevalent and clinically significant respiratory disorders affecting preterm neonates and continues to represent a major challenge in neonatal intensive care worldwide. The condition primarily results from inadequate synthesis and secretion of pulmonary surfactant by immature type II alveolar pneumocytes, leading to impaired alveolar stability and ineffective pulmonary gas exchange. Because surfactant plays a critical role in reducing alveolar surface tension and maintaining functional residual capacity, its deficiency predisposes the lungs to widespread alveolar collapse during expiration, resulting in decreased pulmonary compliance, impaired oxygenation, ventilation-perfusion mismatch, and progressive respiratory insufficiency. The incidence of RDS is inversely proportional to gestational age, with the highest frequency occurring among infants delivered before 34 weeks of gestation due to incomplete structural and biochemical maturation of the lungs. Consequently, RDS remains one of the leading causes of neonatal morbidity and mortality, contributing substantially to prolonged

hospitalization, increased healthcare utilization, and adverse short- and long-term clinical outcomes in premature infants [1][2]. The clinical manifestations of respiratory distress syndrome generally become evident immediately after birth or within the first few hours of life as the newborn experiences increasing respiratory compromise. Affected infants commonly present with tachypnea, expiratory grunting, nasal flaring, intercostal and subcostal chest retractions, diminished breath sounds, and varying degrees of central cyanosis resulting from inadequate oxygenation. As pulmonary dysfunction progresses, persistent hypoxemia, hypercapnia, respiratory acidosis, and respiratory fatigue may develop, necessitating prompt recognition and intervention to prevent irreversible organ injury and cardiorespiratory collapse. Early diagnosis relies on comprehensive clinical assessment combined with radiographic evaluation demonstrating characteristic diffuse reticulogranular infiltrates and air bronchograms, together with arterial or capillary blood gas analysis that confirms impaired oxygenation and ventilation. Accurate and timely diagnosis is essential for initiating evidence-based therapeutic interventions before significant respiratory deterioration occurs [1][2].

Contemporary management of neonatal respiratory distress syndrome is centered on early stabilization of respiratory function while minimizing ventilator-induced lung injury and other treatment-related complications. Exogenous surfactant replacement therapy remains the cornerstone of treatment, effectively restoring alveolar stability, improving pulmonary compliance, and enhancing gas exchange. Noninvasive respiratory support, particularly continuous positive airway pressure (CPAP), is widely recommended as the preferred initial strategy because it maintains alveolar recruitment while reducing the need for invasive mechanical ventilation. Mechanical ventilation is reserved for neonates with severe respiratory compromise or those who fail to respond adequately to noninvasive support. Equally important are preventive strategies, especially the administration of antenatal corticosteroids to women at risk of preterm birth, which significantly accelerates fetal lung maturation, enhances endogenous surfactant production, and reduces both the incidence and severity of RDS. Optimal management requires a coordinated multidisciplinary approach involving neonatologists, neonatal nurses, respiratory therapists, pharmacists, and other healthcare professionals who collaboratively deliver evidence-based care, ensure continuous monitoring, prevent complications, and improve survival while promoting favorable long-term developmental outcomes in this highly vulnerable patient population [1][2].

Etiology

Neonatal respiratory distress syndrome (RDS) is primarily caused by a quantitative deficiency or functional impairment of pulmonary surfactant, a phospholipid-rich substance synthesized by type II alveolar pneumocytes that is essential for maintaining alveolar stability during respiration. Surfactant lowers surface tension at the air–liquid interface within the alveoli, thereby preventing alveolar collapse during expiration and facilitating efficient pulmonary gas exchange. In premature infants, structural and biochemical immaturity of the lungs results in inadequate surfactant synthesis, storage, and secretion, predisposing the neonate to diffuse atelectasis, reduced lung compliance,

impaired oxygenation, and progressive respiratory insufficiency. Prematurity remains the most significant predisposing factor because fetal pulmonary maturation is incomplete before the final weeks of gestation, leaving the lungs incapable of sustaining effective extrauterine respiration. In addition to reduced surfactant production, functional inactivation of surfactant by protein leakage, inflammatory mediators, or pulmonary edema may further exacerbate respiratory dysfunction and contribute to disease severity. Consequently, the etiology of neonatal RDS reflects the combined effects of pulmonary immaturity and surfactant deficiency, both of which are intrinsically linked to gestational age and fetal lung development [1]. A comprehensive understanding of fetal lung development provides the physiological basis for explaining the pathogenesis of neonatal respiratory distress syndrome. Lung development proceeds through five sequential stages, namely the embryonic, pseudoglandular, canalicular, saccular, and alveolar phases, each characterized by distinct structural and functional maturation that ultimately prepares the fetus for effective respiration after birth [1]. The embryonic stage begins approximately 26 days after conception with the appearance of the primitive lung bud as a ventral diverticulum arising from the developing foregut. Rapid elongation and repeated branching of this structure into the surrounding mesenchymal tissue subsequently give rise to the primary bronchial tree. By approximately 37 days of gestation, the mainstem bronchi have formed, while continued branching results in the development of segmental and subsegmental bronchi by approximately 48 days. Simultaneously, pulmonary vascular development progresses through formation of the pulmonary arterial system from the sixth aortic arch, establishing the vascular framework necessary for subsequent gas exchange [2].

The pseudoglandular stage extends from approximately the fifth to the sixteenth week of gestation and is characterized by extensive airway branching and differentiation of the proximal conducting airways. During this period, multiple epithelial cell populations, including ciliated cells, goblet cells, basal cells, cartilage-forming cells, and neuroepithelial cells, undergo progressive differentiation within the developing bronchial tree. Repeated dichotomous branching results in the formation of an increasingly complex airway network, with approximately fifteen to twenty generations of branching completed by the eighteenth week of gestation. Although substantial anatomical development occurs during this stage, the pulmonary parenchyma remains incapable of supporting extrauterine gas exchange because functional respiratory units have not yet matured [2]. The canalicular stage, occurring between approximately the sixteenth and twenty-fifth weeks of gestation, represents a critical milestone in pulmonary maturation because it marks the initial development of structures capable of limited gas exchange. During this phase, terminal bronchioles give rise to respiratory bronchioles and primitive acinar structures, while rapid capillary proliferation progressively reduces the thickness of the intervening mesenchyme. Fusion of the capillary and epithelial basement membranes establishes the primitive blood–air barrier, thereby creating the anatomical foundation necessary for oxygen and carbon dioxide diffusion. Equally important, glycogen-rich cuboidal epithelial cells begin differentiating into type II alveolar pneumocytes, within which lamellar bodies first appear at approximately 20 weeks of gestation. These intracellular organelles serve as storage sites for pulmonary surfactant and signify the onset of endogenous surfactant synthesis, although production

remains insufficient to maintain adequate alveolar stability in extremely premature infants [3].

Further pulmonary maturation occurs during the saccular stage, which extends from approximately the twenty-fourth to the thirty-second week of gestation. This phase is characterized by the formation of terminal saccules and respiratory bronchioles that possess progressively thinner walls and an expanding capillary network capable of supporting increasingly efficient gaseous exchange. Continued differentiation of type II pneumocytes results in greater surfactant synthesis and secretion, thereby improving pulmonary compliance and increasing the likelihood of neonatal survival following premature birth. Nevertheless, infants delivered during this developmental period often remain at considerable risk of respiratory distress syndrome because endogenous surfactant production has not yet reached physiologically adequate levels to sustain normal postnatal respiratory function [3]. The final stage of pulmonary development, known as the alveolar stage, begins at approximately 32 weeks of gestation and continues throughout infancy and early childhood. This stage is characterized by extensive septation of terminal saccules and the progressive formation of mature alveoli, substantially expanding the available surface area for pulmonary gas exchange. By full-term gestation, the neonatal lungs contain approximately 50 to 150 million alveoli, accompanied by significant maturation of both surfactant metabolism and pulmonary microvascular architecture. These developmental changes optimize respiratory efficiency and markedly reduce the risk of surfactant deficiency. Consequently, the progressive maturation of pulmonary structure and surfactant production throughout fetal development explains the strong inverse relationship between gestational age and the incidence of neonatal respiratory distress syndrome, emphasizing why extremely preterm infants remain the population at greatest risk for this potentially life-threatening condition [1][2][3].

Surfactant

Pulmonary surfactant is a highly specialized lipoprotein complex that forms a continuous monolayer along the internal surface of the alveoli, where it performs an indispensable role in maintaining normal pulmonary mechanics and efficient gaseous exchange after birth. During intrauterine life, the fetal lungs remain fluid-filled and do not participate in oxygenation because gas exchange occurs through the placenta. Consequently, surfactant synthesis represents one of the most critical maturational processes that prepares the fetal lungs for the transition to extrauterine life. Production of surfactant begins at approximately 20 weeks of gestation within alveolar type II pneumocytes and progressively increases throughout the later stages of fetal development, reaching functionally sufficient concentrations near term. Premature birth interrupts this developmental process, leaving the immature lungs with inadequate quantities of functionally active surfactant and substantially increasing the risk of neonatal respiratory distress syndrome (RDS) [4][5][6]. The biochemical composition of pulmonary surfactant reflects its highly specialized physiological function. Approximately 70% to 80% of the complex consists of phospholipids, predominantly dipalmitoylphosphatidylcholine, which is primarily responsible for reducing alveolar surface tension. The remaining composition includes nearly 10% neutral lipids and approximately 10% surfactant-associated proteins that

collectively regulate surfactant synthesis, secretion, recycling, and host defense. Four principal surfactant proteins have been identified, namely surfactant proteins A, B, C, and D (SP-A, SP-B, SP-C, and SP-D), each contributing unique structural and functional properties to the surfactant system. SP-A and SP-D are hydrophilic proteins that participate extensively in innate immune defense by modulating inflammatory responses, enhancing pathogen clearance, and regulating pulmonary immune homeostasis. In contrast, SP-B and SP-C are hydrophobic proteins that play essential roles in optimizing surfactant spreading across the alveolar surface and maintaining its stability during repetitive respiratory cycles. SP-B is indispensable for the formation of lamellar bodies and the proper processing of SP-C, whereas SP-C works synergistically with SP-B to enhance adsorption of phospholipids onto the alveolar surface, thereby maximizing surface tension reduction and improving alveolar stability [4][5][6].

The synthesis and secretion of pulmonary surfactant involve a complex sequence of intracellular events that require coordinated cellular metabolism and organelle function. Phospholipid synthesis begins within the endoplasmic reticulum of type II alveolar epithelial cells before the newly synthesized components are transported to the Golgi apparatus for further processing and packaging. These constituents are subsequently assembled into highly organized lamellar bodies, which function as specialized intracellular storage organelles located near the apical membrane of type II pneumocytes. Upon appropriate physiological stimulation, lamellar bodies fuse with the cell membrane and release their contents into the alveolar lumen through exocytosis. Once secreted, the surfactant rapidly disperses across the air-liquid interface to establish a stable monolayer capable of reducing surface tension throughout the respiratory cycle. This intricate secretory process ensures that adequate quantities of surfactant remain continuously available to support effective pulmonary function immediately after birth [7]. The physiological importance of surfactant extends beyond its role as a surface-active agent. During respiration, elastic recoil forces generated by both the lung parenchyma and the thoracic cage, together with the intrinsic surface tension at the alveolar air-fluid interface, create a natural tendency for alveolar collapse, particularly within smaller alveoli. Pulmonary surfactant markedly lowers this surface tension, thereby preventing end-expiratory alveolar collapse, preserving functional residual capacity, and maintaining uniform alveolar inflation. By stabilizing alveoli of varying sizes, surfactant improves pulmonary compliance, reduces the work of breathing, facilitates efficient oxygen diffusion, and minimizes energy expenditure during ventilation. In addition, surfactant limits transudation of fluid from the pulmonary interstitium into the alveolar spaces, thereby reducing the likelihood of pulmonary edema and preserving optimal conditions for gas exchange [7].

Homeostasis of the surfactant system depends not only on continuous synthesis but also on efficient recycling mechanisms. Following secretion into the alveolar space, a substantial proportion of surfactant is reabsorbed by type II pneumocytes through receptor-mediated endocytosis. Internalized surfactant components are transported into multivesicular bodies and subsequently reprocessed within lamellar bodies before being re-secreted into the alveolar lumen. This recycling pathway conserves metabolic resources while maintaining a stable alveolar surfactant pool capable of responding rapidly to changing

respiratory demands. In premature infants, however, both quantitative and qualitative deficiencies impair this finely regulated system. The total amount of surfactant produced is markedly reduced, and alterations in phospholipid composition together with immature surfactant protein expression diminish its functional activity. These deficiencies significantly compromise alveolar stability, leading to widespread atelectasis, impaired lung compliance, ventilation-perfusion mismatch, hypoxemia, and the clinical manifestations of neonatal respiratory distress syndrome [8]. Genetic factors have emerged as important contributors to individual susceptibility and disease severity in neonatal respiratory distress syndrome, complementing the well-established influence of prematurity. Advances in molecular genetics and genomic research have demonstrated that inherited variations affecting lung development, surfactant metabolism, and pulmonary epithelial maturation significantly influence the risk of developing RDS. Increasing evidence indicates that both genetic and environmental determinants interact throughout fetal development, creating substantial variability in disease susceptibility even among infants of similar gestational age. Consequently, abnormalities affecting developmental signaling pathways have become important areas of investigation for future therapeutic interventions, with growing interest in precision medicine approaches that tailor preventive and therapeutic strategies according to individual genetic profiles [9].

Evidence supporting a hereditary component in neonatal RDS has been strengthened by epidemiological observations demonstrating higher concordance rates among monozygotic twins than dizygotic twins, as well as recurrent familial clustering of severe disease. These findings indicate that inherited genetic variants contribute significantly to pulmonary maturation and surfactant function beyond the influence of environmental factors alone. Although prematurity remains the principal determinant of surfactant deficiency, genetic predisposition may explain why some preterm infants experience disproportionately severe respiratory disease despite comparable gestational ages and clinical circumstances [10]. Several rare but clinically significant mutations affecting surfactant-associated proteins have been identified as direct causes of severe neonatal respiratory disease. Autosomal recessive mutations involving the SP-B gene produce profound surfactant dysfunction characterized by severe neonatal respiratory distress, progressive respiratory failure, and frequently fatal outcomes without advanced supportive therapies or lung transplantation. Mutations involving the SP-C gene occur less frequently and generally present later in life with chronic interstitial lung disease rather than classic neonatal RDS, although neonatal manifestations may occasionally occur. Additional pathogenic variants involving the ATP-binding cassette transporter subfamily A member 3 (ABCA3) gene impair intracellular surfactant processing and lamellar body formation, resulting in variable degrees of surfactant deficiency and respiratory failure. Approximately 4% of the general population carries ABCA3 gene variants, although the precise incidence of severe or fatal neonatal RDS associated with these mutations remains incompletely defined. Continued investigation into these genetic abnormalities is expected to improve diagnostic accuracy, facilitate early identification of high-risk infants, and support the development of targeted therapies capable of improving long-term respiratory outcomes in affected neonates [11][12][13].

Epidemiology

Neonatal respiratory distress syndrome (RDS) remains the most prevalent cause of respiratory compromise among preterm infants and continues to represent a major challenge in neonatal intensive care units worldwide. Despite significant advances in perinatal medicine, including the widespread use of antenatal corticosteroids, exogenous surfactant therapy, and improved neonatal respiratory support, RDS continues to contribute substantially to neonatal morbidity, prolonged hospitalization, and mortality, particularly among extremely preterm and very low birth weight infants. In the United States alone, approximately 24,000 newborns develop RDS each year, making it the most frequent complication associated with prematurity and one of the principal causes of admission to neonatal intensive care units. Because respiratory distress in newborns may arise from several pulmonary and extrapulmonary disorders, accurate epidemiological assessment requires careful clinical evaluation and standardized diagnostic criteria to distinguish RDS from other neonatal respiratory conditions. Prematurity remains the single most important determinant of RDS because pulmonary surfactant production and structural lung maturation are highly dependent on gestational age. As gestational age decreases, the risk of surfactant deficiency rises dramatically, resulting in a corresponding increase in disease incidence and severity. Low birth weight, particularly among very low birth weight and extremely low birth weight infants, further amplifies the risk owing to the close relationship between fetal growth restriction, pulmonary immaturity, and inadequate surfactant synthesis. Additional epidemiological studies have identified several independent risk factors that increase susceptibility to RDS, including male sex, White race, late preterm birth, maternal diabetes mellitus, perinatal hypoxia and ischemia, and delivery by elective cesarean section without preceding labor. These factors may interfere with fetal lung maturation or delay the physiological hormonal changes that stimulate surfactant production before birth [14]. The incidence of neonatal RDS demonstrates a strong inverse relationship with gestational age. Data obtained from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network revealed that approximately 98% of infants born at 24 weeks of gestation develop RDS, reflecting the profound immaturity of the fetal lungs at this stage. The incidence decreases progressively with advancing gestational age, falling to approximately 5% among infants delivered at 34 weeks and to less than 1% in term infants born at 37 weeks of gestation or later [15]. These epidemiological trends underscore the critical importance of strategies aimed at preventing preterm birth, promoting fetal lung maturation, and ensuring timely implementation of evidence-based neonatal interventions to reduce the global burden of respiratory distress syndrome.

Pathophysiology

The pathophysiology of neonatal respiratory distress syndrome (RDS) is fundamentally related to pulmonary surfactant deficiency resulting from structural and functional immaturity of the developing lung. Surfactant is synthesized and secreted by alveolar type II pneumocytes and plays an essential role in reducing surface tension at the air-liquid interface within the alveoli. In premature infants, inadequate production or impaired function of surfactant

markedly increases alveolar surface tension, causing widespread alveolar instability and collapse during expiration. As a consequence, lung compliance decreases substantially, the work of breathing increases, and effective pulmonary gas exchange becomes progressively compromised. These physiological disturbances lead to the rapid development of respiratory insufficiency shortly after birth and explain why RDS predominantly affects infants born before complete pulmonary maturation. The mechanical abnormalities observed in RDS can be explained by Laplace's law, expressed by the equation $P = 2T/R$, where P represents the pressure required to maintain alveolar patency, T denotes surface tension, and R represents the radius of the alveolus. According to this principle, increases in alveolar surface tension require proportionally greater distending pressure to prevent alveolar collapse. In the absence of adequate surfactant, small alveoli become highly unstable and repeatedly collapse during expiration, resulting in diffuse atelectasis throughout the lungs. This widespread collapse significantly reduces functional residual capacity, impairs pulmonary compliance, and produces ventilation abnormalities that compromise oxygenation and carbon dioxide elimination. Consequently, affected neonates must generate considerably greater inspiratory effort to reopen collapsed alveoli, further increasing respiratory workload and contributing to respiratory fatigue.

Persistent atelectasis initiates a cascade of pathological events that extend beyond mechanical impairment. Repeated collapse and reopening of alveoli produce mechanical injury to the delicate respiratory epithelium, stimulating the release of inflammatory cytokines and activating local inflammatory pathways. The resulting inflammatory response increases pulmonary vascular permeability, allowing protein-rich fluid to leak from the pulmonary capillaries into the alveolar spaces. This proteinaceous edema fluid further inhibits surfactant activity by disrupting its phospholipid composition and reducing its surface tension-lowering properties, thereby creating a vicious cycle in which surfactant dysfunction promotes additional alveolar collapse and inflammation [16][17]. Many infants with moderate or severe RDS require respiratory support using positive-pressure ventilation to maintain adequate oxygenation and ventilation. Although lifesaving, mechanical ventilation may contribute to further pulmonary injury when excessive airway pressures or tidal volumes produce alveolar overdistension. Ventilator-induced lung injury results in epithelial and endothelial damage, amplifies inflammatory responses, and accelerates pulmonary edema formation. Simultaneously, exposure to high concentrations of supplemental oxygen generates reactive oxygen species that induce oxidative stress within immature pulmonary tissues. Oxidative injury promotes protein oxidation and lipid peroxidation within surfactant molecules, converting active surfactant into biologically inactive forms and further impairing alveolar stability [18][19][20].

The combined effects of surfactant deficiency, alveolar collapse, pulmonary edema, inflammation, and ventilator-associated injury ultimately produce profound abnormalities in pulmonary gas exchange. Hypoxemia develops through multiple interacting mechanisms, including widespread alveolar hypoventilation, impaired diffusion of oxygen across the alveolar-capillary membrane, ventilation-perfusion mismatch, and intrapulmonary right-to-left shunting caused by non-ventilated but perfused alveoli. As oxygen delivery to tissues declines, cellular metabolism shifts from aerobic to anaerobic pathways, leading to excessive lactate

production and the development of metabolic acidosis. If untreated, progressive hypoxemia, hypercapnia, and acidosis further impair cardiovascular function, reduce tissue perfusion, and contribute to multiorgan dysfunction. Understanding these interconnected pathophysiological mechanisms forms the foundation for evidence-based therapeutic strategies, including surfactant replacement therapy, lung-protective ventilation, optimized oxygen administration, and comprehensive supportive care aimed at minimizing pulmonary injury while improving neonatal survival and long-term respiratory outcomes.

History and Physical

The clinical history and physical examination play a fundamental role in the early recognition and diagnosis of neonatal respiratory distress syndrome (RDS), particularly among premature infants who possess multiple risk factors for pulmonary immaturity. The condition predominantly affects neonates born before 34 weeks of gestation, although it may also occur in late preterm infants with delayed pulmonary maturation. A detailed maternal and perinatal history should include gestational age, antenatal corticosteroid administration, maternal diabetes mellitus, mode of delivery, evidence of fetal distress, and any pregnancy or delivery complications that may influence fetal lung development. Symptoms of RDS usually become evident immediately after birth or within the first few minutes of extrauterine life, reflecting the inability of the immature lungs to maintain adequate gas exchange following the transition from fetal to neonatal circulation. Physical examination typically demonstrates progressive signs of respiratory distress resulting from increased work of breathing. Tachypnea is usually the earliest and most consistent clinical manifestation, often accompanied by expiratory grunting, which represents a compensatory mechanism to maintain positive end-expiratory pressure and prevent alveolar collapse. Nasal flaring is commonly observed as the infant attempts to reduce airway resistance and improve airflow, while chest wall retractions involving the intercostal, subcostal, subxiphoid, and suprasternal regions indicate increased inspiratory effort secondary to reduced lung compliance. Recruitment of accessory respiratory muscles further reflects the severity of respiratory compromise and the increasing energy expenditure required to sustain adequate ventilation. Auscultation generally reveals diffusely diminished breath sounds throughout both lung fields because of widespread alveolar collapse and reduced air entry. Cyanosis may be present, particularly around the lips and extremities, indicating inadequate oxygenation despite increased respiratory effort. Poor peripheral perfusion, prolonged capillary refill time, cool extremities, and diminished peripheral pulses may develop as hypoxemia and reduced cardiac output impair systemic tissue perfusion. Continuous assessment of oxygen saturation, heart rate, respiratory rate, and overall clinical appearance is therefore essential to identify progressive deterioration and guide timely therapeutic intervention. Without prompt treatment, the clinical condition usually worsens over the subsequent 48 to 72 hours as surfactant deficiency leads to increasing atelectasis, impaired gas exchange, and respiratory muscle fatigue. Infants may become progressively lethargic, demonstrate reduced responsiveness, and develop recurrent episodes of apnea due to respiratory failure and central respiratory depression [22]. As systemic hypoxemia and tissue hypoperfusion become more severe, additional

findings such as oliguria, decreased urine output, peripheral edema, and metabolic instability may emerge, reflecting compromised renal perfusion and multiorgan involvement. Careful and repeated physical assessment remains essential for monitoring disease progression, evaluating treatment response, and identifying complications that require escalation of respiratory and supportive care.

Evaluation

The evaluation of neonatal respiratory distress syndrome (RDS) requires integration of maternal and perinatal history, clinical findings, imaging studies, and laboratory investigations to establish an accurate diagnosis and assess disease severity. Because the clinical manifestations of RDS overlap with other causes of neonatal respiratory distress, diagnosis relies on a comprehensive assessment rather than a single diagnostic criterion. Infants typically present with tachypnea, expiratory grunting, nasal flaring, chest retractions, cyanosis, and diminished breath sounds, while arterial blood gas analysis commonly demonstrates hypoxemia, hypercapnia, and progressive respiratory and metabolic acidosis, including lactic acidemia in severe cases. Chest radiography remains a key diagnostic tool and classically demonstrates diffuse bilateral reticulogranular or ground-glass opacities, low lung volumes, and prominent air bronchograms caused by widespread alveolar collapse. More recently, lung ultrasound (LUS) has emerged as a highly accurate bedside imaging modality with greater sensitivity and specificity than chest radiography for diagnosing RDS, grading disease severity, and guiding therapeutic decisions such as surfactant administration [23][24]. Additional investigations include echocardiography to identify associated conditions such as patent ductus arteriosus and laboratory studies including complete blood count to detect anemia or evidence of infection. When neonatal sepsis is suspected, blood, cerebrospinal fluid, and tracheal cultures, when clinically indicated, should be obtained to exclude infectious causes of respiratory distress and ensure appropriate management.

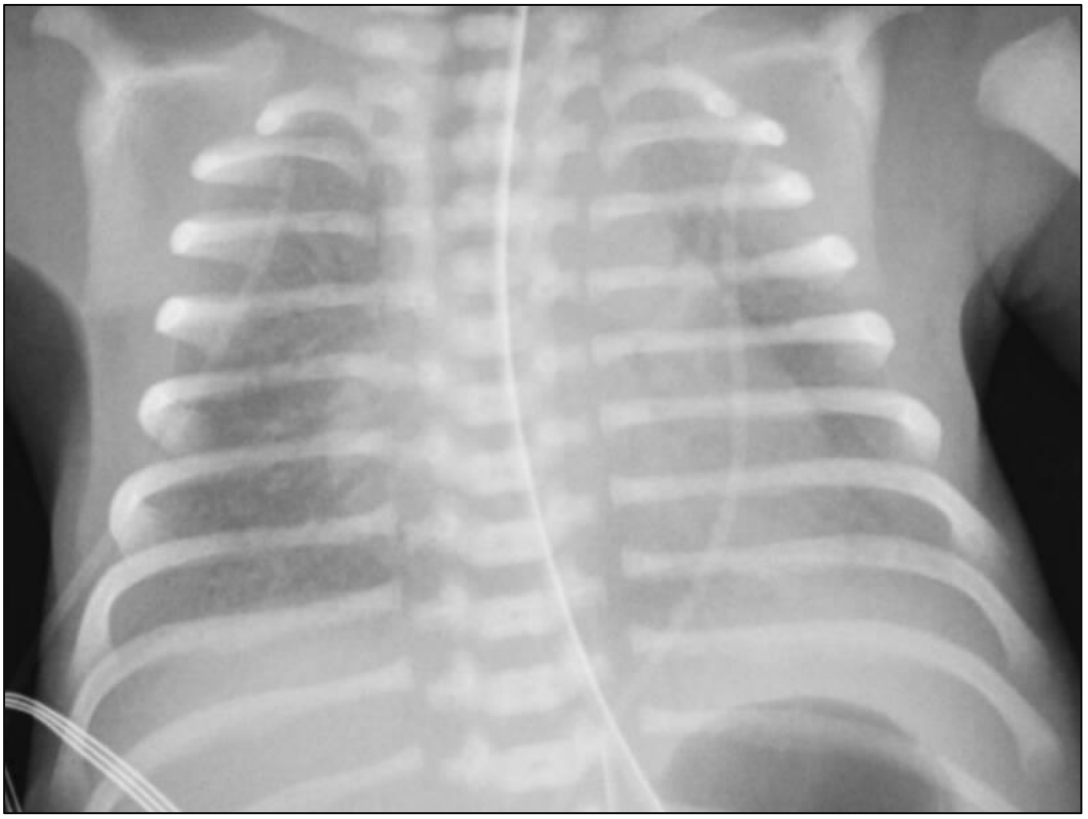

Figure 1: Respiratory distress syndrome

Treatment / Management

The management of neonatal respiratory distress syndrome (RDS) focuses on correcting surfactant deficiency, maintaining adequate oxygenation and ventilation, minimizing ventilator-induced lung injury, and providing comprehensive supportive care to optimize survival and reduce long-term pulmonary complications. Advances in neonatal intensive care have significantly improved outcomes through the integration of preventive strategies, early respiratory support, exogenous surfactant replacement, and individualized management based on the infant's gestational age, clinical condition, and physiological response to treatment. Successful management requires close collaboration among neonatologists, neonatal nurses, respiratory therapists, pharmacists, nutritionists, and other healthcare professionals to ensure continuous monitoring and timely intervention throughout hospitalization. One of the most effective preventive strategies is the administration of antenatal corticosteroids to pregnant women at risk of preterm delivery. Corticosteroids accelerate fetal lung maturation by stimulating the differentiation of type II pneumocytes and increasing endogenous surfactant synthesis, thereby reducing both the incidence and severity of RDS. In addition to lowering respiratory morbidity, antenatal corticosteroid therapy has been associated with reductions in neonatal mortality, intraventricular hemorrhage, and necrotizing enterocolitis, making it a cornerstone of contemporary perinatal care [25][26]. When combined

with delivery in facilities equipped with neonatal intensive care services, antenatal corticosteroids substantially improve outcomes among premature infants. Following birth, continuous monitoring of respiratory function is essential to guide therapeutic decisions and evaluate treatment effectiveness. Arterial blood gas analysis remains an important component of respiratory assessment, particularly in critically ill infants requiring advanced respiratory support. Blood gas measurements are ideally obtained through sterile placement of an umbilical or peripheral arterial catheter to minimize repeated arterial punctures while allowing frequent monitoring. Treatment aims to maintain arterial oxygen tension (PaO_2) between 50 and 80 mm Hg, arterial carbon dioxide tension ($PaCO_2$) between 40 and 55 mm Hg, and an arterial pH above 7.25, thereby ensuring adequate tissue oxygenation while avoiding complications associated with excessive oxygen exposure or severe hypercapnia. Continuous pulse oximetry has become the standard method for noninvasive monitoring of oxygen saturation and facilitates prompt adjustment of inspired oxygen concentration. However, pulse oximetry alone cannot accurately identify hyperoxia at higher saturation levels because arterial oxygen tension may remain excessively elevated despite oxygen saturation values above 95%. Consequently, adjunctive techniques such as transcutaneous carbon dioxide monitoring and noninvasive capnography are increasingly employed to provide more comprehensive assessment of ventilatory status and guide respiratory management.

Respiratory support constitutes the foundation of neonatal RDS treatment. The principal objective is to maintain adequate functional residual capacity, prevent alveolar collapse, improve pulmonary compliance, and reduce the work of breathing while minimizing lung injury. Current evidence strongly supports early initiation of continuous positive airway pressure (CPAP) as the preferred initial respiratory strategy for preterm infants with spontaneous breathing and clinical evidence of RDS. Nasal CPAP provides continuous positive distending pressure that stabilizes alveoli throughout the respiratory cycle, reduces atelectasis, and improves gas exchange without exposing the infant to the risks associated with invasive mechanical ventilation. Several methods are available for CPAP delivery, including ventilator-generated CPAP systems and bubble CPAP devices, which provide comparable clinical effectiveness while offering lower cost and greater accessibility in many healthcare settings. Large randomized clinical trials, including the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT), demonstrated that early CPAP achieves clinical outcomes comparable to prophylactic surfactant administration combined with mechanical ventilation while reducing the need for intubation and surfactant therapy. Early CPAP has also been associated with a lower incidence of bronchopulmonary dysplasia, emphasizing its important role in lung-protective ventilation strategies [25][27][30]. Alternative noninvasive respiratory support modalities have also been investigated. Nasal intermittent positive pressure ventilation (NIPPV) combines continuous airway pressure with intermittent positive-pressure breaths delivered by a mechanical ventilator. Compared with CPAP alone, NIPPV has demonstrated greater effectiveness in reducing extubation failure and decreasing the need for subsequent endotracheal intubation among preterm infants. Nevertheless, its higher cost, greater equipment requirements, and lack of consistent superiority regarding overall safety have limited its widespread replacement of CPAP as first-line therapy [31]. Heated humidified

high-flow nasal cannula (HFNC) therapy has emerged as another noninvasive option because it improves patient comfort and simplifies respiratory support. However, clinical studies indicate that HFNC remains less effective than CPAP in preventing treatment failure among infants with RDS and therefore should be used selectively according to institutional protocols and individual patient characteristics [32].

Despite advances in noninvasive ventilation, some neonates develop progressive respiratory failure requiring invasive mechanical ventilation. Indications include persistent respiratory acidosis with arterial pH below 7.20 and $PaCO_2$ exceeding 60–65 mm Hg, severe hypoxemia despite adequate CPAP support, increasing oxygen requirements exceeding a fraction of inspired oxygen (FiO_2) of 0.40, recurrent apnea, or significant respiratory fatigue. Mechanical ventilation provides life-sustaining respiratory assistance while clinicians attempt to minimize complications associated with positive-pressure ventilation, including barotrauma, volutrauma, atelectrauma, and oxygen toxicity. Time-cycled pressure-limited ventilation remains the preferred initial ventilation mode for most preterm infants because it allows careful limitation of airway pressures while maintaining adequate ventilation. High-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) are frequently employed as rescue modalities in infants requiring very high ventilatory support or those with pulmonary air leaks. These high-frequency techniques deliver extremely small tidal volumes at rapid frequencies, thereby reducing repetitive alveolar overdistension and limiting ventilator-induced lung injury. Exogenous surfactant replacement therapy represents the definitive treatment for neonatal RDS because it directly addresses the underlying pathophysiological defect responsible for the disease. Administration of surfactant rapidly reduces alveolar surface tension, improves pulmonary compliance, enhances oxygenation, and facilitates more uniform lung expansion. Numerous clinical trials have demonstrated that surfactant therapy significantly decreases neonatal mortality while reducing the incidence of pneumothorax, pulmonary interstitial emphysema, bronchopulmonary dysplasia, intraventricular hemorrhage, and other serious complications associated with severe RDS [33][34]. Clinical benefit is greatest when surfactant is administered early after birth before extensive pulmonary injury develops. Current recommendations therefore favor early rescue surfactant administration in infants receiving CPAP who demonstrate increasing oxygen requirements rather than routine prophylactic treatment, which may unnecessarily expose some infants to invasive procedures and potential complications [33][35].

International guidelines recommend surfactant administration for immature infants requiring an FiO_2 greater than 0.30 and for more mature infants requiring an FiO_2 above 0.40 despite optimal CPAP therapy. Several commercially available natural surfactant preparations, including beractant, poractant alfa, and calfactant, have demonstrated comparable clinical effectiveness when administered in appropriate doses, while synthetic surfactant formulations continue to be evaluated in ongoing clinical trials [36]. Traditionally, surfactant has been delivered through endotracheal intubation followed by brief mechanical ventilation. However, this technique may contribute to airway trauma, transient airway obstruction, pulmonary injury, and ventilator associated complications

[42][43]. To reduce these risks, less invasive surfactant administration (LISA) techniques have gained increasing attention. These methods deliver surfactant through thin intratracheal catheters, laryngeal masks, aerosolized nebulization systems, or pharyngeal instillation while allowing infants to continue spontaneous breathing on CPAP. Emerging evidence indicates that LISA is associated with lower rates of bronchopulmonary dysplasia, reduced mortality, decreased need for mechanical ventilation, and shorter durations of respiratory support compared with conventional endotracheal surfactant administration [37][38][39][40][41][44]. Although additional large-scale studies are needed before universal adoption, LISA represents one of the most promising advances in neonatal respiratory care. Following successful surfactant therapy, infants who maintain adequate spontaneous respiration with FiO_2 requirements below 0.30 should be transitioned back to CPAP while continuing close monitoring of oxygen saturation, body temperature, nutritional status, and fluid balance. Comprehensive supportive care remains indispensable throughout the management of neonatal RDS. Caffeine therapy is widely administered to preterm infants with apnea of prematurity because it stimulates respiratory drive, improves diaphragmatic contractility, facilitates successful CPAP therapy, and promotes earlier extubation. Studies have demonstrated that caffeine therapy is associated with reduced bronchopulmonary dysplasia and improved respiratory outcomes, particularly among extremely low birth weight infants born before 28 weeks of gestation [45]. Careful management of fluid and electrolyte balance is equally important because both dehydration and fluid overload may worsen pulmonary function. Some infants require crystalloid volume expansion or vasoactive medications to treat hypotension and maintain adequate tissue perfusion. Additional supportive measures include thermoregulation within a neutral thermal environment, early nutritional support, treatment of anemia through blood transfusion when indicated, management of hemodynamically significant patent ductus arteriosus, and empirical or targeted antibiotic therapy when neonatal infection is suspected [25][26]. Recent advances in neonatal medicine increasingly emphasize precision medicine and individualized treatment strategies for RDS. Considerable heterogeneity exists in disease severity, pulmonary maturity, and response to therapy among premature infants, making standardized treatment algorithms insufficient for all patients. Modern approaches incorporate lung ultrasound findings, advanced oxygenation indices, physiological monitoring, and emerging surfactant biomarkers to personalize decisions regarding respiratory support, surfactant administration, and escalation of therapy. This patient-centered approach enables clinicians to optimize treatment while minimizing unnecessary interventions and reducing the risk of chronic lung disease, reflecting the continuing evolution of evidence-based neonatal intensive care [24].

Conclusion

Neonatal Respiratory Distress Syndrome continues to be a significant cause of respiratory morbidity and mortality among premature infants despite remarkable advances in perinatal and neonatal medicine. The disease originates primarily from pulmonary immaturity and inadequate surfactant production, resulting in impaired alveolar stability, reduced lung compliance, and progressive respiratory failure. A thorough understanding of fetal lung development, surfactant

physiology, and disease pathophysiology is fundamental for timely diagnosis and effective clinical management. Modern evidence strongly supports preventive strategies such as antenatal corticosteroid administration, alongside early initiation of noninvasive respiratory support, selective surfactant replacement therapy, careful oxygen management, and comprehensive supportive neonatal care. Recent innovations including lung ultrasound, less invasive surfactant administration techniques, and individualized precision-based treatment approaches have further enhanced clinical outcomes while minimizing ventilator-associated complications. Equally important is the contribution of nurses and health assistants, whose continuous monitoring, prompt recognition of clinical deterioration, accurate implementation of therapeutic interventions, and family-centered care are essential components of successful neonatal management. Ongoing research and adherence to evidence-based multidisciplinary practice will continue to improve survival rates, reduce chronic respiratory complications, and promote healthier long-term developmental outcomes for premature infants affected by neonatal respiratory distress syndrome.

References

1. Roth-Kleiner M, Post M. Similarities and dissimilarities of branching and septation during lung development. Pediatr Pulmonol. 2005 Aug;40(2):113-34.
2. Herriges M, Morrisey EE. Lung development: orchestrating the generation and regeneration of a complex organ. Development. 2014 Feb;141(3):502-13.
3. Gao Y, Cornfield DN, Stenmark KR, Thébaud B, Abman SH, Raj JU. Unique aspects of the developing lung circulation: structural development and regulation of vasomotor tone. Pulm Circ. 2016 Dec;6(4):407-425.
4. Whitsett JA, Alenghat T. Respiratory epithelial cells orchestrate pulmonary innate immunity. Nat Immunol. 2015 Jan;16(1):27-35.
5. Ariki S, Nishitani C, Kuroki Y. Diverse functions of pulmonary collectins in host defense of the lung. J Biomed Biotechnol. 2012;2012:532071.
6. Whitsett JA, Weaver TE. Hydrophobic surfactant proteins in lung function and disease. N Engl J Med. 2002 Dec 26;347(26):2141-8
7. AVERY ME, MEAD J. Surface properties in relation to atelectasis and hyaline membrane disease. AMA J Dis Child. 1959 May;97(5, Part 1):517-23.
8. Verlato G, Cogo PE, Balzani M, Gucciardi A, Burattini I, De Benedictis F, Martiri G, Carnielli VP. Surfactant status in preterm neonates recovering from respiratory distress syndrome. Pediatrics. 2008 Jul;122(1):102-8.
9. Anciuc-Crauciuc M, Cucerea MC, Tripon F, Crauciuc GA, Bănescu CV. Descriptive and Functional Genomics in Neonatal Respiratory Distress Syndrome: From Lung Development to Targeted Therapies. Int J Mol Sci. 2024 Jan 04;25(1)
10. Levit O, Jiang Y, Bizzarro MJ, Hussain N, Buhimschi CS, Gruen JR, Zhang H, Bhandari V. The genetic susceptibility to respiratory distress syndrome. Pediatr Res. 2009 Dec;66(6):693-7.
11. Cole FS, Hamvas A, Nogee LM. Genetic disorders of neonatal respiratory function. Pediatr Res. 2001 Aug;50(2):157-62.
12. Shulenin S, Nogee LM, Annilo T, Wert SE, Whitsett JA, Dean M. ABCA3 gene mutations in newborns with fatal surfactant deficiency. N Engl J Med. 2004 Mar 25;350(13):1296-303.

13. Wambach JA, Wegner DJ, Depass K, Heins H, Druley TE, Mitra RD, An P, Zhang Q, Nogee LM, Cole FS, Hamvas A. Single ABCA3 mutations increase risk for neonatal respiratory distress syndrome. Pediatrics. 2012 Dec;130(6):e1575-82.
14. Li Y, Wang W, Zhang D. Maternal diabetes mellitus and risk of neonatal respiratory distress syndrome: a meta-analysis. Acta Diabetol. 2019 Jul;56(7):729-740.
15. Smith PB, Ambalavanan N, Li L, Cotten CM, Laughon M, Walsh MC, Das A, Bell EF, Carlo WA, Stoll BJ, Shankaran S, Laptook AR, Higgins RD, Goldberg RN., Generic Database Subcommittee. Eunice Kennedy Shriver National Institute of Child Health Human Development Neonatal Research Network. Approach to infants born at 22 to 24 weeks' gestation: relationship to outcomes of more-mature infants. Pediatrics. 2012 Jun;129(6):e1508-16.
16. Carlton DP, Albertine KH, Cho SC, Lont M, Bland RD. Role of neutrophils in lung vascular injury and edema after premature birth in lambs. J Appl Physiol (1985). 1997 Oct;83(4):1307-17.
17. Nitta K, Kobayashi T. Impairment of surfactant activity and ventilation by proteins in lung edema fluid. Respir Physiol. 1994 Jan;95(1):43-51.
18. Turunen R, Nupponen I, Siitonen S, Repo H, Andersson S. Onset of mechanical ventilation is associated with rapid activation of circulating phagocytes in preterm infants. Pediatrics. 2006 Feb;117(2):448-54.
19. Naik AS, Kallapur SG, Bachurski CJ, Jobe AH, Michna J, Kramer BW, Ikegami M. Effects of ventilation with different positive end-expiratory pressures on cytokine expression in the preterm lamb lung. Am J Respir Crit Care Med. 2001 Aug 01;164(3):494-8.
20. Jobe AH, Hillman N, Polglase G, Kramer BW, Kallapur S, Pillow J. Injury and inflammation from resuscitation of the preterm infant. Neonatology. 2008;94(3):190-6.
21. deMello DE, Chi EY, Doo E, Lagunoff D. Absence of tubular myelin in lungs of infants dying with hyaline membrane disease. Am J Pathol. 1987 Apr;127(1):131-9.
22. Reuter S, Moser C, Baack M. Respiratory distress in the newborn. Pediatr Rev. 2014 Oct;35(10):417-28; quiz 429.
23. Liu J. Ultrasound diagnosis and grading criteria of neonatal respiratory distress syndrome. J Matern Fetal Neonatal Med. 2023 Dec;36(1):2206943.
24. De Luca D, Autilio C, Pezza L, Shankar-Aguilera S, Tingay DG, Carnielli VP. Personalized Medicine for the Management of RDS in Preterm Neonates. Neonatology. 2021;118(2):127-138.
25. Committee on Fetus and Newborn; American Academy of Pediatrics. Respiratory support in preterm infants at birth. Pediatrics. 2014 Jan;133(1):171-4.
26. Sakonidou S, Dhaliwal J. The management of neonatal respiratory distress syndrome in preterm infants (European Consensus Guidelines--2013 update). Arch Dis Child Educ Pract Ed. 2015 Oct;100(5):257-9.
27. American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. Pediatrics. 2004 Sep;114(3):874-7.
28. Verder H, Albertsen P, Ebbesen F, Greisen G, Robertson B, Bertelsen A, Agertoft L, Djernes B, Nathan E, Reinholdt J. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress

syndrome in newborns of less than 30 weeks' gestation. Pediatrics. 1999 Feb;103(2):E24.
29. Ho JJ, Subramaniam P, Davis PG. Continuous distending pressure for respiratory distress in preterm infants. Cochrane Database Syst Rev. 2015 Jul 04;2015(7):CD002271.
30. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Donovan EF, Newman NS, Ambalavanan N, Frantz ID, Buchter S, Sánchez PJ, Kennedy KA, Laroia N, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Bhandari V, Watterberg KL, Higgins RD. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010 May 27;362(21):1970-9.
31. Lemyre B, Laughon M, Bose C, Davis PG. Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants. Cochrane Database Syst Rev. 2016 Dec 15;12(12):CD005384.
32. Roberts CT, Owen LS, Manley BJ, Frøisland DH, Donath SM, Dalziel KM, Pritchard MA, Cartwright DW, Collins CL, Malhotra A, Davis PG., HIPSTER Trial Investigators. Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants. N Engl J Med. 2016 Sep 22;375(12):1142-51.
33. Sardesai S, Biniwale M, Wertheimer F, Garingo A, Ramanathan R. Evolution of surfactant therapy for respiratory distress syndrome: past, present, and future. Pediatr Res. 2017 Jan;81(1-2):240-248.
34. Ramaswamy VV, Bandyopadhyay T, Abiramalatha T, Pullattayil S AK, Szczapa T, Wright CJ, Roehr CC. Clinical decision thresholds for surfactant administration in preterm infants: a systematic review and network meta-analysis. EClinicalMedicine. 2023 Aug;62:102097.
35. van Kaam AH, Niemarkt HJ, Onland W. Timing of surfactant treatment in respiratory distress syndrome. Semin Fetal Neonatal Med. 2023 Dec;28(6):101495.
36. Singh N, Halliday HL, Stevens TP, Suresh G, Soll R, Rojas-Reyes MX. Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. Cochrane Database Syst Rev. 2015 Dec 21;2015(12):CD010249.
37. Dargaville PA, Aiyappan A, Cornelius A, Williams C, De Paoli AG. Preliminary evaluation of a new technique of minimally invasive surfactant therapy. Arch Dis Child Fetal Neonatal Ed. 2011 Jul;96(4):F243-8.
38. Abdel-Latif ME, Osborn DA. Laryngeal mask airway surfactant administration for prevention of morbidity and mortality in preterm infants with or at risk of respiratory distress syndrome. Cochrane Database Syst Rev. 2011 Jul 06;(7):CD008309.
39. Göpel W, Kribs A, Ziegler A, Laux R, Hoehn T, Wieg C, Siegel J, Avenarius S, von der Wense A, Vochem M, Groneck P, Weller U, Möller J, Härtel C, Haller S, Roth B, Herting E., German Neonatal Network. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet. 2011 Nov 05;378(9803):1627-34.

40. Pinheiro JM, Santana-Rivas Q, Pezzano C. Randomized trial of laryngeal mask airway versus endotracheal intubation for surfactant delivery. J Perinatol. 2016 Mar;36(3):196-201.
41. Minocchieri S, Berry CA, Pillow JJ., CureNeb Study Team. Nebulised surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2019 May;104(3):F313-F319.
42. Hatch LD, Grubb PH, Lea AS, Walsh WF, Markham MH, Whitney GM, Slaughter JC, Stark AR, Ely EW. Endotracheal Intubation in Neonates: A Prospective Study of Adverse Safety Events in 162 Infants. J Pediatr. 2016 Jan;168:62-66.e6.
43. Tarawneh A, Kaczmarek J, Bottino MN, Sant'anna GM. Severe airway obstruction during surfactant administration using a standardized protocol: a prospective, observational study. J Perinatol. 2012 Apr;32(4):270-5.
44. Aldana-Aguirre JC, Pinto M, Featherstone RM, Kumar M. Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2017 Jan;102(1):F17-F23.
45. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W., Caffeine for Apnea of Prematurity Trial Group. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006 May 18;354(20):2112-21.