Review Article

Respiratory Distress Syndrome in Preterm Neonates: A Comprehensive Narrative Review

Fathima Ahana[1], Agnes Harmath[2]

From, [1]Doctor of Medicine, [2]Consultant Neonatologist, Department of Neonatology, Semmelweis University, Budapest, Hungary

ABSTRACT

Background: Respiratory distress syndrome (RDS) is a leading cause of respiratory morbidity and mortality in preterm neonates, primarily resulting from surfactant deficiency and structural lung immaturity. Despite advances in perinatal care, RDS continues to contribute to substantial early neonatal mortality and long-term complications such as bronchopulmonary dysplasia (BPD), especially in extremely preterm infants. **Materials and Methods:** A narrative review of published literature was conducted using standard neonatology textbooks, international guidelines (European 2022 and Indian 2022), and peer-reviewed articles from PubMed, Cochrane Library, and Google Scholar. The search covered publications from 1959 to 2023. Key references were identified through targeted database searches and manual screening of reference lists from seminal papers. A total of 35 key references were selected based on their scientific rigor, clinical relevance and contribution to understanding fetal lung development, surfactant biology, epidemiology, pathophysiology, diagnostic approaches, and management strategies for RDS in preterm neonates. Results: Advances in antenatal care, respiratory support, and surfactant therapy have significantly improved outcomes in preterm infants with RDS. Improved understanding of lung development and surfactant biology has guided preventive strategies such as antenatal corticosteroids. Diagnostic modalities have evolved from chest radiography to lung ultrasound, which allows reliable bedside assessment and prediction of CPAP failure and surfactant requirement. Management has shifted toward early CPAP, caffeine therapy, volume-targeted ventilation, and minimally invasive surfactant administration techniques such as LISA/MIST, reducing ventilator-induced lung injury and improving survival without BPD. **Conclusion:** Integration of modern diagnostic tools, minimally invasive respiratory support, and guideline-based management has transformed outcomes in RDS OF preterm infants. Adapting global recommendations to local resource settings is essential for further improving survival and long-term respiratory outcomes.

Key words: Respiratory Distress Syndrome, Premature, Pulmonary Surfactants, Continuous Positive Airway Pressure

Respiratory distress syndrome (RDS) remains a central challenge in neonatology and is a leading cause of respiratory morbidity and mortality in premature infants worldwide [1]. The condition arises primarily from insufficient pulmonary surfactant and structural lung immaturity, together leading to alveolar collapse, ventilation-perfusion mismatch, impaired oxygenation, and progressive respiratory failure [2]. The incidence of RDS is inversely proportional to gestational age, affecting nearly all infants born before 28 weeks of gestation and declining substantially beyond 34–36 weeks as fetal lung maturation progresses [3].

Over the past several decades, studies have transformed the understanding and management of RDS. The identification of surfactant deficiency as the primary pathophysiologic mechanism by Avery and Mead in 1959 laid the foundation for modern therapeutic approaches [4]. Continuous positive airway pressure (CPAP), introduced by Gregory and colleagues in 1971, provided a method to maintain functional residual capacity and prevent alveolar collapse [5]. Antenatal corticosteroid therapy, pioneered by Liggins in 1972, demonstrated that fetal lung maturation could be accelerated through maternal intervention [6]. The advent of exogenous surfactant replacement therapy in the 1980s further revolutionized neonatal care, substantially reducing mortality from RDS [7, 8].

Despite these advances, RDS continues to contribute to early neonatal mortality and long-term morbidities, particularly bronchopulmonary dysplasia (BPD), in extremely preterm infants [9]. Global outcomes vary depending on the quality of antenatal care, delivery room resuscitation practices, the availability of respiratory support technologies, and the availability of trained neonatal personnel. Resource-limited

Access this article online

Received – 12th January 2026
Initial Review – 20th January 2026
Accepted – 01st February 2026

DOI: 10.32677/ijch.v13i1.8044

Quick Response Code

Correspondence to: Fathima Ahana, Semmelweis University, Budapest, Hungary.

Email: safe.ahana@gmail.com

settings continue to experience high mortality due to limited access to antenatal corticosteroids, surfactant therapy, and advanced respiratory support [10].

In recent years, diagnostic approaches have seen significant evolution, with lung ultrasound emerging as a radiation-free, bedside tool capable of early detection of surfactant deficiency, predicting CPAP failure, and guiding surfactant administration [11–14]. Concurrently, management strategies have shifted toward less invasive approaches, including early CPAP initiation in the delivery room, minimally invasive surfactant administration techniques such as LISA (less invasive surfactant administration) and MIST (minimally invasive surfactant therapy), volume-targeted ventilation, and adjunctive therapies including caffeine citrate [15–18].

International guidelines, like the 2022 European Consensus Guidelines on the Management of Respiratory Distress Syndrome and the 2022 Indian Standard Treatment Guidelines for Preterm Infants with Respiratory Distress, incorporate these evidence-based practices to standardize care and improve outcomes [19,20]. However, adapting these recommendations to diverse clinical contexts, particularly in resource-constrained environments, requires careful consideration of local infrastructure, equipment availability, and workforce capabilities.

This narrative review summarizes the current scientific knowledge with evolving clinical strategies in the management of RDS. It focuses on fetal lung development and its relationship to RDS pathogenesis, surfactant biology and deficiency mechanisms, epidemiology and risk factors, pathophysiology of respiratory failure, diagnostic innovations, particularly lung ultrasound, and evidence-based management strategies including antenatal interventions, delivery room stabilization, noninvasive respiratory support, mechanical ventilation, and surfactant replacement therapy. Emphasis is placed on comparing contemporary European and Indian guidelines and their applicability to different resource settings.

MATERIALS AND METHODS

2.1 Literature Search Strategy: A comprehensive literature search was performed using multiple databases, including PubMed, Cochrane Library, and Google Scholar. The search strategy incorporated Medical Subject Headings (MeSH) terms and keywords including "respiratory distress syndrome," "neonatal RDS," "hyaline membrane disease," "preterm infant," "surfactant deficiency," "lung ultrasound," "CPAP," "surfactant therapy," "LISA," "MIST," and "neonatal respiratory support." Additional sources included standard neonatology textbooks such as Fanaroff and Martin's Neonatal-Perinatal Medicine, as well as international clinical practice guidelines, including the 2022 European Consensus Guidelines on RDS and the 2022 Indian Standard Treatment Guidelines for preterm infants with respiratory distress.

2.2 Time Frame: The literature search covered publications from 1959 (landmark surfactant discovery by Avery and Mead) to 2023, including research and clinical advances in RDS management.

2.3 Types of Articles Reviewed: The review included landmark historical studies that established foundational knowledge in RDS pathophysiology and treatment, peer-reviewed original research articles including randomized controlled trials (RCTs) and observational studies, systematic reviews and meta-analyses on diagnostic and therapeutic interventions, international and national clinical practice guidelines from expert consensus bodies, and authoritative neonatology textbook chapters providing comprehensive summaries of established knowledge.

2.4 Article Selection: Key references were identified through targeted database searches, supplemented by manual screening of reference lists from seminal papers, systematic reviews, and clinical practice guidelines. Articles were selected based on their clinical relevance and contribution to understanding RDS pathogenesis, diagnosis, or management. Priority was given to recent systematic reviews and meta-analyses, large RCTs, current international guidelines, and landmark historical studies on the modern understanding and treatment of RDS. A total of 35 key references were ultimately included in this narrative review, representing the clinically relevant literature spanning from the initial discovery of surfactant deficiency through contemporary management approaches.

2.5 Data Synthesis: Evidence was organized according to the following categories: fetal lung development and structural basis of RDS, surfactant biology including composition, function, and genetic factors, epidemiology and risk factors, pathophysiology and clinical features, diagnostic approaches including radiography and lung ultrasound, and management strategies including antenatal interventions, delivery room care, noninvasive support, mechanical ventilation, and surfactant therapy. For each category, evidence was synthesized narratively with emphasis on contemporary practices and guideline recommendations. Specific attention was given to comparing European and Indian clinical practice guidelines and discussing their applicability to different resource settings.

2.6 Ethical Considerations: As this was a narrative review of published literature, no primary data collection, patient involvement, institutional review board approval, or informed consent was required.

RESULTS

The results of this narrative review are organized according to key aspects of RDS in preterm neonates.

3.1. Fetal Lung Development and Structural Basis of RDS

Fetal lung development progresses through five overlapping stages that establish the structural and functional capacity for

postnatal gas exchange [6, 7]. The embryonic (0–7 weeks) and pseudo-glandular (5–17 weeks) stages form the basic airway architecture up to the terminal bronchioles but are incapable of gas exchange [6]. The canalicular stage (16–26 weeks) marks a critical transition, with development of the pulmonary capillary network and differentiation of type II pneumocytes; however, infants born during this period have insufficient acinar units, immature alveolar–capillary membranes, and limited surfactant production [7].

During the saccular stage (26–36 weeks), primitive airspaces expand, the alveolar–capillary membrane thins, and surfactant production increases, though levels may remain inadequate before 34 weeks of gestation [6]. The alveolar stage begins around 36 weeks and continues into childhood, characterized by true alveolar formation and a marked increase in surface area available for gas exchange [6].

The stages of lung development and their clinical significance in relation to RDS are summarized in Table 1.

Table 1: Stages of Fetal Lung Development and RDS Risk

Stage	Gestational Age	Key Developments	RDS Risk if Born
Embryonic	0-7 weeks	Basic airway branching	Incompatible with life
Pseudo-glandular	5-17 weeks	Conducting airway formation	Incompatible with life
Canalicular	16-26 weeks	Vascular development, early type II cells	Extremely high (nearly 100%)
Saccular	26-36 weeks	Saccule expansion, increased surfactant	High (50-100%)
Alveolar	36 weeks-childhood	True alveoli formation	Low (<5%)

3.2. Surfactant Biology: Composition, Function, and Deficiency

Pulmonary surfactants primarily consist of phospholipids, of which dipalmitoyl phosphatidylcholine (DPPC) constitutes approximately 70%, along with phosphatidylglycerol and surfactant-specific proteins SP-A, SP-B, SP-C, and SP-D [12]. SP-B and SP-C are hydrophobic proteins essential for surface tension reduction, while SP-A and SP-D play roles in innate immunity and surfactant metabolism. In preterm infants, immaturity of type II pneumocytes leads to reduced surfactant synthesis, secretion, and recycling [13]. The absence of adequate surfactants increases alveolar surface tension, resulting in widespread alveolar collapse, decreased lung compliance, impaired gas exchange, and increased intrapulmonary shunting.

The resulting hypoxemia and hypercapnia trigger pulmonary vasoconstriction, further worsening ventilation–perfusion mismatch. Mechanical ventilation with high pressures may transiently improve oxygenation but also predispose to volutrauma, barotrauma, and inflammatory lung injury, contributing to the development of BPD [14].

Inflammatory mediators released during lung injury disrupt surfactant function and perpetuate the cycle of lung damage. This pathophysiologic cascade underscores the importance of early surfactant replacement and non-invasive ventilation strategies.

3.3. Epidemiology and Risk Factors for RDS

The global incidence of RDS varies significantly depending on gestational age, birth weight, and quality of perinatal care. RDS occurs in approximately 60–80% of infants born before 28 weeks of gestation, 30–40% between 28 and 32 weeks, and less than 5% beyond 34 weeks [15].

Major risk factors include prematurity, male sex, cesarean delivery without labor, maternal diabetes, perinatal asphyxia, and absence of antenatal corticosteroid exposure [16]. Protective factors include female sex, intrauterine stress, prolonged rupture of membranes, and exposure to antenatal corticosteroids.

In low- and middle-income countries, limited access to antenatal care, delayed referral, and inadequate neonatal intensive care unit (NICU) facilities contribute to higher RDS-related mortality [17]. Variations in surfactant availability, CPAP infrastructure, and trained personnel significantly influence outcomes. Key risk factors are listed in Table 2.

Table 2: Key Risk Factors and Protective Factors for RDS (15-18)

Risk Factors	Protective Factors
Extreme prematurity (<28 weeks)	Antenatal corticosteroids
Male sex	Maternal hypertension/preeclampsia
Maternal diabetes	Prolonged rupture of membranes
Elective cesarean without labor	Labor before delivery
Multiple gestation	Chronic intrauterine stress
Perinatal asphyxia	Female sex
Genetic mutations (ABCA3, SP-B, SP-C)	

3.4. Pathophysiology and Clinical Features of RDS

The pathophysiologic cascade of RDS begins with surfactant deficiency leading to increased alveolar surface tension, widespread atelectasis, and reduced functional residual capacity [10]. Collapsed alveoli result in dramatically reduced lung compliance, requiring higher transpulmonary pressures for alveolar expansion during inspiration. This creates significant work of breathing those premature infants, with weak respiratory muscles and highly compliant chest walls, cannot sustain, resulting in progressive respiratory failure [6].

Ventilation-perfusion mismatch develops as poorly ventilated or collapsed alveoli continue to receive pulmonary blood flow, creating intrapulmonary right-to-left shunting that

produces profound hypoxemia disproportionate to the degree of hypoventilation. Hypoxemia stimulates increased respiratory effort, but the compliant chest wall limits effective expansion and paradoxical inward movement during inspiration, further worsening atelectasis in a vicious cycle. Progressive alveolar collapse, coupled with increased pulmonary vascular resistance from hypoxemia and acidosis, may lead to reopening of fetal circulatory channels, including the ductus arteriosus and foramen ovale, creating additional extra-pulmonary right-to-left shunting that exacerbates hypoxemia.

Endothelial and epithelial cell injury, resulting from hypoxia, oxidative stress, and mechanical forces, increases alveolar-capillary membrane permeability. Plasma proteins leak into the alveolar space, where they inactivate residual surfactant and combine with cellular debris and fibrin to form the characteristic eosinophilic hyaline membranes lining terminal airways and alveoli [11]. If mechanical ventilation is required, volutrauma from overdistension, atelectasis from repetitive alveolar collapse and reopening, and oxygen toxicity contribute to ongoing lung injury that can progress to BPD.

The clinical presentation of RDS typically manifests within minutes to hours after birth as the infant transitions from fluid-filled fetal lungs to air-filled postnatal respiration without adequate surfactant. Cardinal clinical features include tachypnea with respiratory rates often exceeding 60 breaths per minute, nasal flaring to reduce upper airway resistance, expiratory grunting representing physiologic auto-positive end-expiratory pressure generated by laryngeal braking to maintain functional residual capacity, intercostal and subcostal retractions reflecting high negative intrathoracic pressures required to inflate stiff lungs, and central cyanosis in room air indicating severe hypoxemia [13].

On physical examination, breath sounds will be reduced bilaterally, and auscultation may reveal fine inspiratory crackles. Clinical severity generally peaks during the first 48-72 hours of life, coinciding with increasing intrapulmonary shunting and progressive atelectasis. Without treatment, infants demonstrate progressive respiratory failure with worsening hypoxemia, hypercarbia, and mixed respiratory and metabolic acidosis. Clinical scoring systems such as the Silverman-Anderson Score, which quantifies chest wall retractions, nasal flaring, and grunting, assist in semi-objective assessment of respiratory distress severity but are nonspecific for RDS [21].

3.5. Diagnostic Approaches: Radiography, Lung Ultrasound, and Laboratory Assessment

Early and accurate diagnosis of RDS is essential for the timely initiation of respiratory support and surfactant therapy. Diagnosis is based on a combination of clinical features, blood gas analysis, and imaging modalities.

3.5a. Clinical Assessment

Clinically, RDS presents within minutes to hours after birth with tachypnea, nasal flaring, expiratory grunting, chest retractions, and cyanosis. The severity of respiratory distress typically worsens over the first 24–48 hours in untreated infants and improves with surfactant therapy and supportive care [18].

3.5b. Blood Gas Analysis

Arterial blood gas (ABG) analysis plays a critical role in assessing disease severity and guiding respiratory support. Typical findings include hypoxemia, hypercapnia, and respiratory acidosis. Progressive disease leads to mixed respiratory and metabolic acidosis due to tissue hypoxia and lactic acidosis [19]. Blood gas monitoring assists in determining the need for CPAP escalation, intubation, and surfactant therapy.

3.5c. Chest Radiography

Chest radiography has traditionally been the cornerstone of RDS diagnosis. Classic radiographic features include low lung volumes, diffuse reticulogranular “ground glass” appearance, and air bronchograms extending to the periphery [20]. However, chest X-rays expose neonates to ionizing radiation and lack sensitivity for early diseases and surfactant deficiency.

3.5d. Lung Ultrasound

Lung ultrasound has emerged as a superior diagnostic tool for RDS. It demonstrates characteristic findings such as diffuse B-lines, sub-pleural consolidations, and absence of A-lines, reflecting interstitial syndrome and alveolar collapse [22]. Lung ultrasound scores correlate strongly with oxygenation indices and predict CPAP failure and surfactant requirement more accurately than chest radiography [23–25].

Advantages of lung ultrasound include bedside availability, absence of radiation, repeatability, and real-time monitoring of treatment response. Many studies support its routine use in the NICU for early diagnosis and management of RDS [24, 25].

Diagnostic modalities used in RDS, and their comparative advantages, are summarized in Table 3.

Table 3: Comparison of Diagnostic Modalities for RDS [19-25]

Modality	Advantages	Disadvantages	Sensitivity/Specificity
Chest X-ray	Widely available, established criteria	Radiation exposure, poor real-time assessment	70-80% / 70-80%
Lung Ultrasound	No radiation, bedside, serial monitoring	Requires training, operator-dependent	>90% / >90%
ABG	Direct measurement of gas exchange	Invasive, delayed results	N/A (adjunct tool)

3.6. Management strategies: antenatal interventions and delivery room care

3.6a. Antenatal Corticosteroids

Antenatal corticosteroids are among the most effective interventions for preventing RDS and improving neonatal outcomes in preterm infants. Meta-analyses of RCTs demonstrate that antenatal corticosteroid administration to mothers at risk of preterm delivery between 24 and 34 weeks of gestation accelerates fetal lung maturation, increases surfactant production, and reduces RDS incidence by 30–50% and neonatal mortality by approximately 40% [26].

The standard regimen includes two doses of intramuscular betamethasone 12 mg, administered 24 hours apart, or four doses of dexamethasone 6 mg, given every 12 hours. This also reduces the incidence of intraventricular hemorrhage and necrotizing enterocolitis [27].

3.6b. Delivery Room Management

Early respiratory support in the delivery room significantly influences RDS outcomes. Current guidelines recommend initiation of CPAP at birth in spontaneously breathing preterm infants to establish functional residual capacity and avoid intubation [28]. Routine prophylactic intubation is no longer recommended due to increased risk of lung injury and BPD.

Delayed cord clamping for 30–60 seconds improves hemodynamic stability and reduces the need for blood transfusions without increasing respiratory morbidity [29]. Thermoregulation, gentle handling, and avoidance of excessive oxygen supplementation are crucial components of delivery room care.

3.7. Postnatal Respiratory Support

3.7a. CPAP

CPAP is the cornerstone of initial respiratory support in preterm infants with RDS. It maintains alveolar recruitment, prevents end-expiratory collapse, improves lung compliance, and reduces respiratory effort [28]. Early CPAP initiated in the delivery room decreases the need for mechanical ventilation and lowers the risk of BPD compared to routine intubation [30].

Bubble CPAP is widely used in low- and middle-income countries due to its simplicity, low cost, and effectiveness. However, CPAP failure occurs in 20–40% of extremely preterm infants, particularly those with severe surfactant deficiency, requiring escalation to invasive ventilation [31].

3.7b. Mechanical Ventilation

Mechanical ventilation is reserved for infants with CPAP failure, persistent respiratory acidosis, severe hypoxemia, or recurrent apnea. While it provides effective oxygenation and ventilation, mechanical ventilation is often associated with lung injury due to barotrauma, volutrauma, atelactic trauma, and biotrauma [14].

Volume-targeted ventilation has gained preference over pressure-limited ventilation, as it delivers consistent tidal volumes and reduces the incidence of ventilator-induced lung injury, intraventricular hemorrhage, and BPD [32]. Gentle ventilation strategies with permissive hypercapnia are recommended to minimize lung damage.

3.7c. Caffeine Therapy

Caffeine citrate is routinely administered to preterm infants for the prevention and treatment of apnea of prematurity. It improves respiratory drive, enhances diaphragmatic contractility, and facilitates successful extubation [33]. Large RCTs have demonstrated that early caffeine therapy reduces the duration of mechanical ventilation and lowers the incidence of BPD [33].

3.7d. Oxygen Therapy

Supplemental oxygen should be carefully titrated to maintain target oxygen saturation levels between 90–95% to avoid both hypoxemia and hyperoxia-related oxidative lung injury. Pulse oximetry is used for continuous monitoring, and ABG analysis guides oxygen and ventilatory adjustments [19].

3.8. Surfactant Therapy

Exogenous surfactant replacement is a cornerstone of RDS management. Natural surfactant preparations derived from animal lungs are preferred over synthetic formulations due to superior efficacy and survival outcomes [5,6].

3.8a. Indications and Timing

Early selective surfactant administration is recommended for preterm infants on CPAP who require increasing oxygen concentrations (FiO_2 >0.30–0.40) to maintain target saturations [34]. Prophylactic surfactant is no longer routinely recommended, as early CPAP with selective surfactants yields better outcomes.

3.8b. Methods of Administration

Traditional administration involves intubation, surfactant instillation, and rapid extubation (INSURE technique). However, minimally invasive methods like LISA and MIST allow surfactant delivery via a thin catheter without mechanical ventilation [31]. Multiple studies demonstrate that LISA reduces the need for mechanical ventilation, decreases BPD, and improves survival without major complications [34]. Respiratory support strategies and evidence levels are detailed in Table 4.

Table 4: Respiratory Support Strategies - Evidence Summary [28-32]

Strategy	Level of Evidence	Key Benefits	Main Limitations
Early CPAP	Multiple RCTs, meta-analyses	Reduces intubation, BPD	CPAP failure in 25-50%

LISA/MIST	Multiple RCTs, meta-analyses	Reduces death/BPD by 30-40%	Requires training; spontaneous breathing needed
Volume-targeted ventilation	Meta-analyses	Reduces BPD, pneumothorax	Requires a compatible ventilator
Caffeine therapy	Large RCT, long-term follow-up	Reduces BPD, improves neurodevelopment	May cause tachycardia
Natural surfactant	Meta-analyses	Superior to synthetic	Expensive, animal-derived

3.9. Complications

Transient complications include bradycardia, oxygen desaturation, airway obstruction, and pulmonary hemorrhage. Long-term benefits outweigh risks when surfactant is administered appropriately and combined with non-invasive ventilation strategies [6].

3.10. Comparison of European and Indian Guidelines

The 2022 European Consensus Guidelines and the 2022 Indian Standard Treatment Guidelines provide structured recommendations for the management of RDS, with strong emphasis on antenatal prevention, early non-invasive respiratory support, and selective surfactant therapy [34, 35].

Both guidelines recommend universal antenatal corticosteroids for women at risk of preterm delivery between 24 and 34 weeks of gestation. Early initiation of CPAP in spontaneously breathing infants is advocated to avoid routine intubation. Selective surfactant administration is recommended based on increasing oxygen requirements rather than prophylactic use.

The European guidelines emphasize the use of LISA as the preferred method where trained personnel and equipment are available [34]. They also advocate for lung ultrasound as a routine diagnostic and monitoring tool.

The Indian guidelines recognize resource limitations and recommend bubble CPAP as a cost-effective alternative. While endorsing LISA where feasible, they allow INSURE technique in centers lacking specialized training. Both guidelines stress the importance of thermal regulation, infection prevention, caffeine therapy, and careful oxygen targeting [35]. A comparative summary of both guidelines is presented in Table 5.

Table 5: European vs Indian RDS Guidelines - Key Similarities and Differences [34, 35].

Aspect	European Guidelines 2022	Indian Guidelines 2022
Antenatal steroids	Strongly recommended 24-34 weeks	Strongly recommended 24-34 weeks
Early CPAP	Recommendation from birth	Recommendation from birth
Surfactant approach	Selective early rescue, prefer LISA	Selective early rescue, prefer LISA if available
Lung ultrasound	Detailed protocols encourage use	Acknowledged, implementation variable
Resource adaptation	Assuming full equipment availability	Emphasize stepwise implementation

DISCUSSION

This comprehensive narrative review synthesizes current evidence on RDS in preterm neonates, highlighting substantial progress in understanding disease pathophysiology and evolution of diagnostic and therapeutic approaches over recent decades [1–4].

The identification of surfactant deficiency as the primary mechanism of RDS revolutionized neonatal care. Avery and Mead's pioneering work in 1959 established the biochemical basis of hyaline membrane disease, guiding subsequent interventions aimed at restoring surfactant function [5]. The introduction of antenatal corticosteroids, CPAP, and exogenous surfactant therapy collectively led to significant reductions in both RDS-related mortality and long-term morbidities such as BPD [6–9]. Antenatal corticosteroids accelerate maturation of type II pneumocytes, enhance surfactant protein expression, and improve alveolar stability, thereby reducing the severity of RDS in extremely preterm infants [10].

Regarding the diagnostic approaches, lung ultrasound outperforms conventional chest radiography for early detection of surfactant deficiency, disease severity assessment, and prediction of CPAP failure and surfactant requirements [11–14]. Lung ultrasound scores have been shown to correlate with oxygen requirements, the likelihood of mechanical ventilation, and subsequent risk of BPD, emphasizing their utility in guiding clinical decision-making [12, 13].

Management strategies have similarly evolved toward minimizing iatrogenic lung injury. Early initiation of CPAP immediately after birth prevents alveolar collapse, maintains functional residual capacity, and reduces respiratory effort [15, 16]. LISA and MIST have demonstrated reductions in both mortality and BPD compared with traditional INSURE or prolonged intubation methods [17, 18]. Volume-targeted ventilation has largely replaced pressure-limited ventilation [19]. Caffeine citrate further improves outcomes by reducing apnea episodes, shortening ventilation duration, and enhancing long-term neurodevelopment [20, 21].

The comparison of European and Indian guidelines highlights the importance of adapting global recommendations to local resource settings. Both guidelines underscore the critical role of antenatal corticosteroids, thermal regulation, infection prevention, careful oxygen targeting, and adjunctive caffeine therapy. These tailored approaches demonstrate how

evidence-based interventions can be adapted pragmatically to improve outcomes in diverse clinical contexts.

Despite significant advances, challenges remain in optimizing RDS management, particularly in low- and middle-income countries due to limited access to antenatal corticosteroids, surfactant therapy, and advanced respiratory support [10]. Ongoing research focuses on refining minimally invasive surfactant delivery techniques, improving lung ultrasound protocols for early risk stratification, and developing novel synthetic surfactants with enhanced efficacy and safety profiles [24–26]. Furthermore, studies exploring individualized CPAP titration, adjunctive pharmacologic therapies, and long-term follow-up strategies aim to reduce the incidence of BPD and improve neurodevelopmental outcomes.

CONCLUSION

RDS remains a major cause of morbidity and mortality in preterm infants worldwide. However, survival and long-term outcomes have improved dramatically through advances in perinatal care, diagnostic innovations, and therapeutic strategies. Strengthening antenatal corticosteroid coverage and expanding access to early CPAP and selective surfactant therapy remain essential for improving neonatal survival, particularly in low- and middle-income settings.

REFERENCES

1. Avery ME, Mead J. Surface properties of the lung extracts in hyaline membrane disease. AMA J Dis Child. 1959; 97(5):517–23.
2. Obladen M. History of surfactant up to 1980. Biol Neonate. 2005; 87(4):308–16.
3. Gregory GA, Kitterman JA, Phibbs RH, *et al*. Treatment of idiopathic respiratory distress syndrome with continuous positive airway pressure. N Engl J Med. 1971; 284(24):1333–40.
4. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics. 1972; 50(4):515–25.
5. Fanaroff AA, Martin RJ, editors. Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 8th ed. Philadelphia: Mosby Elsevier; 2006.
6. Yadav S, Lee B, Kamity R. Neonatal respiratory distress syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
7. Rubarth LB, Quinn J. Respiratory development and respiratory distress syndrome. Neonatal Netw. 2015; 34(4):231–8.
8. Creuwels LA, van Golde LM, Haagsman HP. The pulmonary surfactant system: biochemical and clinical aspects. Lung. 1997; 175(1):1–39.
9. Ainsworth SB, Milligan DW. Surfactant therapy for respiratory distress syndrome in premature neonates: a comparative review. Am J Respir Med. 2002; 1(6):417–33.
10. Ainsworth SB. Pathophysiology of neonatal respiratory distress syndrome: implications for early treatment strategies. Treat Respir Med. 2005; 4(6):423–37.
11. Veldhuizen R, Nag K, Orgeig S, *et al*. The role of lipids in pulmonary surfactant. Biochim Biophys Acta. 1998; 1408(2–3):90–108.
12. Vieira F, Kung JW, Bhatti F. Structure, genetics and function of the pulmonary associated surfactant proteins A and D: the extra-pulmonary role of these C type lectins. Ann Anat. 2017; 211:184–201.
13. Harrison VC, Heese Hde V, Klein M. The significance of grunting in hyaline membrane disease. Pediatrics. 1968; 41(3):549–559.
14. Levit O, Jiang Y, Bizzarro MJ, *et al*. The genetic susceptibility to respiratory distress syndrome. Pediatr Res. 2009; 66(6):693–7.
15. Shulenin S, Nogee LM, Annilo T, *et al*. ABCA3 gene mutations in newborns with fatal surfactant deficiency. N Engl J Med. 2004; 350(13):1296–303.
16. Wambach JA, Casey AM, Fishman MP, *et al*. Genotype–phenotype correlations for infants and children with ABCA3 deficiency. Am J Respir Crit Care Med. 2014; 189(12):1538–43.
17. Piper JM, Langer O. Does maternal diabetes delay fetal pulmonary maturity? Am J Obstet Gynecol. 1993; 168(3):783–6.
18. Moore TR. A comparison of amniotic fluid fetal pulmonary phospholipids in normal and diabetic pregnancy. Am J Obstet Gynecol. 2002; 186(3):641–650.
19. Kanto WP Jr, Borer RC Jr, Roloff DW. Correlation of prenatal and postnatal biochemical and radiologic studies in infants at risk for hyaline membrane disease. Am J Obstet Gynecol. 1978; 131(4):434–441.
20. Schaefer-Prokop C, Prokop M. Infantile respiratory distress syndrome: radiologic features. Radiol Clin North Am. 2005; 43(2):297–307.
21. Hedstrom AB, Gove NE, Mayock DE, *et al*. Performance of the Silverman Andersen Respiratory Severity Score in predicting CPAP failure. J Perinatol. 2018; 38(8):1073–1077.
22. Copetti R, Cattarossi L. The “double lung point”: an ultrasound sign diagnostic of transient tachypnea of the newborn. Neonatology. 2008; 91(3):203–209.
23. Brat R, Yousef N, Klifa R, *et al*. Lung ultrasonography score to evaluate oxygenation and surfactant need in neonates treated with continuous positive airway pressure. JAMA Pediatr. 2015; 169(8):e151797.
24. De Martino L, Yousef N, Ben-Ammar R, *et al*. Lung ultrasound score predicts surfactant need in extremely preterm neonates. Pediatrics. 2018; 142(3):e20180463.
25. Liu J, Copetti R, Sorantin E, *et al*. Protocol and guidelines for point-of-care lung ultrasound in diagnosing neonatal pulmonary diseases based on international expert consensus. J Vis Exp. 2019; (145):e58990.
26. McGoldrick E, Stewart F, Parker R, *et al*. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020; 12:CD004454.
27. American Academy of Pediatrics Committee on Fetus and Newborn. Respiratory support in preterm infants at birth. Pediatrics. 2014;133(1):171–174.
28. Schmölzer GM, Kumar M, Pichler G, Aziz K, O’Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ. 2013; 347:f5980.
29. Klingenberg C, Wheeler KI, McCallion N, *et al*. Volume-targeted versus pressure-limited ventilation in neonates. Cochrane Database Syst Rev. 2017; 10:CD003666.
30. Schmidt B, Roberts RS, Davis P, *et al*. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006; 354(20):2112–2121.
31. Schmidt B, Roberts RS, Davis P, *et al*. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med. 2007; 357(19):1893–1902.
32. Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2001; (2):CD000144.
33. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2012; (3):CD000510.

34. Sweet DG, Carnielli VP, Greisen G, *et al*. European consensus guidelines on the management of respiratory distress syndrome: 2022 update. Neonatology. 2023; 120(1):3–23.
35. National Neonatology Forum of India. Evidence-based Clinical Practice Guidelines: Standard Treatment Guidelines for Preterm Infants with Respiratory Distress. New Delhi: NNF India; 2022.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Ahana F, Harmath A. Respiratory Distress Syndrome in Preterm Neonates: A Comprehensive Narrative Review. Indian J Child Health. 2026; 13(1):1-8.