Journal of Clinical and Nursing Research, 2025, Volume 9, Issue 12
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Pathogenesis of Hyaline Membrane Disease in Newborns and Advances in Non-invasive Ventilation Therapy

Ying Guo, Jijing Han*

Department of Pediatrics, Affiliated Hospital of Hebei University, Baoding 071000, Hebei, China

**Author to whom correspondence should be addressed.*

Abstract: Hyaline Membrane Disease (HMD) in newborns, also known as neonatal respiratory distress syndrome, is a common critical illness in premature infants, with an incidence inversely correlated with gestational age, posing a serious threat to the life and health of newborns. This paper systematically reviews the core pathogenesis of HMD, focusing on the abnormal metabolism of pulmonary surfactant (PS), genetic factors, immature lung development, and the synergistic effects of inflammatory oxidative stress. It highlights the advances in non-invasive ventilation (NIV) therapy for HMD, including the mechanisms of action, clinical application effects, and optimization strategies of mainstream modalities such as nasal continuous positive airway pressure ventilation (NCPAP), nasal intermittent positive pressure ventilation (NIPPV), and heated humidified high-flow nasal cannula ventilation (HHHFNC). The aim is to provide references for standardized clinical treatment.

Keywords: Hyaline membrane disease in newborns; Pathogenesis; Pulmonary surfactant; Non-invasive ventilation; Therapeutic advances

Online publication: Dec 31, 2025

1. Introduction

Hyaline Membrane Disease (HMD) in newborns is an acute respiratory failure caused by a deficiency or dysfunction of Pulmonary Surfactant (PS), presenting primarily with progressive dyspnea, cyanosis, and respiratory failure shortly after birth [1]. Pathologically, it is characterized by the attachment of eosinophilic hyaline membranes to the alveolar walls and the walls of terminal bronchioles [2]. With the advancement of perinatal medicine, the survival rate of premature infants has significantly improved, yet HMD remains one of the leading causes of mortality among premature infants, particularly those with extremely low birth weights and gestational ages less than 32 weeks [3]. Traditional treatment primarily relies on invasive mechanical ventilation, which is prone to complications such as ventilator-associated pneumonia and bronchopulmonary

dysplasia. In recent years, Non-invasive Ventilation (NIV) technology has emerged as a core treatment for HMD due to its advantages of minimal trauma and fewer complications, with its application scope and treatment strategies continuously being optimized [4]. Meanwhile, in-depth research into the pathogenesis of HMD has provided new targets for clinical intervention.

2. Pathogenesis

The onset of HMD is not the result of a single factor but rather a complex pathological process involving the interplay and synergistic effects of multiple factors, including abnormal PS metabolism, genetic regulation, immature lung development, and inflammatory oxidative stress. These mechanisms collectively exacerbate pulmonary dysfunction, ultimately leading to respiratory failure.

2.1. Abnormal PS metabolism

PS is a crucial substance for maintaining pulmonary ventilation function. It is synthesized, stored, and secreted by alveolar type II epithelial cells, with its main components being phospholipids and surfactant proteins [5]. Its core function is to reduce alveolar surface tension, prevent alveolar collapse at the end of expiration, and maintain alveolar stability, while also participating in processes such as lung defense and inflammation regulation. The core pathogenic mechanism of HMD is PS deficiency or dysfunction, with premature birth being the primary cause of insufficient PS synthesis.

At 18–20 weeks of gestational age, fetal alveolar type II epithelial cells begin to synthesize PS. However, it is not until 35–36 weeks of gestational age that the synthesis amount and activity of PS reach the levels of full-term infants [6]. The alveolar type II epithelial cells in premature infants are immature in development, with low activity of PS synthesis enzymes, leading to an imbalance in the proportion of phospholipid components and insufficient expression of surfactant proteins, particularly the lack of SP-B and SP-C, which directly affects the surface activity and distribution stability of PS [7]. In addition, pathological conditions such as perinatal asphyxia, acidosis, and hypoxemia can inhibit the secretion of pulmonary surfactant (PS) by alveolar type II epithelial cells, while activating the inflammatory response, leading to increased degradation of PS and further exacerbating PS deficiency. Feng Chiguang found that PS dysfunction is closely related to oxidative stress [8]. Reactive oxygen species can damage the phospholipid structure and surfactant proteins of PS, reducing its ability to reduce surface tension, and forming a vicious cycle of “PS deficiency - lung injury - oxidative stress - further impairment of PS function”.

2.2. Regulatory role of genetic factors

Genetic factors play a significant role in the onset of Hyaline Membrane Disease (HMD). Multiple studies have confirmed that variations in surfactant-related genes are closely associated with susceptibility to HMD [9]. Mutations in the SP-B gene (SFTPB) are important genetic factors contributing to severe HMD. For instance, deletion of exon 4 in the SFTPB gene can result in a complete lack of SP-B synthesis, leading to severe respiratory failure in newborns within hours of birth, with a very high mortality rate. Mutations in the SP-C gene (SFTPC) can cause structural abnormalities in SP-C, affecting the assembly and function of PS, increasing the risk of HMD in premature infants, and potentially being associated with the subsequent development of bronchopulmonary dysplasia [10]. In addition, the ATP-binding cassette transporter encoded by the ABCA3 gene

is involved in the processing and secretion of pulmonary surfactant (PS) within alveolar type II epithelial cells, and mutations in this gene can lead to abnormalities in the formation of PS storage vesicles, thereby triggering Hyaline Membrane Disease (HMD). In addition to genes related to surfactant, variations in genes associated with fetal lung development may also increase the risk of HMD by affecting lung tissue differentiation [11].

2.3. Immature lung development and inflammatory oxidative stress

The immature development of lung tissue in premature infants is not only characterized by a low number of alveoli and small alveolar cavities, but also by issues such as delayed pulmonary vascular development and proliferation of pulmonary interstitium. These factors contribute to impaired pulmonary ventilation and gas exchange, serving as an important anatomical basis for the occurrence of HMD. Meanwhile, various factors during the perinatal period can trigger inflammatory responses in lung tissue, further exacerbating lung injury. For example, intrauterine infections (such as chorioamnionitis) can activate the fetal immune system, leading to infiltration of neutrophils and macrophages into lung tissue, releasing inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), damaging alveolar type II epithelial cells, and inhibiting PS synthesis; stimuli such as postnatal infections and mechanical ventilation can intensify the inflammatory response, forming a pathological process of "inflammation-lung injury-respiratory failure" [12]. Oxidative stress is another key mechanism in the pathogenesis of HMD. The antioxidant system in premature infants is not fully developed, with low activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase. Perinatal exposure to hypoxia, hyperoxia, and inflammatory responses can lead to the massive generation of reactive oxygen species (ROS), triggering oxidative stress injury [13]. ROS can disrupt the cell membrane structures of alveolar epithelial cells and vascular endothelial cells, leading to cell apoptosis. At the same time, they can damage the phospholipid and protein components of pulmonary surfactant (PS), reducing its function. ROS can also activate signaling pathways such as nuclear factor-kappa B (NF-κB), exacerbating inflammatory responses and further deteriorating lung function.

3. Advances in treatment

Non-invasive ventilation (NIV) refers to a ventilation mode that provides respiratory support to newborns through nasal masks or face masks without establishing an artificial airway. Its core advantage lies in avoiding complications associated with invasive ventilation, such as airway injury and infection, thereby protecting lung function. In recent years, the application of NIV technology in the treatment of hyaline membrane disease (HMD) has become increasingly widespread, forming a treatment system based on nasal continuous positive airway pressure (NCPAP) and complemented by modes such as nasal intermittent positive pressure ventilation (NIPPV) and heated humidified high-flow nasal cannula (HHHFNC).

3.1. Nasal continuous positive airway pressure (NCPAP)

3.1.1. Mechanism of action and clinical application

NCPAP serves as the first-line modality for non-invasive ventilation therapy in HMD. By continuously delivering positive pressure to the airways, it maintains alveolar patency at the end of expiration, prevents alveolar collapse, improves the ventilation/perfusion ratio in the lungs, reduces intrapulmonary shunting, thereby enhancing blood oxygen saturation and reducing respiratory work [14]. Concurrently, NCPAP can reduce

the consumption of pulmonary surfactant (PS), buying time for alveolar type II epithelial cells to synthesize PS. Multiple randomized controlled trials (RCTs) have confirmed that for neonates with mild to moderate HMD, early application of NCPAP can significantly reduce the rate of endotracheal intubation, shorten the duration of mechanical ventilation, and decrease the incidence of bronchopulmonary dysplasia (BPD) and ventilator-associated pneumonia. For instance, an analysis incorporating 47 RCT studies revealed that compared to pulmonary surfactant therapy, NCPAP can significantly improve blood gas parameters and enhance clinical outcomes in neonates with HMD [15].

3.1.2. Optimization strategies

The therapeutic efficacy of NCPAP is closely related to pressure settings and interface selection. Currently, the clinically recommended initial pressure ranges from 5 to 8 cm H_2O, which should be dynamically adjusted based on the neonate's respiratory status and blood oxygen saturation to avoid complications such as pneumothorax and circulatory depression caused by excessive pressure, or the inability to maintain alveolar patency due to insufficient pressure. Regarding interface selection, nasal masks and nasal prongs are commonly used types. Nasal masks offer superior sealing and are suitable for neonates with rapid breathing or significant nasal congestion; nasal prongs have minimal impact on oral care and are more appropriate for neonates requiring oral feeding. In recent years, the research and development of new types of interfaces (such as bilateral nasal prongs and integrated nasal masks) have further enhanced wearing comfort and ventilation effectiveness. In addition, the combined use of pulmonary surfactant (PS) replacement therapy represents a significant optimization direction for nasal continuous positive airway pressure (NCPAP) treatment. For neonates with moderate to severe hyaline membrane disease (HMD), early intratracheal administration of PS under NCPAP support can rapidly improve lung function, increase the success rate of non-invasive ventilation (NIV), and reduce the need for intubation [16].

3.2. Nasal intermittent positive pressure ventilation (NIPPV)

3.2.1. Mechanism of action and clinical application

Building upon NCPAP, NIPPV cyclically delivers inspiratory positive pressure higher than the baseline pressure, simulating the assisted ventilation mode of invasive mechanical ventilation. It provides stronger respiratory support, helping neonates overcome airway resistance, increase tidal volume, and improve ventilation efficiency [17]. Compared to NCPAP, NIPPV is more suitable for neonates with moderate to severe HMD or cases where NCPAP treatment has failed. Studies have shown that NIPPV can significantly reduce the intubation rate and mortality rate in neonates with severe HMD, particularly in extremely preterm infants with a gestational age of less than 28 weeks, where NIPPV better maintains respiratory stability and reduces the occurrence of apnea.

3.2.2. Technological advancements

Traditional Non-Invasive Positive Pressure Ventilation (NIPPV) suffers from poor synchronicity, which can easily lead to patient-ventilator asynchrony. In recent years, the development of synchronous triggering technologies has significantly improved the therapeutic efficacy of NIPPV, such as flow triggering, pressure triggering, and diaphragmatic electrical activity (EAdi) triggering. These technologies can precisely provide inspiratory positive pressure in accordance with the spontaneous breathing rhythm of newborns, thereby

reducing patient-ventilator asynchrony [18]. Additionally, Bilevel Positive Airway Pressure (BiPAP), as a special form of NIPPV, provides respiratory support while preserving the spontaneous breathing function of newborns by setting a higher inspiratory positive airway pressure (IPAP) and a lower expiratory positive airway pressure (EPAP). It is suitable for newborns with Hyaline Membrane Disease (HMD) who have severe respiratory failure but still retain some degree of spontaneous breathing.

3.3. Heated humidified high-flow nasal cannula (HHHFNC)

3.3.1. Mechanism of action and clinical application

HHHFNC delivers heated (37 ℃) and humidified (relative humidity 100%) high-flow gas to newborns through nasal cannulas. Its mechanisms of action include establishing positive airway pressure to maintain alveolar patency, flushing out the nasal dead space to improve ventilation efficiency, enhancing oxygenation and carbon dioxide elimination, and reducing respiratory mucosal injury. HHHFNC offers the advantages of comfort and ease of use, making it suitable for initial treatment of mild HMD in newborns or as a sequential ventilation mode following NCPAP/NIPPV therapy. Research has shown that for newborns with mild HMD, there is no significant difference in the success rate of treatment between HHHFNC and NCPAP. However, HHHFNC offers better tolerance and reduces complications such as facial pressure ulcers and nasal injuries [19].

3.3.2. Application controversies and optimization

Currently, there is some controversy regarding the application of HHHFNC in the treatment of HMD, with the core focus being whether its ventilatory support intensity can meet the needs of moderate to severe HMD. Some studies suggest that the positive airway pressure provided by HHHFNC is unstable and significantly influenced by factors such as the newborn's respiratory rate and tidal volume. For newborns with severe respiratory failure due to HMD, HHHFNC may delay treatment and increase the risk of intubation [20]. Therefore, strict indications should be followed in clinical practice. For newborns with moderate to severe HMD, NCPAP or NIPPV is recommended as the priority choice; for newborns treated with HHHFNC, close monitoring of respiratory status and blood oxygen saturation is necessary, and timely adjustment of the ventilation mode should be made if the condition worsens.

4. Conclusion

The pathogenesis of HMD is complex, involving multiple aspects such as abnormal PS metabolism, genetic factors, immature lung development, and inflammatory oxidative stress. These mechanisms interact with each other, collectively leading to pulmonary dysfunction. As a core treatment for HMD, NIV has established a treatment system based on NCPAP, complemented by modes such as NIPPV and HHHFNC. Combined with measures such as PS replacement therapy and lung protection strategies, it can significantly improve the prognosis of newborns with HMD and reduce complications associated with invasive ventilation. In the future, with the in-depth research on the pathogenesis and the innovation of non-invasive ventilation technology, individualized and precise treatment will become the development trend for the treatment of Hyaline Membrane Disease (HMD), providing stronger guarantees for the life and health of premature infants.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Zhai C, Guo J, Han W, 2025, Comparative Study on the Application Accuracy of DR and CT in the Severity Assessment of Hyaline Membrane Disease in Newborns. Heilongjiang Medicine and Pharmacy Science, 48(9): 172–174.

[2] He R, 2021, Analysis of Imaging Features and Value of X-Ray and CT in the Diagnosis of Hyaline Membrane Disease in Newborns. Modern Medical Imaging, 30(10): 1830–1832 + 1837.

[3] Li F, Han L, 2023, Effect of Pulmonary Surfactant on Hyaline Membrane Disease in Newborns and Its Impact on Procalcitonin and High-Sensitivity C-Reactive Protein. China Journal of Pharmaceutical Economics, 18(5): 61–64.

[4] Tan G, Huang Y, Li M, et al., 2022, Analysis of the Efficacy of Positive Pressure Ventilation in the Treatment of Newborns with Respiratory Diseases. Harbin Medical Journal, 42(4): 28–29.

[5] Du Q, Zhang S, Wang W, et al., 2010, Research and Management Progress of Pulmonary Surfactant in the Prevention and Treatment of Neonatal Respiratory Distress Syndrome. Hainan Medical Journal, 21(4): 122–125.

[6] Zhang B, Deng X, Lan S, et al., 2016, Treatment of Neonatal Hyaline Membrane Disease with Natural Bovine Pulmonary Surfactant Supported by CPAP Ventilation and Its Effects on Blood Gas Indicators. China Medical Equipment, 13(9): 83–86.

[7] Yin X, Li M, Shi Y, et al., 2024, Correlation Between Pulmonary Surfactant Protein-B Deficiency and Respiratory Distress Syndrome in Full-Term Neonates. Journal of Developmental Medicine (Electronic Version), 12(1): 25–29.

[8] Feng C, 2017, Effects of Pulmonary Surfactant on Oxidative Stress Products and Aquaporin Levels in Premature Infants with Respiratory Distress Syndrome. Maternal and Child Health Care of China, 32(16): 3836–3840.

[9] Wang Y, Yao X, Li N, et al., 2019, Research Progress on the Characteristics and Functions of Alveolar Surfactant. Journal of Medical Research, 48(11): 180–183.

[10] Lu D, Li N, et al., 2017, Potential Inflammatory Markers in Obstructive Sleep Apnea–Hypopnea Syndrome. Bosnian Journal of Basic Medical Sciences, 17(1): 47–53.

[11] Schindlbeck U, Wittmann T, Höppner S, et al., 2018, ABCA3 Missense Mutations Causing Surfactant Dysfunction Disorders Have Distinct Cellular Phenotypes. Human Mutation, 39(6): 1–10.

[12] Ou X, Huang A, Huang L, et al., 2025, Changes in Serum IL-6, IL-10, and TNF-α Levels in Preterm Premature Rupture of Membranes and Their Predictive Value for Chorioamnionitis. Shandong Medical Journal, 65(10): 76–78 + 83.

[13] Zheng X, Chen X, 2016, Research Progress on the Role of Oxidative Stress in Hyperoxic Lung Injury in Critically Ill Neonates. Journal of Nanchang University (Medical Science), 56(1): 92–95.

[14] Huang J, Wei E, Li Z, 2021, Clinical Observation of Nasal Biphasic Positive Airway Pressure Ventilation in the Treatment of Apnea in Premature Infants. Fujian Medical Journal, 43(1): 22–25.

[15] Zhang Y, 2016, Clinical Effect of Nasal Continuous Positive Airway Pressure Ventilation in Neonatal Hyaline Membrane Disease. Modern Diagnosis and Treatment, 27(24): 4688–4690.

[16] Zhao J, 2019, Clinical Efficacy of Pulmonary Surfactant Combined with Nasal Continuous Positive Airway Pressure Ventilation in Neonatal Hyaline Membrane Disease. Journal of Clinical Rational Drug Use, 12(18): 71–72.

[17] Fu C, Xia S, 2014, Clinical Application of Nasal Intermittent Positive Pressure Ventilation in Initial Treatment of Respiratory Distress Syndrome in Premature Infants. Chinese Journal of Contemporary Pediatrics, 16(5): 460–464.

[18] Liu C, Guan H, 2015, Efficacy of Three Non-Invasive Mechanical Ventilation Modes in Neonatal Respiratory Distress

Syndrome. Journal of Practical Medicine, 31(5): 734–736.

[19] Jia J, Chen Y, Li R, et al., 2024, Meta-Analysis of Heated Humidified High-Flow Nasal Cannula Ventilation for Preventing Nasal Injury in Preterm Infants with Respiratory Distress Syndrome. Military Nursing, 41(9): 99–103.

[20] Lei H, Shi H, Zhang C, et al., 2025, Initial Heated Humidified High-Flow Nasal Cannula Ventilation for Respiratory Distress Syndrome in Preterm Infants and Its Impact on Cardiac Function. Journal of Medical Research, 54(3): 114–119.