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# Progress in the Treatment of Neonatal Respiratory Distress Syndrome

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**Abstract**: With the rapid development of perinatal medical technology and the maturity of the neonatal transport system, the survival rate of premature infants, especially the very low and extremely low birth weight infants, has increased significantly, which has prompted various problems of neonatal respiratory distress syndrome became the research focus of neonatologists, it also makes many scholars at home and abroad increased the research depth of the disease. In the treatment, the continuous improvement of the quality of pulmonary surfactant, the application of various ventilation modes and the clinical application of INSURE and LISA technology have also greatly improved the survival rate of children with NRDS. In recent years, fluid ventilation and extracorporeal membrane lung (ECMO) have also emerged, which alleviates the difficult situation of transport and rescue of critically ill children to a certain extent. This paper reviews the progress of diagnosis and treatment of NRDS.

**Keywords**: Neonatal, Neonatal Respiratory Distress Syndrome, Progress in Treatment

**Introduction**:

Neonatal respiratory distress syndrome (NRDS) is one of the common diseases of the respiratory system in premature infants, The smaller the gestational age, The higher the incidence rate, It is caused by the lack of pulmonary surfactant. The disease starts rapidly and advances rapidly, and can develop into progressive aggravated dyspnea, cyanosis, and even respiratory failure several hours after birth. In addition, the disease is prone to various complications, such as patent ductus arteriosus, pulmonary hypertension, bronchopulmonary dysplasia, intraventricular hemorrhage, neonatal necrotizing enterocolitis, pneumothorax, retinopathy of prematurity, etc. At present, the diagnosis and treatment methods of this disease are constantly improving, but how to make the clinical diagnosis and treatment of this disease more accurate and standardized after birth has always been the focus of neonatologists' research. This paper aims to summarize the new progress in diagnosis and treatment of NRDS in recent years by reading domestic and foreign clinical research literature.

**1 Nutritional support and fluid management**

Due to the rapid progress in neonatal treatment technology and intensive care, more than 90% of extremely premature infants survive in the neonatal period [1], so nutrition has become a key factor for their future health status. Neonatal nutritional support is mainly divided into two categories, namely, enteral nutrition (EN) and parenteral nutrition (PN). Before the birth of the fetus, who in the maternal uterus, in an almost sterile, mild hypoxic environment, through the umbilical vein to receive continuous intravenous nutrition. Premature infants are faced with a cold environment with high bacteria and oxygen content at birth, not only the nutritional supply is cut off, but also the lack of nutritional reserves. At this time, its demand for nutrition is undoubtedly huge. Due to the transient intestinal immaturity, most premature infants receive parenteral nutrition (PN) within a few weeks after birth [2], and then combine with enteral nutrition support when the condition becomes stable. Studies have confirmed that a small amount of enteral nutrition combined with parenteral nutrition in the early stage is beneficial to the establishment of intestinal flora, increase intestinal tolerance, maintain intestinal function and reduce gastrointestinal complications [3].Although PN can improve the early growth of children, it may also lead to serious complications (such as sepsis, cholestasis, thrombosis, and temporary hyperglycemia of newborns), and the nutrient content is far less than that given to the fetus by the mother through the placenta, which often fails to meet the needs. Lack of fine regulation of parenteral nutrition supply, combined with failure or delay in providing adequate parenteral nutrition, often results in extrauterine growth restriction (EUGR) [4]. However, providing these babies with adequate protein and energy for optimal growth and development remains a challenge that neonatologists will have to overcome.

For newborn, especially premature infants, the organs and systems of the body have not been fully developed, and it is easy to occur water, electrolyte and acid-base balance disorder under pathological conditions. Liquid therapy can not only meet the nutrition needed for the growth and development of the children, but also make the children pass through the "crisis period" more smoothly. Some scholars have pointed out that fluid overload can easily lead to the opening of the ductus arteriosus and even pulmonary edema, which can eventually lead to the deterioration of the clinical outcome of NRDS infants [5]. Therefore, restricted fluid management is particularly critical in the treatment of children with NRDS. Fluid management in


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children with severe NRDS should avoid increasing the risk of pulmonary edema due to fluid overload while ensuring hemodynamic stability and tissue perfusion.

**2 Pulmonary Surfactant (PS)**

Lung surfactant is divided into two kinds, one is natural PS or animal source PS: pig lung, bovine lung lavage fluid or lung homogenate extract; The other is synthetic PS, and although the composition of animal-derived therapeutic PS and endogenous human PS are slightly different, they both overall contain approximately 90% lipids (primarily phospholipids plus cholesterol) and 10% surfactant proteins. Clinical studies have shown that natural PS works faster and improves respiratory support more obviously, which is obviously better than synthetic PS. In recent years, with the clinical popularization of pulmonary surfactant, the mortality of NRDS has been greatly reduced.

Hyun Chang Kim et al. [6] proposed Polymer lung surfactants for the first time in recent years to help overcome the limitations of current animal-derived surfactants in the treatment of NRDS: high production and treatment costs, short supply, complex delivery process and longer active life. It is easier to operate, and does not require any complicated pretreatment process before treatment. Unlike lipid-based lung surfactants, polymer-based dynamic surfactants do not degrade even in the presence of competitive surfactants. In preliminary animal studies, the authors also demonstrated that intratracheal polymeric lung surfactant can be tolerated without causing lung damage to mice and can produce dose-dependent effects to improve lung compliance in mice with acid injury. At present, polymer lung surfactant is still in the conceptual stage, and its safety and efficacy need to be further studied and confirmed. It is expected to be applied in clinical practice in the future.

The way of receive pulmonary surfactant is administered is also being constantly updated. The endotracheal intubation-injection-extubation (INSURE) technology, which was first described by Verder et al. 30 years ago, is getting more and more applications [7].

Leone et al [8] showed that during invasive mechanical ventilation, more lasting oxygenation could be obtained with INSURE technology compared with surfactant. In addition, preterm infants treated with INSURE could reduce the incidence of respiratory comorbidities, including pneumothorax, BPD, and death [9]. However, the sedation required for endotracheal intubation may have adverse effects on children, while endotracheal intubation may cause direct damage to the airway, and positive pressure ventilation and mechanical ventilation may also cause a certain degree of damage to the lungs of premature infants.It is the limitation of INSURE technology that gives more room for the development of new drug delivery methods. That is PS injected through thin tubes. It mainly including less invasive PS treatment (LISA)technology and minimally invasive surfactant therapy (MIST) technology, and it is considered that LISA and MIST technology can replace INSURE technology for children with spontaneous breathing and not requiring mechanical ventilation and endotracheal intubation [10]. Under the condition of non-invasive ventilation, a thin catheter is inserted into the trachea under the glottis through a directly or visual laryngoscope, and PS is injected into the lungs, which can avoid tracheal intubation. Compared with INSURE technology, LISA technology can not only shorten the time of endotracheal intubation and reduce the damage of tracheal mucosa, but also do not need to interrupt NCPAP support when delivering medication, which can make PS spread to the lungs of children better. A meta-analysis of trials comparing LISA with other surfactant dosing methods showed that LISA can reduced the need for MV at any time during neonatal intensive care and reduced the combined risk of death or BPD without increasing the risk of pneumothorax, even in extremely premature infants [11].The latest European guidelines for the treatment of RDS [12] advocate that minimally invasive surfactant therapy as the preferred technique for delivering surfactant to the lung of premature infants with RDS.

But other studies have shown that in addition to surfactant reflux and repeated attempts to insert a tracheal tube into the trachea, 40% of children may experience adverse side effects such as asphyxia, bradycardia, decreased oxygen saturation, apnea, and reduced regional cerebral oxygenation, which are often associated with direct laryngoscopy. It is usually controlled by a brief period of noninvasive positive pressure ventilation and slowing the speed of surfactant application [13-15].It has been reported that the only potential side effect of LISA is a slight increase in local intestinal perforation in infants born at 23-24 weeks [16].It can be concluded that the injection of PS using LISA technology is more helpful for the short-term lung protection of premature infants and the reduction of the incidence of complications, but the long-term prognosis of PS has not been reported, and the exact details of the use of LISA are not yet available. Therefore, further studies are needed to clarify the optimal use mode and long-term impact of LISA.

In recent years, the atomization inhalation method of pulmonary surfactant is also popular, which is non-invasive and easy to operate. Its advantage is that surfactant can be more evenly dispersed in the alveoli, avoiding direct damage to the airway and reducing the need for mechanical ventilation in children [17], but it may make the drugs volatile and affect the efficacy.In the current era, prophylactic surfactants are not recommended as it may increase the risk of lung injury or death. Using a higher initial dose of porcine surfactants may provide better results than using a lower dose of cattle surfactants, possibly due to differences in composition and/or dose. Third generation synthetic surfactants containing protein B and C peptide analogs are being investigated. [18]

In clinical use, PS needs to be rationally selected according to the specific situation of children. Therefore, it is the research focus of neonatologists in China to actively develop better quality pulmonary surfactant, refine the optimal timing and dose of administration, improve minimally invasive or non-invasive drug delivery technology, and continuously improve the short-term and long-term efficacy of NRDS in the future.

### 3. non-invasive ventilation ( NIV )

#### 3.1 nasal continuous positive airway pressure （NCPAP）

Kattwinkel et al [19] first reported the use of continuous positive pressure ventilation (CPAP) for bilateral nasal obstruction (NCPAP) in newborns in 1973.Currently NCPAP has become the most commonly used non-invasive ventilation mode for premature infants. NCPAP refers to a ventilation method that provides a certain pressure level through a nasal mask to maintain airway pressure higher than atmospheric pressure throughout the entire breathing cycle. Early treatment with NCPAP induces alveolar development and restores volume, and early use of NCPAP after birth reduces the need for intubation in children with NRDS. In the early stages of NRDS, PS combined with NCPAP is more effective than NCPAP alone [20], and can reduce the risk of respiratory distress, ventilator-induced lung injury, and bronchopulmonary dysplasia [21].

#### 3.2 nasal Intermittent positive pressure ventilation （NIPPV）

According to whether the change of intermittent positive pressure ventilation is synchronized with the spontaneous breathing of the child, it can be divided into Synchronized nasal intermittent positive pressure ventilation and Nasal non-synchronous intermittent positive pressure ventilation. nasal intermittent positive pressure ventilation is a respiratory support mode that gives a certain frequency of intermittent positive pressure on the basis of NCPAP, which combines continuous positive end-expiratory pressure (PEEP) with intermittent high pressure provided by the nose mask [22].In SNIPPV, the intermittent increase of nasal pressure into the lower airway increases tidal volume (Vt), minute ventilation (Vm), and the work of breathing (WOB).In addition, higher mean airway pressure (MAP) is associated with better alveolar filling and improvement of functional residual capacity (FRC) [23].NIPPV is more effective than NCPAP in providing respiratory support and preventing intubation for premature infants, which can reduce respiratory failure and the need for endotracheal intubation [24].In studies on premature infants after extubation, NIPPV was found to be more effective in reducing the incidence of extubation failure and re-intubation, but the risk of chronic lung disease was not reduced [25].

#### 3.3 nasal Bilevel positive airway pressure ventilation （nBiPAP）

BiPAP is composed of two pressures , peak inspiratory pressure and end expiratory pressure, which makes the airway pressure fluctuate from the set upper limit to the lower limit, and can be adjusted according to the condition of the child. BiPAP can provide two different levels of continuous positive airway pressure alternating with each other, so that children can form two different functional residual capacity under different stress levels, with the increase of pressure, thus improve the tidal volume, eventually increase the minute ventilation and reduce the work of breathing, so BiPAP has better respiratory support effects than NCPAP [26]

In 2016, Alireza Sadeghnia et al [27] conducted a clinical randomized controlled study of NBiPAP and NCPAP on children with RDS whose body weight was less than 1500g, and found that there was no significant difference in the treatment effects of non-invasive ventilation, duration of oxygen need, subsequent need for mechanical ventilation and complications. There was no obvious clinical bias between the two non-invasive breathing support mode. However, Vincenzo Salvo et al. [63] and Letizia Capasso et al. [28] found that NBiPAP was more conducive to reducing the failure rate and complications compared with NCPAP in the study of RDS children with very low birth weight and newborns with gestational age less than 30 weeks. Carla Cimino et al. [29] conducted a retrospective study on children with full-term infants with NRDS and found that BiPAP ventilation at the early stage of RDS was more effective compared with NCPAP. Although it failed to change non-invasive ventilation time and length of hospital stay, it was more helpful to improve CO2 retention and reduce the demand for FiO2 at the early stage. In recent years, NIPPV has gradually been replaced nCPAP, and is becoming the preferred non-invasive respiratory support mode for newborns with mild to moderate dyspnea.

#### 3.4 Heated Humidified High-Flow Nasal Cannula (HHHFNC)

Recently, Guimaraes et al. [30] of 135 preterm infants with birth weight less than 1500g who received CPAP found that 65% had nasal trauma and 26% had skin lesions of varying severity. Therefore, many scholars have been looking for alternative treatments. As the primary treatment for mild and moderate respiratory distress in preterm infants, heating and humidifying high-flow nasal catheter (HHHFNC) has shown similar efficacy and safety to CPAP, and may reduce the likelihood of nasal trauma and pneumothorax, but it is not recommended for preterm infants of small gestational age [31].

In the future, non-invasive respiratory support will continue to develop, update and improve, or become the mainstream direction of respiratory support for premature infants. As a novel method of non-invasive support, neuromodulation ventilatory assistance (NAVA) has been successfully applied to neonates. The time and degree of ventilation assistance are controlled by the children, which can better achieve the synchronization of the ventilator and the spontaneous breathing of the newborn [32].We are currently conducting large-scale clinical trials of new non-invasive respiratory support models to identify their strengths and weaknesses.

**4 Invasive mechanical ventilation（IMV）**

Mechanical ventilation is necessary for premature infants with severe pulmonary diseases, but is also considered to be one of the causes of ventilator-associated pneumonia, pneumothorax and BPD. Reducing the need and duration of invasive mechanical ventilation can improve the outcome of premature infants [33]. According to the ventilation frequency, it can be divided into conventional mechanical ventilation (CMV) and high frequency ventilation (HFV).

**4.1 conventional mechanical ventilation**

conventional mechanical ventilation of newborns has been used for decades to treat respiratory failure, and the technology has greatly developed during this period. However, the basis of CMV remains unchanged: humidified, heated, oxygen-filled gas enters the lungs of infants at a certain pressure (peak inspiratory pressure or PIP) for a period of time (inspiratory time or Ti) , and followed by a fixed period of expiratory phase (expiratory time or Te) which positive end expiratory pressure (PEEP) is maintained. This cycle is repeated several times a minute, creating a certain breathing rate, or rhythm. Positive end-expiratory pressure (PEEP), which can be considered as the continuous pressure applied throughout the respiratory cycle, plays an important role in keeping the lung open and preventing collapse, enabling all areas of the lung to participate in gas exchange [34].In recent years, CMV, which can provide appropriate positive end-expiratory pressure, can reduce mortality to a certain extent, but lung injury may occur in the process of treatment, resulting in pulmonary hemorrhage, pulmonary air leakage and other complications.

**4.2 High frequency oscillation ventilation**

As a protective ventilation strategy, HFOV can regulate positive end-expiratory pressure or average airway pressure by ventilation with low tidal volume, high frequency and low airway pressure, so as to expand lungs to an appropriate volume and maintain stability, thus improving ventilatory oxygenation. Studies have shown [35] that HFOV can significantly improve the fraction of inspired oxygen, oxygen index and average airway pressure in premature infants with RDS compared with CMV, especially in the early reduction of ventilator parameters. One trial demonstrated that initial use of HFOV reduced the need for ventilatory support and re-intubation in very low birth-weight infants and shortened the hospital stay and costs in the NICU [36].This is because the high speed gas of HFOV can increase convection and diffusion, in this state, alveoli can be directly ventilated and evenly expanded, the gas in the lung can be quickly exchanged, the blood oxygen is fully oxygenated, which is more conducive to avoid alveolar collapse, low blood oxygen, carbon dioxide retention and other adverse phenomena. Low pressure, low volume and hypoxia ventilation provide a safety guarantee to avoid lung volume injury, barometric injury and high oxygen injury [37].

However, according to current studies, high-frequency oscillatory ventilation may lead to the risk of intraventricular hemorrhage and leukomalacia [38], as well as hemodynamic changes and air trapping [39]. It is necessary to make a reasonable choice according to the condition of children to get the best ventilation effect.

**5 Liquid Ventilation**

Liquid ventilation is expected to be a rescue method for patients with respiratory failure such as NRDS after the failure of conventional treatment. Liquid ventilation is operated through the medium of perfluorocarbons (PFC) , which characterized by high respiratory gas solubility and low surface tension, is divided into total liquid ventilation (TLV) and partial liquid ventilation (PLV).At present, there are few studies on liquid ventilation therapy, among which Carmen Rey-Santano et al. [40] conducted a study on premature lambs and proposed that in the model of premature lambs, the younger the gestational age is, the more likely it is to develop severe RDS, but PLV treatment can achieve the same degree of improvement in lung function regardless of gestational age. It may help to improve the lung dysplasia of children who do not respond to PS treatment, but the study is still limited, and it is unable to clearly evaluate the distribution of perfluorocarbons in the lungs, and the specific mechanism remains to be further discovered. At present, there are few clinical applications of liquid ventilation therapy in the treatment of NRDS at home and abroad, and it is basically in the experimental stage of animal model. However, the potential of liquid ventilation technology cannot be denied. In the near future, liquid ventilation therapy may become another important life support for critically ill children.

**6 Extracorporeal membrane oxygenation (ECMO)**

Extracorporeal membrane oxygenation (ECMO) is a treatment for severe respiratory and circulatory failure. It was first used in neonates in 1970. Over the years, the indications for ECMO have changed, but it is still clinically used as an alternative to conventional mechanical ventilation and adjuvant therapy after failure [41]. ECMO is divided into veno-venous (V-V) diversion and veno-arterial (V-A) diversion. VV diversion is to make up for insufficient lung function by increasing the oxygen content in venous blood, and it can only replace part of the lung function. It is generally applicable to patients with heart failure or cardiopulmonary failure, while V-A diversion can provide hemodynamic support by increasing systemic blood flow in addition to increasing blood oxygen content [42]. ECMO technology has also been widely applied and have better effect on neonatal respiratory diseases in China, especially for NRDS, PPHN, meconium aspiration syndrome, sepsis and congenital diaphragmatic hernia. It is often used to rescue the transport of critically ill children with cardiopulmonary failure and provide an important basis for the subsequent improvement of neonatal survival rate [43]. Due to the high cost of treatment, ECMO has limitations in clinical application. In the use of ECMO, it is necessary for technicians to choose the correct flow reversal mode, establish the correct concept of ECMO start-up and removal, and operate with a rigorous and meticulous attitude, so as to ultimately reduce ECMO-related complications and mortality, and improve the success rate of ECMO in the treatment of neonatal respiratory failure and heart failure.

## 7 Outlook and Summary

To sum up, after years of exploration and research, the treatment of NRDS has made breakthrough progress. However, with the opening of the national three-child policy and the increase of elderly mothers, NRDS will still be a common disease of the respiratory system of premature infants. The incidence of NRDS-related complications also increases year by year. Therefore, the exploration and in-depth treatment of NRDS cannot be stopped. I believe that we can overcome technical difficulties and escort the safety of children with neonatal respiratory distress syndrome in the near future.

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