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Research Progress on Surfactant and Non-Invasive Respiratory Support for Neonatal Respiratory Distress Syndrome

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Abstract

Neonatal respiratory distress syndrome (NRDS) mainly affects preterm infants and remains one of the leading causes of early neonatal death. Survivors are at considerable risk of bronchopulmonary dysplasia (BPD), which worsens quality of life and long-term outcomes. The management of NRDS is multidisciplinary, and the 2025 European Consensus Guidelines on the Management of Respiratory Distress Syndrome recommend early pulmonary surfactant (PS) combined with non-invasive respiratory support, and advise limiting the use of invasive mechanical ventilation as much as possible to reduce lung injury and its downstream complications. Minimally invasive techniques for PS delivery have been refined over recent years, and the clinical evidence for various non-invasive ventilation modes has grown quickly. However, consensus regarding the optimal indications and the appropriate gestational-age subgroups for each non-invasive modality remains to be established. In this review, we summarize current evidence on exogenous PS administration strategies and non-invasive respiratory support modalities, with the aim of informing standardized clinical practice for the management of NRDS.

Keywords

Neonatal Respiratory Distress Syndrome, Pulmonary Surfactant, Minimally Invasive Surfactant Administration, Non-Invasive Respiratory Support, Preterm Infant

1. Introduction

Neonatal respiratory distress syndrome (NRDS) arises principally from impaired synthesis and secretion of pulmonary surfactant (PS) in the immature preterm

lung. In the absence of timely intervention, affected infants develop reduced lung compliance and progressive hypoxemia, and may progress to overt respiratory failure [1]. A Chinese multicenter epidemiological investigation reported an NRDS incidence of 15.3% among preterm infants; the case-fatality rate of 10.5% substantially exceeded the 0.8% mortality observed in RDS-free preterm infants [2]. The risk of RDS is inversely related to gestational age, and RDS remains a leading cause of death within the first 24 h of life among preterm infants with a gestational age < 32 weeks and a birth weight < 1500 g. In 1959, Avery and Mead established a direct causal relationship between PS deficiency and NRDS. Exogenous PS replacement substantially reduces NRDS-related mortality and the subsequent risk of BPD [3]. Meta-analyses have identified mechanical ventilation exposure as a principal modifiable risk factor for BPD, and the appropriate implementation of non-invasive ventilation can reduce the composite risk of BPD and mortality [4]. Invasive mechanical ventilation has improved survival in very-low-birth-weight infants, but barotrauma, volutrauma and oxidative stress from the ventilator itself increase the susceptibility to BPD [5]. Infants who develop BPD often have persistent respiratory dysfunction, cerebral palsy, visual and auditory impairment and other neurodevelopmental problems, all of which are linked to higher long-term mortality [6]. For this reason, current management of NRDS favors non-invasive respiratory support plus selective PS replacement, and avoids endotracheal intubation whenever the clinical situation allows. With growing experience, minimally invasive PS delivery has been optimized and several non-invasive ventilation modes have entered routine practice. This review summarizes the current evidence on PS-related strategies and on the main non-invasive respiratory support modes.

2. Application of Exogenous Pulmonary Surfactant

Fujiwara and colleagues treated NRDS with bovine surfactant for the first time in 1980, which opened the era of animal-derived PS replacement [7]. Many randomized controlled trials since then have confirmed its efficacy. The 2025 European Consensus Guidelines give animal-derived PS a strong recommendation in infants with RDS (evidence level A1) [8].

Traditionally, PS has been administered via endotracheal intubation under positive-pressure ventilation. To reduce iatrogenic airway injury, treatment strategies have progressively shifted from the "intubation-administration of pulmonary surfactant-extubation" (INSURE) protocol to less invasive surfactant administration (LISA; also referred to as minimally invasive surfactant therapy, MIST). LISA permits PS instillation while preserving spontaneous breathing, thereby reducing the duration of exposure to invasive mechanical ventilation [9].

2.1. The INSURE Technique

In INSURE, PS is instilled through the endotracheal tube, the tube is removed immediately, and nasal continuous positive airway pressure (NCPAP) is then ap-

plied. The aim is to shorten the time on invasive mechanical ventilation. It was once used widely in preterm infants with RDS who breathed adequately on their own. Even so, brief intubation is still required, with the attendant risks of airway mucosal injury, hypoxia and bradycardia during the procedure. Meta-analyses comparing LISA with INSURE report more frequent exposure to mechanical ventilation and higher odds of BPD after INSURE. INSURE therefore has a place mainly as a backup option in centers that cannot perform LISA [9].

2.2. LISA/MIST: Minimally Invasive Surfactant Administration

LISA is done while the infant breathes spontaneously on non-invasive support. Under laryngoscopy, a thin catheter is passed into the trachea and PS is instilled through it; neither intubation nor positive-pressure ventilation is needed. The drug spreads through the lungs with the infant's own breathing, so airway trauma and barotrauma are kept to a minimum. The technique requires considerable skill in neonatal airway management. Reflux of PS, hypoxia and bradycardia during the procedure occur in about 10% - 30% of cases. Video-laryngoscope-assisted catheter placement mitigates these procedural complications; the 2025 European Consensus Guidelines on the Management of Respiratory Distress Syndrome recommend video-laryngoscope-assisted LISA (evidence level C2) [8].

Large-scale cohort data from the German Neonatal Network (n = 7533 very-low-birth-weight infants) show that LISA, relative to surfactant delivery via an endotracheal tube, is associated with lower odds of mortality (OR 0.66), BPD (OR 0.55) and grade II-IV intraventricular hemorrhage (OR 0.55), conferring favorable short-term outcomes for preterm infants. Special vigilance is warranted for infants < 26 weeks' gestation, because LISA correlates with an elevated risk of focal intestinal perforation, which was reported in 10.0% versus 7.4% of infants treated with LISA and with an endotracheal tube, respectively (P = 0.029). For this high-risk subgroup, clinicians must carefully weigh benefit-risk profiles and closely monitor abdominal clinical signs [10]. When surfactant is indicated, the 2025 European RDS guidelines suggest a protocol in which PS is given to infants on non-invasive support who meet any one of the following criteria: a mean airway pressure of ≥6 cmH_2O, a fraction of inspired oxygen (FiO_2) of ≥0.3, or lung ultrasonography findings suggestive of PS deficiency. These thresholds are alternatives within one suggested protocol rather than independent criteria; in practice, oxygen requirement and distending pressure are judged together. A mean airway pressure of ≥6 cmH_2O alone, in an infant whose oxygen need is low and whose lung ultrasound does not suggest surfactant deficiency, is not in itself a reason to give surfactant. For spontaneously breathing preterm infants with RDS on non-invasive support, LISA is the preferred route (evidence level A1) [8]. Pooled data show a lower BPD incidence after LISA than after INSURE, with similar overall mortality. LISA significantly reduces mechanical-ventilation exposure and improves respiratory outcomes at 20 months corrected age, whereas neurodevelopmental outcomes are similar across the two techniques [9] [11].

The magnitude of benefit, however, depends on the comparator and on the population studied. The OPTIMIST-A trial randomized 485 infants of 25 - 28 weeks' gestation who were supported with CPAP and required an $FiO_2 \geq 0.30$ within 6 h of birth to thin-catheter surfactant (200 mg/kg poractant alfa) or to a sham procedure. The primary composite outcome of death or physiological BPD at 36 weeks' postmenstrual age occurred in 43.6% and 49.6% of infants, respectively (risk difference −6.3%, 95% CI −14.2 to 1.6; RR 0.87, 95% CI 0.74 - 1.03; P = 0.10), so the reduction did not reach statistical significance, although the confidence interval does not exclude a clinically important effect. BPD among survivors was lower with LISA (37.3% vs 45.3%; RR 0.83, 95% CI 0.70 - 0.98), mortality before 36 weeks was similar (10.0% vs 7.8%; P = 0.51), and an exploratory analysis raised a signal of higher mortality in the 25 - 26-week stratum. The advantage of surfactant delivery by thin catheter over a sham procedure, or over INSURE, should therefore not be generalized to every comparison, and in the most immature infants this mortality signal has to be weighed against the benefit [12].

Recent international multicenter studies suggest that combining LISA with nasal intermittent positive-pressure ventilation (NIPPV) may further reduce the need for invasive ventilation and for a second dose of surfactant; larger randomized trials are still needed to confirm this [13].

2.3. PS Dosing, Repeated Administration and Innovative Delivery Modalities

The 2025 European guidelines favor an initial poractant alfa dose of 200 mg/kg over 100 mg/kg (evidence level A1). A second or even a third PS dose may be considered for persistent high oxygen demand after confounding etiologies such as infection and cardiac dysfunction have been excluded [8]. Novel non-invasive delivery strategies remain investigational and are supported by insufficient evidence for routine clinical implementation; such strategies should therefore be restricted to research settings [8]. Surfactant administration through laryngeal or supraglottic airways (SALSA) is performed with a laryngeal mask or another supraglottic device placed without laryngoscopy; it has been evaluated mainly in infants of 27 - 36 weeks' gestation and >800 g, in whom it was non-inferior to brief tracheal intubation (INSURE) in avoiding mechanical ventilation. The 2025 European guidelines accordingly state that supraglottic airway devices may be used for surfactant delivery in larger infants (evidence level B2). Because the procedure avoids laryngoscopy, it may be considered in units where laryngoscopy skills are limited, but the available trials are small and mainly enrolled more mature infants, and the evidence is insufficient in infants < 32 weeks or <1500 g. Nebulized PS is likewise not recommended for routine use [8] [14]. Prophylactic PS is suggested only for extremely preterm infants < 28 weeks' gestation who manifest early features of RDS following delivery-room stabilization (evidence level B2), and universal prophylactic PS administration is discouraged [8].

3. Non-Invasive Respiratory Support

Non-invasive respiratory support is the foundation of modern NRDS care. The overarching goals are to recruit the alveoli, reduce the work of breathing, and avoid intubation and invasive ventilation whenever possible. The main modes in clinical use are NCPAP, NIPPV and non-invasive neurally adjusted ventilatory assist (NIV-NAVA). They differ in how they work, in which infants they suit, and in the risk of treatment failure.

3.1. Nasal Continuous Positive Airway Pressure (NCPAP)

NCPAP in neonates was first described by Kattwinkel and colleagues in 1973 [15]. It holds the functional residual capacity, lowers the work of breathing and keeps the upper airway open, and it remains the basic non-invasive intervention for NRDS. The 2025 European Consensus Guidelines on the Management of Respiratory Distress Syndrome recommend early initiation of NCPAP in high-risk preterm infants with RDS following delivery-room resuscitation, with an initial pressure setting of 6 - 8 cmH_2O [8].

The efficacy of early NCPAP as initial support, rather than as post-extubation support, is best documented in randomized trials that compared early NCPAP with primary intubation and mechanical ventilation. A Cochrane review of eight trials (3201 infants) found that, compared with primary mechanical ventilation, prophylactic or very early NCPAP reduced BPD at 36 weeks (RR 0.89, 95% CI 0.80 - 0.99), the composite outcome of death or BPD (RR 0.89, 95% CI 0.81 - 0.97) and the need for mechanical ventilation (RR 0.49, 95% CI 0.45 - 0.54) in very preterm infants. The absolute benefit was modest, and no reduction in mortality alone was demonstrated [16]. Nevertheless, NCPAP failure occurs in up to 50% of very-low-birth-weight infants. Recognized risk factors include male sex, birth weight ≤ 800 g, and $FiO_2 > 0.25$ within the first 1 - 2 h after birth. Prompt identification of high-risk infants permits timely escalation of respiratory support and prevents delays in PS therapy or endotracheal intubation [8].

NCPAP is the reference standard against which the other modes are judged. When NCPAP fails, the options are to step up to NIPPV, NHFOV or another non-invasive mode, or to move to invasive mechanical ventilation as the clinical situation demands [8] [17].

3.2. Nasal Intermittent Positive-Pressure Ventilation (NIPPV)

NIPPV adds intermittent positive pressure on top of NCPAP, which enlarges tidal volume and helps clear carbon dioxide. It exists in a synchronized form (SNIPPV) and a non-synchronized form. The synchronized form has theoretical and clinical advantages yet imposes higher hardware requirements; substantial circuit leaks under non-invasive conditions create technical obstacles to reliable triggering and synchronization [17].

Evidence on NIPPV should be read separately for initial support and for post-extubation support. For the post-extubation setting, a Cochrane review of 19 trials

(2738 infants) found that NIPPV, compared with NCPAP, reduces the risk of respiratory failure (RR 0.75, 95% CI 0.67 - 0.84) and endotracheal reintubation (RR 0.78, 95% CI 0.70 - 0.87), with little difference in bronchopulmonary dysplasia, mortality or gastrointestinal perforation. These findings establish NIPPV as effective transitional support after extubation [18]. As initial support, the position of NIPPV is less certain. Oncel's randomized trial in 200 infants of 26 - 32 weeks' gestation receiving surfactant by MIST showed that initial NIPPV, compared with NCPAP, reduced the need for invasive ventilation within 72 h (13% vs 29%) and the proportion requiring surfactant (38% vs 60%), but the difference in BPD was not confirmed in multivariable analysis. Kirpalani's large multicenter trial of 1009 infants of 1000 - 1500 g at birth found no significant reduction in death or BPD with NIPPV compared with NCPAP when used as primary support, although NIPPV reduced the need for intubation and for respiratory support at 36 weeks in secondary analyses. Taken together, the reduction in reintubation after extubation does not establish that NIPPV is superior to NCPAP as initial treatment for NRDS, and the choice of initial mode should therefore rest on the available initial-support evidence as well as on the availability of synchronization [13] [19].

According to the 2025 European guidelines, synchronized NIPPV may be deployed as escalation therapy following NCPAP failure or as post-extubation transitional support, and the guidelines now regard nasal ventilation as the most potent form of non-invasive support both after initial stabilization and after weaning from mechanical ventilation. Favorable evidence also supports its use as initial respiratory support for infants ≥ 28 weeks' gestation with RDS (evidence level A2), whereas further data are required to define its value in extremely preterm infants < 26 weeks' gestation [8].

3.3. Bilevel Positive Airway Pressure (BiPAP)

BiPAP delivers alternating high- and low-pressure cycles while permitting unimpeded spontaneous breathing throughout the respiratory cycle. The pressure gradient between the high and low levels should generally not exceed 3 - 4 cmH_2O, and cycling frequencies are relatively low. Single-center studies with small samples have demonstrated that BiPAP shortens respiratory support and oxygen therapy and the hospital length of stay for preterm infants with moderate RDS relative to NCPAP [20]. A Chinese retrospective cohort study showed that BiPAP reduced the 72-h intubation rate for preterm infants ≤ 32 weeks' gestation with RDS, without producing measurable benefit in BPD outcomes [21].

Meta-analyses and the European guideline agree that BiPAP is not superior to NCPAP overall. Differences in non-invasive support failure, air-leak events and BPD incidence between groups are not statistically significant. BiPAP is not recommended as first-line initial therapy for RDS and is best kept as an alternative backup option [8] [20].

3.4. Heated Humidified High-Flow Nasal Cannula (HHFNC)

HHFNC delivers heated, humidified blended air-oxygen mixtures. It is easy to

operate and carries a relatively low risk of nasal mucosal injury. However, the pharyngeal positive end-expiratory pressure (PEEP) it produces cannot be measured directly and changes with the infant's posture and nasal anatomy. As primary support, HHFNC has not been shown to be non-inferior to NCPAP: in infants ≥ 28 weeks' gestation randomized after birth, treatment failure within 72 h was significantly more frequent with HHFNC than with NCPAP in a pre-specified non-inferiority analysis. In the post-extubation setting, by contrast, randomized trials and meta-analyses that used treatment failure, defined as a composite of oxygen requirement beyond a prespecified threshold, respiratory acidosis, recurrent apnea requiring positive-pressure support, or the need for reinstitution of CPAP/NIPPV, reported failure rates that were similar between HHFNC and NCPAP, with a lower incidence of nasal trauma under HHFNC. Even in that setting, failure of HHFNC frequently required escalation to NCPAP rather than immediate intubation, so the reported reintubation rates were similar in the two groups and the non-inferiority claim for reintubation as an isolated outcome is weaker than that for treatment failure. Because infants assigned to HHFNC in these trials retained access to rescue NCPAP/NIPPV, the reported failure rates describe the performance of HHFNC within a unit able to escalate promptly, and not the outcome of HHFNC used without a rescue option [22]-[24]. In contrast, infants < 28 weeks' gestation demonstrate a markedly elevated risk of non-invasive support failure under HHFNC. Both the Chinese 2023 Clinical Practice Guideline for Neonatal High-Flow Nasal Cannula Oxygen Therapy and the 2025 European RDS guidelines discourage the use of HHFNC as initial respiratory support for preterm infants < 28 weeks' gestation diagnosed with RDS; HHFNC may be reserved for mild RDS or for post-extubation transitional respiratory support [8] [25] [26].

When HHFNC is used, clinical units must maintain the capability for rapid conversion to NCPAP/NIPPV. Continuous monitoring of oxygenation status, respiratory rate, and blood-gas parameters is mandatory for the timely detection of impending non-invasive support failure [8] [26].

3.5. Non-Invasive High-Frequency Oscillatory Ventilation (NHFOV)

NHFOV transmits high-frequency oscillatory pressure waveforms via the nasal route to enhance carbon dioxide elimination and, theoretically, to promote alveolar recruitment. A Chinese randomized controlled trial enrolling preterm infants of 29 - 34 weeks' gestation with grade II-III NRDS found that, as the initial non-invasive mode, NHFOV improved the oxygenation index, lowered the partial pressure of carbon dioxide, and increased the success rate of non-invasive ventilation compared with NCPAP (13/17 vs 9/21), although the duration of non-invasive support and the incidences of BPD, intraventricular hemorrhage, mortality, air leak and abdominal distension did not differ. These findings are limited by the modest sample size and the exclusion of infants < 28 weeks' gestation, which restricts their generalizability [27].

More recent moderate-sized studies indicate that NHFOV after extubation shortens the duration of invasive ventilation and lowers the reintubation rate. The main adverse effects are upper-airway mucus obstruction and abdominal distension, and the high cost of the equipment limits wider use [28]. The available evidence does not support NHFOV as routine first-line therapy for uncomplicated RDS. It has a role as a rescue non-invasive option in moderate-to-severe RDS after NCPAP/NIPPV failure, when immediate intubation is not mandatory. Its safety in infants below 26 weeks of gestation still needs clinical validation [8].

3.6. Non-Invasive Neurally Adjusted Ventilatory Assist (NIV-NAVA)

NIV-NAVA is triggered by the electrical activity of the diaphragm (Edi). Because assistance follows the infant's own breathing effort, patient-ventilator synchrony is close to optimal, and in theory the work of breathing and patient-ventilator asynchrony are minimized. Small clinical observations support its use after extubation to reduce extubation failure, and a systematic review suggests that post-extubation NIV-NAVA may reduce reintubation and intrapharyngeal pressure swings, though the certainty of this evidence is low. As initial therapy for NRDS, no high-quality randomized trial has yet shown it to be superior; this distinction between the post-extubation and initial settings matters when NIV-NAVA is chosen [29]. In practice, the need for special hardware, the difficulty of electrode positioning and signal artifacts all limit its wider use. NIV-NAVA is a promising new mode that still needs multicenter trials on safety, efficacy and cost-effectiveness [8].

4. Summary and Perspectives

Based on the 2025 European Consensus Guidelines and on clinical studies from home and abroad, modern NRDS management rests on three pillars: antenatal corticosteroids, non-invasive respiratory support started in the delivery room, and early selective PS replacement. The shared aim is to limit exposure to invasive mechanical ventilation [8].

With regard to PS delivery, LISA/MIST constitutes the preferred PS administration strategy for spontaneously breathing preterm infants with RDS, subject to adequate operator training; the size of the benefit depends on the comparator, being clearest against INSURE and less certain against continued CPAP in 25 - 28-week infants, in whom the OPTIMIST-A trial did not show a statistically significant reduction in death or BPD. Clinicians must remain vigilant regarding the risk of focal intestinal perforation when performing LISA in infants < 26 weeks' gestation [10]. Surfactant instillation via laryngeal or supraglottic airway devices (SALSA) may be used in larger infants, although the evidence in infants < 32 weeks or <1500 g remains insufficient, and nebulized PS is not recommended for routine clinical application [8] [14].

When choosing a non-invasive mode, the evidence should be interpreted sepa-

rately for initial and for post-extubation support. For initial support, NCPAP at 6 - 8 cmH_2O remains the first-line choice, with synchronized NIPPV as an alternative where available; HHFNC is suitable only for infants of at least 28 weeks' gestation with mild RDS; NHFOV and NIV-NAVA serve as rescue options rather than routine front-line therapy. After extubation, synchronized NIPPV reduces the need for re-ventilation compared with NCPAP, without a proven benefit in BPD or mortality, and HHFNC may be used as part of step-down from NCPAP in more mature infants [8] [18] [24].

Specific clinical findings mandate immediate intubation rather than further trials of non-invasive modalities. The most consistent triggers are recurrent or persistent apnea that requires assisted ventilation, and worsening respiratory acidosis, that is, a pH < 7.20 with $PaCO_2$ > 60 mmHg that is confirmed on repeated blood-gas analysis and persists despite optimization of the interface, position and pressure; a sustained oxygen requirement of $FiO_2 \geq 0.4$ to maintain the target saturation range despite an adequate mean airway pressure and, where used, surfactant; and hemodynamic instability, an acute air leak such as pneumothorax, or an inadequate gag or airway protective reflex. In units with a documented escalation policy, these criteria should be applied within a predefined time window, so that failure of one non-invasive modality is followed by prompt escalation to the next modality or to intubation rather than by prolonged observation [8] [30].

Multiple clinically relevant questions remain to be resolved, including objective thresholds for switching between non-invasive modalities across gestational-age subgroups; optimal combinatorial regimens coupling LISA with various non-invasive ventilation modalities; lung-ultrasound-guided precision PS administration protocols; minimally invasive respiratory support algorithms for extremely preterm infants (22 - 24 weeks' gestation); and long-term respiratory and neurodevelopmental follow-up of NRDS survivors. Further Chinese multicenter randomized controlled trials are warranted in order to establish individualized NRDS respiratory-management protocols adapted to domestic neonatal-care realities [30].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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