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EDUCATIONAL REVIEW

Update on ventilatory management of extremely preterm infants—A Neonatal Intensive Care Unit perspective

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Abstract

Extremely preterm infants commonly suffer from respiratory distress syndrome. Ventilatory management of these infants starts from birth and includes decisions such as timing of respiratory support in relation to umbilical cord management, oxygenation targets, and options of positive pressure support. The approach of early intubation and surfactant administration through an endotracheal tube has been challenged in recent years by primary noninvasive respiratory support and newer methods of surfactant administration via thin catheters. Available data comparing the thin catheter method to endotracheal tube and delayed extubation in extremely preterm infants born before 28 weeks of gestation did not show differences in survival free of bronchopulmonary dysplasia. Data from numerous randomized trials comparing conventional ventilation with high-frequency oscillatory ventilation did not show differences in meaningful outcomes. Among conventional modes of ventilation, there is good evidence to favor volume-targeted ventilation over pressure-limited ventilation. The former reduces the combined risk of bronchopulmonary dysplasia or death and several important secondary outcomes without an increase in adverse events. There are no evidence-based guidelines to set positive end-expiratory pressure in ventilated preterm infants. Recent research suggests that the forced oscillation technique may help to find the lowest positive end-expiratory pressure at which lung recruitment is optimal. Benefits and risks of the various modes of noninvasive ventilation depend on the clinical setting, degree of prematurity, severity of lung disease, and competency of staff in treating associated complications. Respiratory care after discharge includes home oxygen therapy, lung function monitoring, weaning from medication started in the neonatal unit, and treatment of asthma-like symptoms.

KEYWORDS
Neonate, NICU, respiration

1 | INTRODUCTION

Respiratory distress syndrome (RDS) is the single most important cause of morbidity and mortality in preterm neonates. Ventilatory management of extremely preterm infants, that is, those born before 28 weeks of gestation, includes three distinct time periods: (1) respiratory support in the delivery room, (2) ventilatory support in the neonatal intensive care unit (NICU), and (3) postdischarge management of respiratory issues. This review highlights recent developments in ventilatory management of these highly vulnerable infants along this critical timeline of early life.

2 | RESPIRATORY SUPPORT IN THE DELIVERY ROOM

2.1 | Timing of respiratory support in relation to umbilical cord management

Extremely preterm birth is associated with immaturity of multiple organ systems, resulting in frequent need of resuscitation at birth and substantially increased morbidity and mortality compared to more mature preterm and term infants.[1] Traditionally, rapid initiation of respiratory support was the dominant task at delivery of extremely preterm neonates with neonatal care teams counting the time from birth to having the baby on the resuscitation table and providing positive pressure support as soon as possible. Although timely provision of positive pressure support is still a priority, several strategies of timing of respiratory support in relation to umbilical cord management are under investigation. These include deferring cord clamping for 30–120 s or delaying cord clamping until the infant is breathing regularly (so-called "physiology-based cord clamping") and cord milking with or without intact cord. If cord clamping is delayed, placental transfusion improves blood transfer toward the infant. Based on a recent meta-analysis, delayed cord clamping and intact cord milking probably improve hematological measures but do not seem to affect major neonatal morbidities although earlier studies suggested an increased risk of severe intraventricular hemorrhage attributable to intact cord milking in extremely preterm neonates.[2,3] Delayed cord clamping may offer a small survival benefit but the certainty of this evidence is only moderate.[4] The risk-benefit ratio of both physiology-based cord clamping and cord milking is still unclear and under current investigation.[4]

2.2 | Oxygen concentration and oxygen saturation targets at birth

Extremely preterm neonates have limited antioxidant capacity and are probably more prone to the toxic effects of oxygen than late preterm or term infants.[5] Over the last decade, reference ranges of oxygen saturation in the first 10 min of life have become available through cohort studies. Contemporary practice includes targeting of those reference values, for example, by using the interquartile range of preductal pulse oximetric oxygen saturation levels (SpO_2) during resuscitation to adjust oxygen concentration of respiratory support.[6] Based on those cohort studies, it is evident that nearly all extremely preterm neonates require supplemental oxygen during the first 5 min of life, with a median requirement of about 30% O_2. Assuming that caregivers use SpO_2 targeting to reach SpO_2 reference values, it is currently unclear whether starting resuscitation of preterm neonates with low (21%–39%) vs. high (≥40%) oxygen concentration offers any short- or long-term benefits, that is, adjusting initial oxygen concentration to match reference SpO_2 targets during early transition is probably the key strategy.[7,8] One pragmatic approach is to start resuscitation with 30% O_2 and affix the 25th percentile of the 3, 5, and 10 min SpO_2 target values (≈70%, 80%, >90% SpO_2) to the resuscitation table with the recommendation to adjust oxygen concentration to achieve those targets (Table 1).[9]

TABLE 1 Target oxygen saturation in neonates shortly after birth

Time from birth	Target oxygen saturation (%)
3 min	70
5 min	80
10 min	>90

Note: Based on preductal oxygen saturation as outlined in Berger et al.[9]

2.3 | Options of positive pressure support in the delivery room

At birth, the lungs of preterm infants are filled with amniotic fluid. In some preterm infants, clearance of fluid from the lungs and establishing regular respiration occurs without any intervention. Those presenting with respiratory distress, irregular breathing, or bradycardia typically receive intermittent positive pressure support.[10] Based on well-controlled animal studies, sustained inflations were believed to establish lung volume faster than intermittent positive pressure ventilation, potentially improving early lung aeration in human neonates. Unfortunately, the multi-center SAIL trial comparing sustained inflations over 15 s vs. intermittent positive pressure ventilation in extremely preterm neonates was stopped early after enrolling 426 babies. Blinded adjudication suggested increased mortality in the sustained inflation group, possibly attributable to the mode of resuscitation.[11] A current Cochrane Review including 9 trials of which the SAIL trial is by far the largest, found no evidence to support the use of sustained inflations for prevention of mortality and respiratory morbidity in neonates.[12]

In extremely preterm infants with respiratory failure, the traditional approach of intubation, surfactant administration, and intermittent positive pressure ventilation (IPPV) has been challenged by short-term intubation for surfactant instillation with immediate extubation to continuous positive airway pressure (CPAP)

(Intubate-Surfactant-Extubate approach) and the primary use of CPAP in order to reduce injury to airways and lungs and to decrease the risk of prematurity-associated chronic lung disease (bronchopulmonary dysplasia, BPD).

Early prophylactic CPAP vs. intubation and IPPV in preterm infants born <32 weeks of gestation reduces the risk of BPD or death, reduces exposure to IPPV, and decreases the need for postnatal corticosteroids.[13] However, the superiority of early CPAP vs. IPPV in the subgroup of extremely preterm neonates, particularly those born at the border of viability, has not been established yet. In these infants, clinicians primarily have to balance the risk of BPD or death being aggravated by IPPV with that of hypoxemia from apnea of prematurity under conditions of CPAP which may contribute to poor neurodevelopment.[14] Additionally, the benefit of surfactant to improve clinical outcomes needs to be considered. While instillation of surfactant through an endotracheal tube is standard of care in intubated extremely preterm neonates, newer approaches favoring the primary use of CPAP focus on less invasive surfactant administration (LISA) via thin catheters. Recent meta-analysis suggests that surfactant instillation via LISA is associated with less BPD or death compared to an Intubate-Surfactant-Extubate approach in preterm neonates <37 weeks. However, included trials almost exclusively enrolled infants above 28 weeks of gestation and were at considerable risk of bias.[15] The single randomized study ($n = 211$) comparing LISA to giving surfactant via an endotracheal tube and delayed extubation in extremely preterm neonates found no difference in survival without BPD.[16] Other new approaches of surfactant administration such as adding a recruitment maneuver to the Intubate-Surfactant-Extubate technique prior to giving surfactant or delivering aerosolized surfactant on CPAP show promising short-term outcomes, that is, reduced need of IPPV within 72 h, but require further study of long-term effects.[17,18] Table 2 provides a summary of above findings.

TABLE 2 Respiratory support options in preterm infants

	Respiratory support		
	1st choice	2nd choice	3rd choice
Infant respiratory distress syndrome (RDS)			
≤28 weeks GA[a,b]	CPAP	MV	
>28 weeks GA[a,b]	CPAP	HHHF	MV
Postextubation	Sync. NIPPV	CPAP	HHHF

Abbreviations: CPAP, continuous positive airway pressure; GA, gestational age; HHHF, heated humidified high flow; mechanical ventilation; MV; Sync. NIPPV, synchronized nasal intermittent positive pressure ventilation.

[a]Avoid mechanical ventilation if possible. In infants requiring mechanical ventilation, administer endotracheal surfactant (eg, Poractant alfa 200 mg/kg).

[b]In infants requiring surfactant, consider intubation with delayed extubation, LISA (less invasive surfactant administration), or Intubate-Surfactant-Extubate technique.

3 | VENTILATORY SUPPORT IN THE NICU

Over the last two decades, the paradigm of respiratory support in the NICU has shifted from primary mechanical ventilation of extremely preterm neonates toward a strategy of early CPAP in order to limit damage from ventilator-associated lung injury and pneumonia.[19,20] Nevertheless, approximately 50% of extremely preterm neonates born at 25–28 weeks of gestation are intubated due to severe RDS and/or poor control of breathing. Intubation rates below this age range progressively increase with the level of immaturity.[21] Table 3 shows a summary of the following invasive and noninvasive ventilation modes.

3.1 | Modes of invasive ventilation

The general aim of modern ventilation techniques in preterm neonates is to ventilate the fragile lung during its canalicular and saccular stage of development in a protective yet effective manner for the shortest possible time. An impressive number of ventilation modes along with different types of triggers (flow-, volume-, and diaphragm triggers) and cycle rates have been studied in preterm neonates.[22] To date, there is little evidence to favor one particular mode of ventilation over another, except for the strong case of using volume-targeted ventilation. Figure 1 outlines the working principle of volume-targeted ventilation: This mode requires the user to set a target tidal volume ($V_{T,set}$) and maximum allowable inspiratory pressure ($P_{insp,max}$) based on patient characteristics. Breath-by-breath, the ventilator measures expiratory tidal volume ($V_{T,exp}$) at the airway opening and adjusts inspiratory pressure (P_{insp}) to approach $V_{T,set}$ depending on pressure requirements and $V_{T,exp}$ recorded over the previous few breaths. Distinct algorithms for both triggered and untriggered breaths exist. Given that inspiratory effort of the patient and mechanical properties of the lung frequently change, P_{insp} fluctuates to minimize differences between $V_{T,set}$ and $V_{T,exp}$. An updated Cochrane Review including 20 randomized trials involving a total of 977 predominantly preterm neonates showed that volume-targeted ventilation vs. pressure-limited ventilation reduces the combined risk of BPD or death (relative risk (RR) 0.73, 95% CI 0.59 to 0.89; number need to benefit (NNTB) 8, 95% CI 5 to 20), rates of pneumothorax (RR 0.52, 95% CI 0.31 to 0.87; NNTB 20, 95% CI 11 to 100), mean days of mechanical ventilation (mean difference −1.35 days, 95% CI −1.83 to −0.86), rates of hypocarbia (RR 0.49, 95% CI 0.33 to 0.72; NNTB 3, 95% CI 2 to 5), rates of high-grade intraventricular brain hemorrhage (RR 0.53, 95% CI 0.37 to 0.77; NNTB 11, 95% CI 7 to 25), and periventricular leukomalacia (RR 0.47, 95% CI 0.27 to 0.80; NNTB 11, 95% CI 7 to 33) without any increase in adverse outcomes. Given the clinical relevance of above outcomes, it is very hard to justify not using volume-targeted ventilation in preterm neonates. There are remaining questions such as the range of accepted target tidal volumes which depends on factors such as stage of lung development, severity of RDS, type of ventilator, and

TABLE 3 Characteristics of various ventilation modes in preterm infants

Mode	Major characteristics
Invasive endotracheal ventilation modes	
Conventional mechanical ventilation	Typically, time-cycled or flow-cycled and pressure-controlled; RR approaches physiological RR; V_T varies with PIP
Volume-targeted ventilation	Time-cycled or flow-cycled and pressure-controlled; RR approaches physiological RR; V_T kept within narrow range by fluctuating PIP; preset maximum PIP
High-frequency oscillatory ventilation	Pressure oscillates around MAP at a frequency of 5–20 Hz; active in- and expiration
High-frequency jet ventilation	Short inspiratory pulses of gas through special ET adaptor at a frequency of 4–12 Hz; passive expiration; second ventilator required for oxygenation
Noninvasive (nasal prongs or face-mask applied) ventilation modes	
Bubble CPAP	Expiratory circuit submerged in known depth of water; bubble pressure fluctuations contribute to ventilation
Ventilator CPAP	Expiratory valve of ventilator modulates pressure; little pressure fluctuations
Variable flow CPAP	Baseline flow and expiratory valve of ventilator modulate pressure; minimal pressure fluctuations
Infant Flow Driver CPAP	Redirected expiratory gas flow through large bore aperture; reduced work of breathing
Heated humidified high flow	Flow range of about 2–12 L/min; pressure unmeasured and depends on flow rate and nasal leak
NIPPV, nonsynchronized	CPAP with intermittent increase in nasal flow, results in cyclic pressure rise, t_i range typically 0.5–1.0 s
NIPPV, synchronized	Flow or pressure sensors synchronize patient effort with delivery of increased nasal flow, t_i typically <0.5 s
Noninvasive NAVA	Diaphragmatic activity triggers proportional increase in nasally applied gas flow and pressure above CPAP

Abbreviations: CPAP, continuous positive airway pressure; ET, endotracheal tube; MAP, mean airway pressure; NAVA, neurally adjusted ventilatory assist; NIPPV, nasal intermittent positive pressure ventilation; PIP, peak inspiratory pressure; RR, respiratory rate; t_i, inspiratory time; V_T, tidal volume.

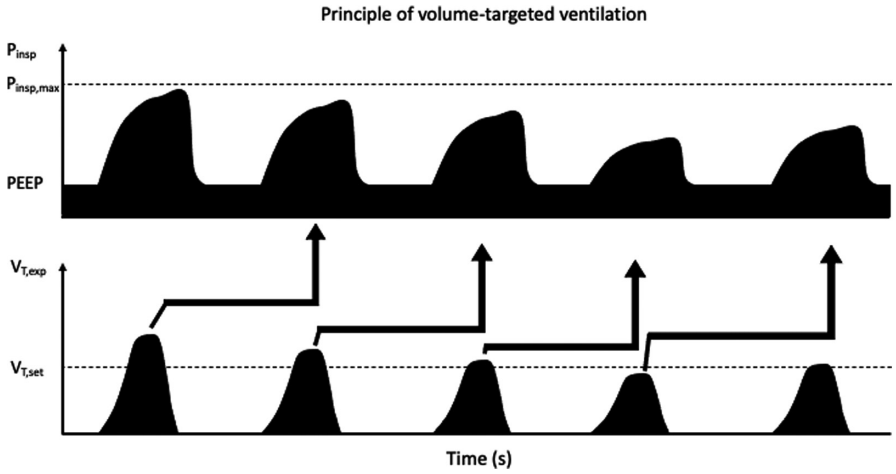

FIGURE 1 The ventilator consecutively reduces inspiratory pressure (P_{insp}) from breath No 1 to breath No 4 with subsequently decreasing expiratory tidal volume ($V_{T,exp}$). P_{insp} is always below preset maximum allowable inspiratory pressure ($P_{insp,max}$). Upon breath No 5, the ventilator slightly increases P_{insp} because the previous $V_{T,exp}$ was below the set target tidal volume ($V_{T,set}$) and $V_{T,exp}$ increases to a value just above $V_{T,set}$. Typically, volume-targeted ventilation does not deploy a fixed, constant tidal volume as in volume-controlled ventilation. $V_{T,exp}$ rather undulates around $V_{T,set}$ using automatically adjusted inspiratory pressures above positive end-expiratory pressure (PEEP)

appliance dead space.[23] Often, target tidal volumes of 4–8 ml/kg body weight are required. Additionally, there are no data on the influence of volume-targeting on long-term respiratory or neurodevelopment, however, the same is true for control interventions. Limitations of volume-targeted ventilation in extremely preterm neonates include the heavy dependence on a well-functioning proximal flow-sensor measuring very small tidal volumes in the range of 1–10 ml under conditions of a variable tube leak as most

clinicians would refrain from using cuffed endotracheal tubes in preterm infants in order to limit tracheal damage.

Nineteen randomized trials including over 4000 neonates have compared conventional vs. high-frequency oscillatory ventilation (HFOV). In HFOV, the ventilator creates pressure fluctuations through oscillating pistons or diaphragms around a set mean airway pressure, resulting in active inspiratory and expiratory phases. To date, there is no conclusive evidence of differences in long-term respiratory or neurodevelopmental outcomes when comparing conventional ventilation with HFOV.[24] There is some evidence that using HFOV may slightly reduce the risk of BPD at the expense of higher rates of air leak and a trend toward more short-term neurological adverse events.[24] Some of the latter may be attributable to hypocarbia. This outlines that installation of HFOV should be accompanied by prolonged, careful monitoring of CO_2 levels as HFOV offers very powerful CO_2 clearance. Recent studies demonstrated the feasibility of combining volume-targeting with HFOV in small preterm neonates.[25] This upcoming new technique theoretically minimizes lung damage due to a predetermined, extremely small target tidal volume approaching respiratory dead space. At a fixed oscillatory frequency in the range of 12–20 Hz, the pressure amplitude is automatically adjusted based on a set HFOV target tidal volume. Studies reporting on meaningful clinical outcomes have not been published yet, thus, this mode of ventilation requires urgent study.

The use of high-frequency jet ventilation (HFJV) in extremely preterm neonates has been a matter of re-instigated debate in recent years. HFJV delivers very short inspiratory pulses of gas into the airways while exhalation is passive. A second ventilator is required to maintain oxygenation through application of PEEP and superimposed conventional breaths. HFJV enables ventilation with very small tidal volumes and very low ratios of inspiratory:expiratory time (typically about 1:6); therefore, it is an attractive mode of ventilation in the presence of air leak. Although studies from the 1990s suggested that rescue HFJV compared to conventional ventilation in preterm neonates with air leak may reduce the risk of BPD, current evidence is insufficient to substantiate this view.[26,27] Similarly, a well-conducted, controlled study in a preterm lamb model of RDS showed that HFJV vs. volume-targeted, lung-protective conventional ventilation resulted in comparable gas exchange, pulmonary blood flow, static lung compliance, and histological markers of acute lung injury.[28]

All of the above-mentioned modes of ventilation can be used in the operating room or for supporting bedside anesthesia, in particular volume-targeted ventilation and HFOV, as many modern neonatal ventilators allow switching between those two modalities. Standard operating procedures of the current authors indeed include supporting anesthesiologists in theater or bedside anesthesia during surgery of infants < 1000 g body weight. The team uses volume-targeting or HFOV through dedicated ventilators from the NICU in those situations. This approach greatly encourages team spirit and has resulted in excellent collaboration. Disadvantages include the lack of an anesthetic gas and the fact that not all surgeons are entirely happy to accept the tissue vibrations caused by using HFOV.

3.2 | The optimal level of PEEP

Maintaining adequate lung volume is important to minimize lung injury from over- or underrecruitment. PEEP is a powerful tool to influence lung volume in ventilated extremely preterm infants.[29] In clinical practice, a combination of local policy and clinical tests such as chest inspection/auscultation, level of the diaphragm on chest X-ray, blood gases, oxygen requirements, and pressure-volume curves on the ventilator are used to set the level of PEEP. A recent international study in 34 NICUs revealed that the level of PEEP in ventilated extremely preterm infants was very wide and ranged from 3 to 9 cm H_2O. In this post hoc analysis of a randomized trial, the center variable alone explained a greater proportion of variation in PEEP than all clinical characteristics combined, that is, local policy seemed to be the major driving force in setting PEEP.[30] Not surprisingly, the authors from a related Cochrane Review concluded that the evidence to set PEEP in preterm infants with RDS is very sparse, with a side note that selecting PEEP levels through an oxygenation-guided lung recruitment maneuver may result in short-term clinical benefits although data quality was deemed to be low.[31] Fortunately, efforts to overcome this knowledge gap show promising results: In animal studies, the respiratory input reactance measured by the forced oscillation technique (FOT) has been shown to identify the lowest PEEP at which lung recruitment is optimal during a decreasing PEEP trial.[32] FOT has also been shown to be feasible in ventilated preterm infants.[33] Very recently, FOT studies in a cohort of preterm infants born at the border of viability (mean gestational age, 24 weeks) revealed FOT-optimized PEEP to be lower than the clinically set PEEP. The authors also highlighted longitudinal changes of FOT-optimized PEEP over the first week of life, indicating that FOT-optimized PEEP on day 1 of life, that is, within 24 h of surfactant treatment, may be considerably lower than on day 3 or 7 of life. They concluded that surfactant-treated lungs of preterm neonates born at the border of viability can easily be overdistended and that FOT may be a clinically useful tool to optimize PEEP in this population.[34] Long-term effects of this approach on respiratory disease in preterm neonates are eagerly awaited.

3.3 | Noninvasive ventilation

This includes CPAP, heated humidified high flow (HHHF), nasal intermittent positive pressure ventilation (NIPPV), noninvasive neurally adjusted ventilatory assist (NIV-NAVA), and nasal high-frequency ventilation. For the purpose of this review, we will focus on the modalities CPAP, HHHF, and NIPPV followed by a short section on NIV-NAVA. In addition, we will provide evidence on which mode of noninvasive respiratory support we would use primarily or after extubation.

3.4 | CPAP

CPAP was implemented for the treatment of respiratory distress in neonates in 1971.[35] Positive effects of CPAP include reduced work of breathing due to enhanced lung compliance and reduced airway resistance,

improved lung expansion, and prevention of alveolar collapse during expiration as well as preservation of endogenous surfactant. These effects result in less ventilation/perfusion mismatch and improved oxygenation.[36] Nowadays, at least four different techniques are used to generate the positive pressure required for CPAP: (1) bubble CPAP, where the expiratory limb of the CPAP circuit is submerged into a known depth of water; (2) ventilator CPAP, where the expiratory valve of the ventilator is used to modulate the pressure; (3) variable flow ventilator CPAP, in which the ventilator modulates circuit flow and the PEEP valve; (4) infant flow driver, where a high gas flow through a nasal device with increased resistance directs the gas flow under pressure into the nose of the infant.[37] Despite the many options to generate positive airway pressure, the debate about the ideal pressure level when using CPAP is still ongoing.

3.5 | HHHF

HHHF should be seen as an entity of respiratory support different from CPAP even though a positive pressure is applied to the airways due to the high-flow rates. In contrast to CPAP, the pressure delivered by HHHF is highly variable and depends not only on the flow rate but also on the size of the infant and the nasal prongs and the leak around the nose. As the name implies, the air administered to the infant's airway is heated and humidified, which prevents the airway mucosa from exsiccation.

3.6 | NIPPV

The term NIPPV includes multiple techniques that deliver CPAP with intermittent increase in pressure applied at the nose of the patient.[38] NIPPV is either used in a synchronized or nonsynchronized mode. Synchronizing seems to improve pulmonary gas exchange and reduce respiratory effort.[39] However, controlled studies comparing synchronized vs. nonsynchronized NIPPV are ongoing.[40]

3.7 | NIV-NAVA

More recently, NIV-NAVA, which is a diaphragm-triggered, noninvasive respiratory support mode was implemented in NICUs. Diaphragmatic activity is measured by a special nasogastric tube and positive inspiratory pressure applied proportionally to diaphragm activity. We did not find robust evidence from randomized trials to support or refute the use of NIV-NAVA in extremely preterm neonates, that is, this mode requires future study.

3.8 | Primary mode of respiratory support in infants with RDS

In a recent Cochrane review, CPAP for the treatment of RDS was associated with reduced respiratory failure, use of mechanical ventilation, and mortality. However, the rate of pneumothorax on CPAP compared to spontaneous breathing with supplemental oxygen was increased about threefold.[41] Two large studies investigating CPAP vs. HHHF in a total of 1218 infants were published in recent years. The investigators of the HIPSTER trial reported 25.5% vs. 13.3% treatment failure when using HHHF compared to CPAP as primary mode of respiratory support for the treatment of RDS in infants born ≥28 weeks gestation. Treatment failure was defined as the requirement of either CPAP or intubation in the HHHF group and requirement for intubation in the CPAP group within 72 h after randomization. Despite the higher treatment failure rate in the HHHF group, the rate of intubation within 72 h did not differ significantly between groups and the rate of adverse events was comparable.[42] The same research group reported the results of the HUNTER trial in 2019. Here, HHHF used in nontertiary special care nurseries as the primary source of respiratory support in the treatment of RDS in infants born >31 weeks gestation was inferior compared to CPAP.[43] No data exist on HHHF vs. CPAP in infants born <28 weeks gestation.

Systematic review indicated that early NIPPV vs. CPAP reduced the risk for respiratory failure and the need for mechanical ventilation in preterm infants with RDS without an increased risk in pneumothorax.[44] Nevertheless, using NIPPV did not reduce the risk of BPD or death.

3.9 | Respiratory support after extubation

Synchronized NIPPV compared to CPAP reduced the incidence of re-intubation within 48 h to 1 week after extubation. These findings are based on the results of 10 trials involving a total of 1431 infants. However, even though re-intubation can be prevented when using NIPPV after extubation, the rate of BPD or death and the incidence of necrotizing enterocolitis were not different between groups. Nevertheless, synchronized NIPPV seems to become increasingly popular after extubation.[45]

3.10 | Oxygen saturation levels and control of oxygenation in the NICU

A long-lasting debate regarding the optimal SpO_2 target range in extremely preterm infants ended with the publication of the Neonatal Oxygenation Prospective Meta-Analysis in 2018 (NeOProM). The authors summarized data from five large randomized controlled trials (SUPPORT, COT, BOOST New Zealand, BOOST II Australia, and BOOST II United Kingdom, referenced in NeOPrOM).[46] Important neonatal outcomes were compared between a lower (85%–89%) and a higher SpO_2 target range (91%–95%). The lower SpO_2 target range was associated with higher mortality and an increased incidence in necrotizing enterocolitis but with a lower incidence in retinopathy of prematurity. Despite these findings, SpO_2 target ranges still vary in NICUs across the globe.[47] Moreover, keeping an infant's SpO_2 in

a target range between 91 and 95% remains challenging considering the almost vertical shape of the oxyhemoglobin dissociation curve at 90% SpO_2. At this point, a small change in the inspired oxygen pressure results in a large change in SpO_2, causing considerable variations of SpO_2 in clinical practice.

In the past, FiO_2 was adjusted manually in order to keep an infant's SpO_2 within a predefined target range. This task is very difficult to fulfill in a busy NICU with nurses often caring for two to three infants on respiratory support at any given time. Automated FiO_2-SpO_2 systems or so-called closed-loop systems were developed in recent years to increase time spent within a predefined SpO_2 target range. Early studies using such automated FiO_2-SpO_2 systems indeed suggested an increased time spent within the SpO_2 target range.[48–50] However, data on clinically relevant long-term outcomes are not yet published. A variety of closed-loop systems are available on the market. There is ongoing debate about detailed settings of a closed-loop system in order to best achieve the overall aim, that is, to increase time spent in the SpO_2 target range, while avoiding potentially dangerous desaturations (increasing the risk of mortality and necrotizing enterocolitis) as well as time spent above the SpO_2 target range (with the risk of retinopathy of prematurity).[51,52] Another unsolved problem is the direct connection between the infant's standard NICU monitor and the automated FiO_2-SpO_2 system. Usually, SpO_2 is displayed and SpO_2 alarms are triggered on the standard NICU monitor. Depending on the manufacturer, no commercially available cable to directly feed the SpO_2 signal from the automated FiO_2-SpO_2 system into the standard NICU monitor might be available. This requires staff to use two different SpO_2 sensors, one for standard NICU monitoring and alarm triggering and a second one for the automated FiO_2-SpO_2 system. Given that SpO_2 values of two sensors attached to different limbs are rarely identical, staff can become genuinely confused by those discrepancies in SpO_2. Ongoing research focuses on the best settings in FiO_2-SpO_2 systems and on how to enhance the performance of automated FiO_2-SpO_2 systems with artificial intelligence.[53]

4 | POSTDISCHARGE MANAGEMENT OF RESPIRATORY ISSUES

Gestational age at birth and intrauterine growth are the primary determinants of prematurity-associated chronic lung disease assessed at 7–12 years of age, thus, follow-up of extremely preterm neonates after the neonatal period into adulthood is warranted.[54] A 2020 task force guideline of the European Respiratory Society on the long-term management of these children summarized the available evidence to inform decisions regarding long-term monitoring and treatment.[55] The guideline was based on predefined questions relevant for clinical care, a systematic review of the literature, and assessment of the evidence. The task force made conditional recommendations for monitoring and treatment of former extremely preterm infants based on very low to low quality of evidence. The authors suggested monitoring with lung imaging using ionizing radiation in a subgroup only, for example, in case of severe BPD or recurrent hospitalizations, and monitoring with lung function in all children. They further suggested individualized advice to parents regarding day care attendance but no general recommendation not to attend day care in the first year of life. With regard to treatment, the use of bronchodilators was recommended in a subgroup only, for example, in children with asthma-like symptoms or reversibility in lung function; treatment with inhaled or systemic corticosteroids was not recommended but natural weaning of diuretics by the relative decrease in dose with increasing weight gain if diuretics were started in the neonatal period. Oxygen saturation targets for supplemental home oxygen therapy should be in the range of 90%–95%. These recommendations of the task force should be considered until new and urgently needed evidence becomes available.

5 | REFLECTIVE QUESTIONS

- Is there a specific mode of conventional ventilation that offers clinically relevant benefits over other modes in preterm infants?
- Are target oxygen saturation levels within the first 10 min of life identical to those used for extremely preterm neonates in the neonatal intensive care unit?
- Is heated humidified high-flow therapy equally effective compared to continuous positive airway pressure for primary respiratory support of preterm infants?

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CONFLICT OF INTEREST

SMS and BS have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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