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Non-Invasive Ventilatory Support in Preterm Neonates in the Delivery Room and the Neonatal Intensive Care Unit: A Short Narrative Review of What We Know in 2024

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Abstract

Background: Guidelines recommend non-invasive ventilatory (NIV) support as first-line respiratory support mode in preterm infants as NIV is superior to intubation and mechanical ventilation in preventing death or bronchopulmonary dysplasia. However, with an ever-expanding variety of NIV modes available, there is much debate about which NIV modality should ideally be used, how, and when. The aims of this work were to summarise the evidence on different NIV modalities for both primary and secondary respiratory support: nCPAP, nasal high-flow therapy (nHFT), and nasal intermittent positive airway pressure ventilation (nIPPV), bi-level positive airway pressure (BiPAP), nasal high-frequency oscillatory ventilation (nHFOV), and nasally applied, non-invasive neurally adjusted ventilatory assist (NIV-NAVA) modes, with particular focus on their use in preterm infants. ***Summary:*** This is a narrative review with reference to published guidelines by European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update. nCPAP is currently the most commonly used primary and secondary NIV modality for premature infants. However, there is increasing evidence on the superiority of nIPPV over nCPAP. No beneficial effect was found for BiPAP over nCPAP. For the use of nHFT, nHFOV, and NIV-NAVA, more studies are needed to establish their place in neonatal respiratory care. ***Key Messages:*** The superiority of nIPPV over nCPAP needs to be confirmed by contemporaneous trials comparing nCPAP to nIPPV at comparable mean airway pressures. Future trials should study NIV modalities in preterm infants with comparable respiratory pathology and indications, at comparable pressure settings and with different modes of synchronisation. Importantly, future trials should not exclude infants of the smallest gestational ages.

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Introduction

Improvements in perinatal, intra-partum, and neonatal care over the past decades have led to increasing survival with decreasing morbidity of premature infants [1–3]. Respiratory distress syndrome (RDS), caused by functional, structural, and biochemical immaturity of the respiratory system, is the leading cause for ventilatory insufficiency of preterm infants [4]. Clinical signs of RDS include tachypnoea, recessions, and cyanosis. If untreated, infants may succumb to hypoxia. Treatment recommendations for initial respiratory support have evolved from advising immediate endotracheal intubation and mechanical ventilation (MV) to using early non-invasive ventilatory (NIV) support [5, 6]. However, in times where there are infants of less than 25 weeks of gestation increasingly offered life-sustaining measures, it is worth noting that these treatment recommendations are largely based on trials of infants of greater than 25 weeks of gestation [7]. With this proviso explicitly in mind, the European RDS Consensus Guidelines recommend that "CPAP or (s)NIPPV should be started from birth in all babies at risk of RDS, such as those <30 weeks of gestation who do not need intubation for stabilization" [5]. These recommendations are based on meta-analyses, showing a decrease in death or bronchopulmonary dysplasia (BPD) when using nasal continuous positive airway pressure (nCPAP) rather than MV [8, 9]. Thus, NIV is now being increasingly adopted as the primary (initialised directly following stabilisation at birth) and secondary mode of ventilatory support (i.e., as a continuation of respiratory support, following a period of MV) for preterm infants [5, 10–13]. When used as the primary mode of support, NIV can be combined with less-invasive exogenous surfactant replacement and early caffeine administration [5, 14–16]. While this combination has now found its way into international treatment recommendations, there remain still questions regarding the optimal timing, thresholds, and route of early nCPAP, caffeine, and surfactant treatment, as well as the generalisability of efficacy in high and middle-income countries, and regarding the most premature infants born at or below 25 weeks of gestation [5, 17–21].

Thanks to many recent technological advances, present-day neonatologist now can choose from a range of NIV modalities, including [11–13, 21–23] the following:

- Nasal continues positive pressure ventilation (nCPAP)
- Heated and humidified high-flow nasal cannula (HFNC), also referred to as humidified HFNC or nasal high-flow therapy (nHFT)
- Nasal intermittent positive pressure ventilation (nIPPV)
- Nasal synchronised intermittent positive pressure ventilation (nSIPPV)
- Bi-level positive airway pressure (BiPAP)
- Nasal high-frequency oscillatory ventilation (nHFOV),
- Non-invasive ventilation-neurally adjusted ventilatory assist (NIV-NAVA).

With a growing variety of NIV modes available for the initial, primary, and secondary respiratory support, guidance is needed on which device and settings to use for the particular patient characteristics and pulmonary pathology, taking into consideration local skill sets, resources, and facilities [5, 22]. In this review, we summarise the available evidence on the above NIV modalities, with particular focus on their use in the care of VLBWI (infants of less than 1,500 g birth weight) and ELGANs (infants of gestational ages [GAs] less than 28 weeks).

Nasal Continuous Positive Airway Pressure

In 1971, Gregory et al. [24] published their seminal paper on the effectiveness of nCPAP in preterm infants with RDS. Decades later, nCPAP is now the most commonly used and best-researched NIV modality [9–13]. According to recent data from the UK by Sand et al. [13], the nCPAP is currently being used in >80% of babies cared for in the UK NICUs. Ramaswamy et al. [11] have recently reviewed the many applications of nCPAP and other NIV modes in great detail [12, 25], and Lavizzari et al. [22] recently illustrated the mechanisms of action of nCPAP and many other forms of NIV [22]. Briefly, in continuous flow nCPAP, the pressure limit is often determined at the expiratory limb of the breathing circuit. This can be either achieved by the use of a pressure ventilator (ventilator-derived CPAP) or by submerging the expiratory limb in water ("Bubble CPAP"). Bubble CPAP is relatively easy to set up and is used in NICUs around the world [21]. In contrast, the pressure in variable flow nCPAP is created by a flow generator, usually by MV devices, requiring a more formal technical setup [22].

nCPAP Patient Interfaces

With nCPAP, as all other modes of NIV, the incoming continuous gas flow can be directed to the nares via a range of patient interfaces: the most effective seems to be a strategy of using small masks, covering the nose, or

short nasal prongs [26]. Use of long prongs should be discouraged as these increase the resistance in the pressure-delivery system and because even minor secretions may lead to significant obstructions and thus increased work of breathing [26]. In case of nasal short-prongs and masks, care must be taken to balance the need for an appropriate fit of the interface to minimise leak, and the risk of pressure-related skin breakdown when the interface is too tight [27].

A further challenge to the delivery of adequate nCPAP pressures occurs when the infant's mouth is open. This natural "leak" will cause large pressure drops to occur, meaning the patient will not receive the prescribed distending pressure [26, 28]. Such leak through the mouth with nasal interfaces can be addressed by using a gentle chin strap or pacifier to keep the mouth closed. When providing nCPAP for a longer time, alternating the nasal interface, that is, cycling the use of nasal masks and prongs, should be considered to avoid nasal trauma [29].

Timing of nCPAP Initiation

Meta-analysis of large randomised controlled trials (RCTs) investigating the use of nCPAP as initial mode of respiratory support compared to routine intubation and ventilation in ELGANs, with and without early surfactant administration, suggests improved outcomes for death or BPD at 36 weeks of GA, and favourable rates for the need for re-intubation, reduced need for postnatal corticosteroids, and lower oxygen requirements at 28 days of age [8, 9]. Thus, the early administration of nCPAP as primary respiratory support for preterm infants is currently strongly recommended in international guidelines [5, 6]. Little information is available regarding the optimal timing of nCPAP as primary respiratory support and with regards to which GA at the early initiation of nCPAP as primary respiratory support is advisable [11, 30, 31].

Equally, nCPAP is recommended as a secondary mode of respiratory support, following extubation, to prevent re-intubation [5]. However, recent meta-analyses suggest that while nCPAP is very effective in preventing re-intubation, there is now a stronger signal for the effectiveness of nIPPV [12, 31].

Defining the Optimal nCPAP Level

The optimal nCPAP level which effectively maintains thoracic gas volume while ensuring adequate tidal volumes remains to be determined. The 2022 European Consensus Guideline on the Management of RDS suggests starting CPAP levels between 6 and 8 cm H_2O for initial and primary respiratory support [5]. According to centre reports from a questionnaire study from Germany, Austria, and Switzerland, applied nCPAP levels ranged from 3 to 10 cm H_2O for primary or secondary respiratory support [32]. Extubating VLBWI to higher nCPAP levels proves to be more effective. An earlier trial by Buzzella et al. [33] compared extubation failure rate with two ranges of nCPAP in preterm infants and found that extubation to nCPAP of 7–9 cm H_2O resulted in fewer re-intubations than when extubated to 4–6 cm H_2O. The very recently published ÉCLAT Trial by Kidman et al. [34] compared nCPAP pressures of 6–8 cm H_2O with 9–11 cm H_2O in 483 ELGAN infants ready for extubation and found higher extubation success rates in the high nCPAP level group (failure rate 35% in higher nCPAP group vs. 57% in lower nCPAP group, risk difference −21.7%, 95% CI: −38.5% to −3.7%).

NIV Support in Delivery Room

In the UK, the use of NIV as the initial mode of respiratory support increased between 2010 and 2017 (CPAP, 21.5%–28.0%; HFNC, 1%–7% [$p < 0.001$]) [13]. However, despite increased use, the NIV failure rates remained quasi-static. Thus, much debate has recently ensued on the optimal device, device-patient interface, and device settings for primary support [35]. Applying the optimal combination of the above-discussed devices and settings to an individual patient can be challenging, especially when providing the immediate care to a very premature infant, and numerous studies have illustrated the pitfalls in providing adequate non-invasive ventilation in the delivery room setting [13, 36, 37]. Therefore, the search for the optimal device and settings continues [37]. Recently, Donaldsson et al. [38] studied 250 infants less than 28 weeks GA, comparing the T-piece resuscitator with face mask to a newly designed T-piece device, referred to as rPAP-device (Healthcare Inspire rPAP, UK). The rPAP simulates the fluidic-flip principle of the Benveniste valve and delivers its pressures through short bi-nasal prongs [39]. The authors found that one-third of infants receiving ventilatory support via the device were intubated or died in the delivery room, compared to 45.1% receiving standard care ($p = 0.03$) [39]. There was no significant difference regarding secondary outcomes. In another study, a retrospective single-centre study compared the support of VLBW infants at birth with either nIPPV or mask CPAP [39]. In this study, the use of

nIPPV resulted in less intubation events, reduced MV and less frequent use of chest compression and epinephrine [40]. Concerning the use of nHFT (for definition see next paragraph) from birth, data from a large RCT showed that especially for ELGANs, primary nHFT was inferior to nCPAP [41].

HFNCs in the Neonatal Unit

nHFT or HFNC oxygen describes the application of heated and humidified medical gases via small nasal prongs at flow rates between 2 and 8 L/min [42]. Physiological effects of nHFT include reduction of ventilation dead space, airway splinting, and improved oxygenation [43]. The European RDS Guidelines recommend that "HFNC can be used as an alternative to CPAP for some babies, with the advantage of less nasal trauma, provided centres have access to CPAP or NIPPV for those failing this mode" [5]. Important but less quantifiable advantages of nHFT, compared to other forms of NIV, include the over-all ease of use and application, perceived lower work of breathing, and a preference by nurses and parents [44, 45]. A criticism of nHFT is that the generated distending pressures are not objectively displayed.

Nasal high flow therapy as primary ventilatory support was studied by several investigators. Regarding the use of nHFT as initial respiratory support, meta-analysis of 21 randomised trials involving 2,886 preterm infants, comparing HFNC and nCPAP found that nHFT treated infants had comparable rates of treatment failure to those supported by nCPAP, but nHFT was associated with reduced risks of nasal trauma [46]. Concurrently, a recent Cochrane review by Hodgson et al. [47] on topic concluded that there was little to no difference in death or BPD, compared with CPAP or nIPPV. In addition, infants supported by nHFT had fewer pneumothoraces and less nasal trauma, when compared with CPAP controls [47]. This confirms earlier, single-centre reports on the successful initial use of nHFT from birth [48].

The use of nHFT as secondary mode of respiratory support was meta-analysed by Fleeman et al. [49]. Data from ten RCTs, including over 1,200 neonates, suggest that nHFT following extubation is as effective and safe as nCPAP, but very few ELGANs were enrolled in these RCTs. Chen et al. [50] studied 94 ventilated ELGANs (mean GA 27 weeks), ready for extubation. The group extubated to nHFT, compared to nCPAP, had comparable rates of extubation failure but reduced oxygen requirements and significantly fewer reports of nasal injury and necrotising enterocolitis. These reports are in keeping with the updated Cochrane Review by Wilkinson et al. [42]. Recently, Hodgson et al. [51] reported on the use of nHFT during endotracheal intubation. In their large RCT, the nHFT use during intubation improved the likelihood of successful intubation on the first attempt without physiological instability. Nonetheless, one needs to be aware that most research for both early use and post-extubation use relates to infants >28 weeks of gestation, the most recent Cochrane review cautions for greater failure rates during the initial 72 h compared to CPAP, and general certainty of evidence was very low for most clinical outcomes [42].

Nasal (Synchronised) Intermittent Positive Pressure Ventilation

nIPPV is defined as any mode of assisted ventilation that delivers a set peak inspiratory pressure (PiP) on top of the background pressure of CPAP throughout the respiratory cycle at the nasal interface, without endotracheal intubation [52]. nIPPV augments nCPAP with its superimposed inflations by a set PiP, typical PiPs of 15–22 cm H_2O over a CPAP of 5–8 cm H_2O, delivered at rates between 20 and 50 inflations per minute, thus mimicking settings commonly used during MV [22]. The predominant clinical effect of nIPPV is attributed to the delivery of higher mean airway pressure (MAP) than with CPAP alone [22, 52, 53]. Synchronisation of nIPPV with the patients' respiratory efforts was found to be more effective in preventing intubation [12, 22, 54]. While many modern ventilators now allow for synchronisation of patient breaths and ventilator-derived nIPPV, these technical advances are rather recent, and therefore, the majority of trials on nIPPV included babies treated with non-synchronised nIPPV. This is reflected in the number of babies in RCTs comparing nIPPV to other forms of NIV, for example, in meta-analysis by Rüegger et al. [52] for the comparison between nIPPV and nCPAP as primary respiratory support, there are 5 trials (449 infants) that used synchronised nIPPV as compared to 10 trials (1,157 infants) that used non-synchronised nIPPV.

Indications for using neonatal nIPPV include initial, primary, and secondary ventilatory support, scenarios where higher MAP than CPAP may be required [52–56]. In a set of comprehensive network meta-analyses, Ramaswamy et al. [11] studied the currently available NIV modes, either when used as initial, primary, or secondary mode of respiratory support [11, 12]. In brief, when using nIPPV as a primary mode of ventilatory

support, authors found nIPPV to be more effective for preventing NIV treatment failure and decrease the need for MV when compared to nHFT and CPAP and for post-extubation support synchronised nIPPV slightly more so than non-synchronised [12]. nIPPV was associated with a lower incidence of air leak when compared to both CPAP and BiPAP and resulted in reduced incidence of BPD or mortality when compared to CPAP [11, 12, 25]. These results are in keeping with the recently updated Cochrane systematic reviews by Lemyre et al. [55, 56].

Despite the illustrated benefits, proven in clinical trials, clinicians seem still widely hesitant to use nIPPV as the primary mode of NIV. This may be because most of the trials comparing nIPPV to other NIV modes were performed with nCPAP levels that would in current practice be considered sub-optimal. As reviewed by Rüegger et al. [52] many of the studies comparing nIPPV to nCPAP were done before NIV became a more commonly applied form of respiratory support for ELGANs, and therefore, studies did not include a sufficient number of extremely premature infants. These comparisons are, therefore, not applicable in current practice where evidence is urgently needed to demonstrate how nIPPV, when used as primary respiratory support in VLBWI, compares with nCPAP used at higher PEEPs as would be in keeping with current practice. In addition, many of the trials are small, lack detailed reporting of how nIPPV was used, for example, scanty information about nIPPV settings, and often pool trials that used BiPAP with those that used nIPPV in meta-analyses [55, 56]. Lemyre et al. [55, 56], in their recent Cochrane review, have considered this and appropriately concluded that more up-to-date trials are needed with data from the most premature infants (below 25 weeks of gestation), comparisons between different devices, impact of synchronisation, and the best combinations of nIPPV settings (rate, PiP, PEEP) and where trials match MAPs between intervention groups to allow better comparisons.

Bi-Level Positive Airway Pressure

The term BiPAP is often, inappropriately, synonymously used for nIPPV. BiPAP provides two CPAP levels (3–6 cm H_2O and a higher setting of up to 11–15 cm H_2O), over which the infant breathes independently [57]. There is a much smaller difference between the two pressures as compared to the difference between the PEEP and PiP in nIPPV, and therefore, the MAP generated by BiPAP may not be too different from that seen with high levels of CPAP. Furthermore, another important difference in inspiratory time between nIPPV (short) and BiPAP (long) again contributes to the differences in achieved MAP per modality [22].

Nasal High-Frequency Oscillation Ventilation

HFOV is considered to be lung protective [58]. HFOV is, therefore, often used in neonates as an initial ventilation strategy or as a rescue intervention when conventional ventilation fails. nHFOV is the non-invasive application of HFOV, delivered via pharyngeal or nasal application. The rationale for its use includes the use of higher MAPs, presumedly improved alveolar recruitment and excellent CO_2 clearance due to the oscillatory pressure waves [58].

According to a recent European survey, nHFOV is presently not often used in ELGANs [59], despite encouraging results from recent clinical trials comparing nHFOV to other forms of NIV. For instance, Zhu et al. [60] reported on the reduced need for MV in infants supported with nHFOV, compared to nCPAP (24.3% vs. 56.4%, $p < 0.01$) although incidences for IVH, air leaks, BPD or mortality were similar between the groups. Mukerji et al. [61] randomised 39 infants with RDS to either nHFOV or BiPAP and found that 6/16 (37.5%) infants on nHFOV as compared to 15/23 (65.2%) on BiPAP failed the assigned NIV mode, but the difference was not statistically significant, possibly due to small sample size, and moreover, there were no differences in rates of MV at 72 h and 7 days post-randomisation. To conclude, the use of nHFOV in preterm infants is still being debated and, for the above-illustrated reasons and due to the heterogeneity within populations and design of the trials, it has been difficult to make firm recommendations at this stage [5, 12].

Non-Invasive Neurally Adjusted Ventilatory Assist

NAVA adjusts ventilatory pressures to diaphragmatic electrical activity, created when the diaphragm contracts. Physiologically, the diaphragm creates negative alveolar pressure when it is activated by the phrenic nerve. NAVA detects baseline or tonic electrical diaphragmatic activity and triggers ventilator pressure in proportion to this signal. With NAVA, synchronisation is achieved by responding to the neural signal of the infant's respiratory drive rather than airflow and therefore may reflect physiological breathing more accurately. NAVA is a

proportional mode of ventilation, which can improve patient-ventilator synchrony, reduce the risk of ventilator-associated barotrauma, and reduce air leaks.

By way of contrasts, synchronised nIPPV uses patient respiratory flow as a trigger for pressure. It is well recognised that synchronisation in NIV can be challenging due to interface leaks, small tidal volumes, and fast and variable breathing patterns of VLBWI, irrespective of the technology used to achieve synchronisation. Similarly, some studies question whether the neural feedback from small preterm infants is sufficient to ensure optimal ventilation, with the consequent risk of hypo- or hyperinflation [62–64].

Similarly to NAVA, in NIV-NAVA, the NAVA interface is a catheter with miniature electrodes. This catheter is placed in the lower oesophagus at the level of the diaphragm and the electrodes detect the phrenic nerve activity [22]. Due to this setup, there are contraindications to NIV-NAVA including structural abnormalities; concomitantly used agents that reduce, inhibit, or block respiratory drive, for example, muscle relaxants and heavy sedation; and neurological conditions such as phrenic nerve injury.

Only few small-scale trials have yet assessed NIV-NAVA as primary support and as post-extubation support for VLBWI, leaving much uncertainty on many of the practical aspects of NIV-NAVA in the neonatal setting. More information is come from ongoing, large studies, including the Diaphragmatic Initiated Ventilatory Assist (DIVA^3) Trial, which compares rates of extubation failure in extremely preterm infants extubated to either NIV-NAVA or nIPPV [65].

Conclusion

A care strategy for preterm infants of prioritising NIV over MV will benefit VLBWI infants by improving survival and reduced rates of BPD. However, while there is a large variety of NIV modes and devices available, the search for the most optimal NIV mode and strategy continues. Finding the most appropriate form and setting of NIV for a specific patient involves taking into consideration the underlying pathology, patient GA, size and weight, maturity, and the strengths and limitations of the local team. Future trials should pay attention to including infants with comparable underlying pathology and include all GA groups, specific device settings, and, where appropriate, modes of synchronisation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.C.R. conceived the structure and content of the article. C.C.R. and M.R. provided the first draft. S.O. and H.F. made significant contributions. All authors have read and approved the final version of the manuscript.

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