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Review article

Practical aspects on the use of non-invasive respiratory support in preterm infants

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A B S T R A C T

Preterm infants frequently present with respiratory insufficiency requiring respiratory assistance. Invasive mechanical ventilation has been associated with several short and long term complications. Therefore, the practice of early use of non-invasive ventilation has been adopted. Nasal CPAP proved efficacy as an initial therapy for preterm infants. Non-invasive positive pressure ventilation is an alternative used to mitigate CPAP failure in infants with apnea or increased work of breathing. High flow nasal cannula gained popularity primarily due to the ease of its use, despite multiple prominent trials that demonstrated its inferiority. Bi-level positive airway pressure and neurally adjusted non-invasive ventilatory are used in infants with apnea and increased work of breathing. The effectiveness of non invasive ventilation tools can be augmented by having a proper protocol for initiation, weaning, skin care, positioning, and developmental care during their application.

1. Introduction

Invasive mechanical ventilation has been widely used to support neonates with respiratory failure over the past decades. However, its use, particularly in preterm infants, was associated with various respiratory and non-respiratory complications. Short term reported respiratory complications include air leak syndromes, pulmonary hemorrhage, lung atelectasis, airway inflammation, subglottic stenosis, and ventilation associated pneumonia [1]. Bronchopulmonary dysplasia (BPD) is the most important and serious long-term respiratory complication which affects the lifestyle of preterm infants [1,2]. Accordingly, the use of non-invasive ventilation gained the interest of health care practitioners in an attempt to avoid respiratory morbidity related to invasive mechanical ventilation.

1.1. Physiological concepts

Preterm infants are vulnerable to respiratory insufficiency because of immaturity of respiratory centers in the brain, increased upper airway resistance secondary to muscle hypotonia, increased lower airway resistance, weakness of respiratory muscles, and decreased lung compliance in association with surfactant deficiency [3]. Oxygen therapy as a treatment for hypoxemia does not overcome the physiological aspects of respiratory insufficiency. Continuous positive airway pressure (CPAP) was first introduced in 1968 as a supportive tool to maintain patency of upper airways, prevent alveolar space loss secondary to atelectasis, and support the weak respiratory muscles and respiratory drive of preterm infants [4]. However, CPAP was mainly used to transition preterm infants after extubation from mechanical ventilation. As a consequence to increasing incidences of BPD in extremely preterm infants, practitioners tended to shift from initial invasive to non-invasive mechanical ventilation. The concept of early initiation of nasal CPAP in the delivery room as a rescue therapy to avoid mechanical ventilation in preterm infants with respiratory distress was described in 1980s and early 1990 [5–7]. The use of non-invasive nasal intermittent positive pressure breaths (NIPPV), bi-

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Abbreviations

BiPAP	Bi-level positive airway pressure
BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
FRC	Functional residual capacity
HHHFNC	Heated humidified high flow nasal cannula
NAVA	Neurally adjusted ventilatory assist
NIPPV	Nasal intermittent positive pressure ventilation
NIV	Non invasive ventilation
NHFV	Nasal high frequency ventilation
IVH	Intra-ventricular hemorrhage
NEC	Necrotizing enterocolitis
PDA	Patent ductus arteriosus
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity

level pressures, or nasal high frequency ventilation were introduced to augment the effect of regular CPAP and overcome the needs for mechanical ventilation in extreme preterm infants with recurrent apneas. Studies on non-invasive ventilation have shown variable effects on different diseases and outcomes of preterm infants [8]. These variations are related to different practice in regards to time of initiation, delivered pressure, device or interface used, additional care for skin, and positioning.

2. Modes of non invasive respiratory support

2.1. Nasal continuous positive airway pressure (NCPAP)

2.1.1. Mechanism of action

Nasal CPAP creates a constant positive pressure during infant's respiratory cycle by delivering a constant gas flow through an interface sealed against the upper airways. The created pressure increases in the cross-sectional area of the naso-pharynx, decreases airway resistance, improves lung compliance, increases endogenous release of surfactant, enhances diaphragmatic activity, decreases frequency of apnea and improves ventilation-perfusion matching [9,10]. In addition, the CPAP pressure, when applied for extended time, stimulates lung growth and increases functional residual capacity [11,12].

2.1.2. Delivering system and interface

Nasal CPAP can be delivered via bubble CPAP, infant flow CPAP, or conventional ventilator with nasal prongs. Positive end expiratory pressure is created by variable distal expiratory flow under water in bubble CPAP, kinetic energy flow in infant flow CPAP, and expiratory valve in conventional ventilator CPAP. The use of infant flow CPAP did not differ from conventional ventilator CPAP in term of incidence of post-extubation failure [13]. However, duration of oxygen therapy and length of hospital stay were significantly shorter in preterm infants treated with infant flow CPAP compared to conventional ventilator CPAP [13]. Infant flow CPAP was not different compared to bubble CPAP in the incidence of treatment failure within 72 h of therapy, CPAP failure within 7 days of life, need for surfactant post-randomization, time to CPAP failure, duration of CPAP and complications of prematurity [14–16].

Different designs of nasal interfaces such as short or long binasal prongs, single nasopharyngeal prong, nasal masks, nasal cannulas, or nasal pillows are available. A suitable interface should maintain proper seal with the infant's nose during movement to preserve the desired pressure without compromise to the nasal septum to avoid pressure injury. In a randomized clinical trial, Buettiker and colleagues compared the duration of interface use and associated nasal septum injury between Hudson RCI nasal prongs, nasopharyngeal prong and infant flow prongs and did not find significant differences between the three interfaces [17]. In a meta-analysis of two trials, short binasal prongs were found to be more effective in prevention of extubation failure than a single nasopharyngeal prong [18]. Authors in the same meta-analysis did not find a significant difference between different types of short binasal prongs in terms of efficacy of respiratory support or safety on skin integrity [18]. More recently, the nasal mask was found to significantly reduce incidence of CPAP failure, nasal septum injury, BPD, and the need for subsequent surfactant administration compared to nasal prongs in VLBW infants [19,20]. Our position is that the short curved binasal prongs are shown to be the most effective and to associate with the least incidence of BPD [21]. Nasal injury is mostly related to unfamiliarity with nasal prongs and can be ameliorated with experience gained at the bedside.

2.1.3. CPAP as a post-extubation tool

The use of nasal CPAP as a step-down intervention after mechanical ventilation for preterm infants was associated with significant success and less incidence of re-ventilation [22,23]. In a large meta-analysis by Ferguson and colleagues, nasal CPAP was associated with a significant reduction in the incidence of extubation failure in comparison with head-box oxygen (risk ratio [RR] = 0.59; 95% CI, 0.48–0.72; number needed to treat [NNT] = 6; 95% CI, 3-9) [24].

2.1.4. Early nasal CPAP in the delivery room

Clinical trials of early initiation of CPAP have shown that CPAP was as effective as mechanical ventilation in treatment of respiratory distress in preterm infants particularly those less than 29 weeks gestation [25–28]. Aly and colleagues reported that 84.6% of ELBW infants will not need intubation and surfactant therapy if nasal CPAP is initiated immediately in the delivery room [29]. Lindner et al., reported a significant decline in the need for mechanical ventilation from 84% to 40%, incidence of BPD from 32% to 12% and severe intra-ventricular hemorrhage from 38% to 16% if nasal CPAP was initiated early in the delivery room [30]. In the COIN trial early use of infant flow CPAP at a pressure of 8 cmH2O with short single or binasal prongs was not associated with decreased incidence of death and BPD at 36 weeks corrected gestational age (33.9% vs 38.9%, $P = .19$). However, pneumothorax was significantly increased (9% versus 3%, $P < .01$) compared to mechanical ventilation [25]. In the SUPPORT trial early initiation of CPAP in the delivery room with T-piece at a pressure of 5 cmH2O with continued application in the NICU did not significantly decrease the incidence of death and BPD at 36 weeks corrected gestational age (47.8% versus 51.0%, $P = .3$) compared to mechanical ventilation [26]. In the CURPAP trial, early initiation of CPAP with pressure of 7 cmH2O without intubation and surfactant therapy in the delivery room was as effective as elective intubation and surfactant therapy followed by either nasal CPAP or mechanical ventilation in term of the need for mechanical ventilation and incidence of BPD at 36 weeks gestation [27]. The VON DRM study showed that early use of bubble CPAP in the delivery room was as effective as both prophylactic surfactant administration followed by immediate extubation to CPAP or prophylactic surfactant administration followed by continuing mechanical ventilation in regards to the combined incidence of death and BPD at 36 weeks (30.5%, 28.5%, and 36.5% respectively) in preterm neonates [28].

2.1.5. Early use of nasal CPAP with surfactant therapy

In an attempt to minimize the duration or the initiation of invasive ventilation in preterm infants with respiratory distress, intubate-surfactant-extubate (INSURE) practice and minimal invasive surfactant therapy (MIST) practice or less invasive surfactant administration (LISA) practice have been often used by practitioners. In a meta-analysis of 9 randomized trials, INSURE practice was not statistically different compared to nasal CPAP alone in decreasing incidence of death and BPD [31]. However, INSURE was associated with 12% RR reduction in combined BPD and/or death and 14% RR reduction in the incidence of BPD compared to nasal CPAP alone suggesting that INSURE practice augments the beneficial effect of early CPAP therapy [31]. The use of MIST or LISA techniques in combination with nasal CPAP in spontaneously breathing preterm infants with respiratory distress seems to reduce failure of non-invasive ventilation, avoids mechanical ventilation and manual inflation, and possibly reduces lung injury due to barotraumas or volutrauma [32]. Our position in this regards is that intubation in the delivery room is a potentially hazardous procedure that is shown to cause IVH in premature infants [33]. Therefore preterm infants should be intubated only when they cannot be managed non-invasively.

2.1.6. Weaning off CPAP

Efficacy of nasal CPAP on supporting preterm infants depends on proper selection of criteria to initiate and more importantly to wean off support. Multiple criteria for readiness to wean off CPAP have been developed [34]. Gradual weaning of pressure and oxygen was associated with higher chances of success compared to sudden discontinuation of CPAP in preterm infants [35]. Weaning to high flow nasal cannula (HFNC) was associated with unnecessary increase in duration of oxygen therapy and length of hospital stay [36]. Graded-cycling-off strategy significantly increased the total time on nasal CPAP, oxygen therapy and hospital stay [37].

In summary, despite the availability of multiple trials and meta-analyses related to initiation and weaning off CPAP, there is not clear explanation for the disparity in BPD incidences among different centers. It is clear, however, that the lowest incidence of BPD was reported from centers that use bubble CPAP with short binasal prongs. It is also clear that centers will need to develop experience over time before a decrease in BPD incidence is appreciated [38].

2.2. Heated humidified high flow nasal cannula (HHHFNC)

2.2.1. Mechanism of action

HHHFNC delivers heated and humidified blended oxygen and air via small loose-fitting prongs, which does not occlude the nostril, at a flow rate of >1 L/min [39]. HHHFNC is considered easier to use, less traumatic to nasal septum, and more comfortable for the infant compared to nasal CPAP thus has gained considerable popularity in clinical practice [40]. The proposed working mechanism of HFNC is by generation of gas flow in the naso-pharynx that washes out the pharyngeal dead space [41]. With the nasal interface that does not occlude >50% of the nostrils, its potential of delivering positive distending pressure is unreliable [42]. Meanwhile it is prohibited to occlude >50% of the nostrils to prevent generation of unintended dangerously high pressure. Of note, the RAM nasal cannula (Neotech, Valencia, CA, USA) is intended to deliver flow and oxygen. Its use to deliver CPAP is considered an “off label” use.

2.2.2. Efficacy and safety of HHHFNC as a non-invasive respiratory support

HHHFNC was compared to nasal CPAP as a primary respiratory support early in the delivery room and as a post-extubation tool after mechanical ventilation. When used as a primary mode of respiratory support, HHHFNC was shown to be inferior to CPAP. In fact, the two largest clinical trials that were conducted in premature infants with gestational age of >28 weeks and >31 weeks, showed doubling of the failure rate when using HHHFNC when compared to CPAP [43,44], Therefore, other than the ease of care and convenience, it is not justifiable to use HFNC as a primary mode of respiratory in premature infants. The support of infants after extubation using HFNC instead of CAPP is sub-optimal. Multiple studies proved that intrapulmonary sustained pressure, stimulates premature lungs to grow and increases functional residual capacity [12,36,45].

In summary, HFNC does not provide reliable pressure that is needed to stimulate the growth of the lungs. The use of oxygen with HFNC will mask the underlying respiratory insufficiency without providing the pressure needed for the lung to heal and grow. The authors of this review are not aware of any study that claimed improved outcomes when using HFNC instead of CPAP. Therefore, HFNC should be reserved for individuals in situations were CPAP can not be applied due to nasal injury or home support.

2.3. Nasal intermittent positive pressure ventilation (NIPPV)

2.3.1. Mechanism of action

NIPPV adds intermittent positive pressure breaths over a baseline positive end expiratory pressure (PEEP) with a specified peak inspiratory pressure (PIP), respiratory rate, and inspiratory time. The intermittent positive breaths improve naso-pharyngeal inflation, increase the delivered tidal volume, augment the pressure delivered to lower airways, and improve alveolar recruitment [46]. These effects increase CO2 elimination and decrease apnea episodes in preterm infants.

2.3.2. Delivering system

NIPPV can be provided in either synchronized or non-synchronized ways. Most of the conventional mechanical ventilator can drive a non-synchronized form of NIPPV. Synchronized NIPPV can be provided by infant flow SiPAP which use of Graseby capsule over xiphoid process to detect initiation of a breath, or more recently by neurally adjusted ventilators which use electrical activity of the diaphragm to detect initiation of a breath [47]. Similar to CPAP, the delivering interface is short and long bi-nasal prongs, single nasopharyngeal tube and nasal mask.

2.3.3. Efficacy and safety of NIPPV as a non-invasive respiratory support

Initial treatment of respiratory distress in preterm infants with NIPPV was associated with decreased needs for endotracheal intubation, requirement for mechanical ventilation at day 3 of life, and requirement for mechanical ventilation at day 7 of life when compared to nasal CPAP [48]. In extremely low birth-weight infants, Kirpalani and colleagues found no difference in chances to survive at 36 weeks gestation without BPD between infants managed with NIPPV or nasal CPAP [49]. Ramanathan et al. found that preterm infants < 30 weeks who were immediately extubated within 60 min following surfactant therapy to NIPPV had a lower need for re-intubation, duration of mechanical ventilation, and BPD compared to infants' extubation to nasal CPAP [50]. Following intubation surfactant and extubation (INSURE) therapy, the use of NIPPV significantly decreased the need for re-intubation from 17.6% with nasal CPAP to 6% with NIPPV [51]. Following minimal invasive surfactant therapy (MIST), the use of NIPPV significantly decreased the need for re-intubation from 29% with nasal CPAP to 13% with NIPPV [52]. Lemyre and colleagues conducted two meta-analyses; the first tested early use of NIPPV as an initial therapy for preterm infants with respiratory distress and the second tested post-extubation use of NIPPV compared to nasal CPAP [53,54]. As an initial therapy, Lemyre did not find superiority of NIPPV over nasal CPAP for decreasing respiratory failure and the need for intubation and mechanical ventilation among preterm infants with respiratory distress syndrome [54]. As a post-extubation service, Lemyre found that NIPPV decrease the possibility of extubation failure compared to nasal CPAP53. In a meta-analysis of 50 trials by Ferguson and colleagues to test different interventions to improve rates of successful extubation in preterm infants, NIPPV was superior to nasal CPAP in preventing extubation failure (RR, 0.70; 95% CI, 0.60–0.81; NNT, 8) [24].

In summary, the authors support the use of NIPPV in situations where apnea is significant or work of breathing is increasing thereby avoiding intubation and invasive mechanical ventilation. However, the routine use of NIPPV in non-apneic infants is an unjustified escalation of care that can potentially harm the lungs [55]. Of note, non-invasive ventilation can potentially cause all complications associated with mechanical ventilation apart from intubation-related complications.

2.3.4. Bi-level positive airway pressure (BiPAP, DUPAP, and SiPAP)

Bi-level positive airway pressure is considered as a form of NIPPV which provides alternating cycles of low pressure and high pressure CPAP at pre-specified intervals with longer time on high pressure (inspiratory time) than NIPPV. Similar to the concept of NIPPV, BiPAP may be beneficial in preterm infants with increased work of breathing on nasal CPAP or inconsistent respiratory drive with a difference of allowing infants to breathe on top of both low and high pressure cycles. The efficacy of BiPAP as a non-invasive respiratory support has been tested against all other modalities of non invasive ventilation.

Compared to nasal flow CPAP, early use of BiPAP as a primary therapy in preterm infants with respiratory distress was associated with a significant decrease in the need for intubation within the first 72 h of life, and subsequent intubation after the initial 72 h with no difference in the incidence of BPD [56]. Compared to bubble CPAP, the early use of BiPAP was associated with insignificant differences in terms of duration for non-invasive respiratory support, duration of oxygen therapy, need for invasive ventilation, BPD, IVH, pneumothorax, need for additional dose of surfactant, and infant mortality [57]. As a post-extubation tool there was no statistically significant benefit for BiPAP over regular nasal CPAP in terms of decreasing the need for re-intubation, oxygen requirement at 36 weeks' corrected gestation, IVH, NEC, or pneumothorax [58]. Compared to other NIPPV, early use of BiPAP as a primary therapy for preterm infants with RDS did not show difference in terms of needs for mechanical ventilation or pulmonary outcomes [59]. Similarly, early use of BiPAP compared to HHHFNC as a primary therapy for preterm infants with RDS did not show a difference in terms of needs for mechanical ventilation, duration of respiratory support, need for surfactant, air leaks, or BPD [60].

2.3.5. Neurally-adjusted non invasive ventilatory assist (NIV-NAVA)

Neurally-adjusted ventilatory assist (NAVA) is a form of synchronized NIPPV using the electrical activity of the diaphragm (Edi) as a trigger for initiation of assisted breaths. NAVA has been shown to improve infant-ventilator synchrony, improve comfort, reduce the requirement for sedation, and reduced the length of hospital stay [61]. Neurally-adjusted non-invasive ventilatory assist (NIV-NAVA) can be provided in spontaneously breathing preterm infants via nasal prongs or single nasal-pharyngeal tube or a mask allowing a leak compensation system as high as 95%. One theoretical benefit for the NIV-NAVA system is the ability to diagnose central apnea in preterm infants as of cessation of electrical diaphragmatic impulses "Edi" which allows for back up breaths to initiate. In clinical evidence, NIV-NAVA as a post-extubation support for VLBW infants was associated with an insignificant difference in the rate of re-intubation compared to nasal CPAP and an insignificant effect on the incidence of BPD, IVH, pneumothorax or death [62,63]. Similarly, NIV-NAVA as a post-extubation support was associated with an insignificant reduction in the risk of treatment failure compared to NIPPV (40% compared to 47.4%) without adverse events [64]. More clinical trials are needed to evaluate the efficacy of NIV-NAVA compared to nasal CPAP and NIPPV, particularly in the context of the high expenses of Edi catheters.

2.4. Nasal high frequency ventilation (NHFV)

High frequency ventilation can be provided by non-invasive route through nasal interface. Oscillatory waves with constant frequency generates variable flow in the nasopharyngeal pouch similar to bubble CPAP with the difference being that expiratory flow is active in NHFV compared to the passive expiratory flow in bubble CPAP. This, at least in theory, gives NHFV superiority over nasal CPAP and NIPPV in terms of CO2 elimination and decrease the frequency of apnea episodes [65]. In preterm infants with respiratory distress, the use of NHFV as initial therapy compared to nasal CPAP was associated with significant decrease in the duration of non-invasive respiratory support, significant decline in the need for mechanical ventilation, significant decrease in the incidence of IVH without a significant effect on the incidence of pneumothorax, BPD, pulmonary hemorrhage and NEC [66]. Post-extubation use of NHFV was associated with significant reduction in the reintubation rate and pCO2 concentration compared to nasal CPAP [67]. The main side effect of NHFV is upper airway obstruction secondary to increased thick and viscous secretions and increased abdominal distention which can be minimized by using a high frequency and low amplitude strategy to decrease mucous membrane irritation [68]. In summary, it is too early to make a statement of recommendation for the use of NHFV in the NICU and probably its use should be reserved to research protocols.

3. Care of preterm infants on non invasive respiratory support

3.1. Care of skin and nasal septum

Skin injury is mainly caused by misalignment and improper fixation of the interface, which results in pressure ulcers and necrosis secondary to a tight interface against the infant's skin and nose, friction between the interface and skin as the infant moves, and skin inflammation with secondary infection of accumulated secretions. Nasal septum injury represents a risk for long-term nasal disfigurement and cosmetic sequelae. Nasal septum injury is simply classified into mild (grade I) if redness and hyperaemia exists, moderate (grade II) if bleeding exists, and severe (grade III) if necrosis exists [17]. The application of a protocalized nursing care bundle includes; regular physical assessment of the nasal skin, ensuring proper placement of the prongs inside the nostril or the mask on the nose, ensuring a distance of 2 mm between the nasal septum and the prongs, delivering humidified gas, using a tape to secure the nasal prongs, daily gentle massage for the nasal septum and bridge, lubrication of nasal skin with hydrogel, use of hydrocolloid skin barriers, and use of antimicrobial ointment for skin breakdown have been shown to reduce the risk of nasal injury with non invasive ventilation [69]. Without meticulous attention to nasal care, all types of interfaces used to deliver non-invasive ventilation can potentially cause injury to the skin, nasal septum and deformity in the nose of preterm infants. Training of staff and having reliability measures to erasure compliance with nasal care are critical to prevent nasal injury.

Table 1
Summary of different non-invasive modalities for respiratory support.

Mode of support	Pros	Cons
CPAP	CPAP stimulates lung growth in preterm infants Bubble CPAP is associated with lowest incidence of BPD in multiple anecdotal reports	Requires experience and hand on training before success can be reproduced
Non-invasive positive pressure ventilation	A good option to use when infants have central apnea and increased work of breathing	It is considered an escalation of care that can be associated with lung injury if used excessively as a replacement to CPAP
High flow nasal cannula	It is easy to use and comfortable to infants	It is an inferior therapy when used as the primary mode of support

3.2. Developmental positioning

Preterm infants are preferred to lie in a midline position during the first 72 h of life to minimize the risk of intra-ventricular hemorrhage [70]. However, prolonged lying on one position increases preterm infant's stress responses and pain sensation [71]. Moreover, keeping preterm infants in one position for a long time increases the risk of skull deformities like brachycephaly, dolichocephaly, or plagiocephaly at term equivalent age which may later require intervention with physiotherapy or using helmets [72]. Nursing preterm infants in prone position was found to improve quality of sleep and decrease stress responses compared to supine position [71]. Left lateral position and prone position were associated with higher arterial oxygen saturation and tidal volume and better synchronization of thoraco-abdominal movement compared to supine position in preterm infants supported with CPAP [73]. Preterm infants nursed on right lateral position were associated with increased incidence of gastro-esophageal reflux, particularly fluid reflux, compared to left lateral position [74]. Skin-to-skin (kangaroo) care was associated with significant positive effects on physiological functions such as respiration rate, increasing maternal-infant attachment, and reducing maternal stress [75]. In summary, it is recommended for preterm infants supported with CPAP to alternate positions similar to other newborns. Nasal interface and breathing circuits should be adjusted when alternating positions to prevent nasal injury.

4. Keys to improve non invasive ventilation practice

Owing to variability in clinical practice among health care professionals, preterm infants managed with NIV have varied clinical responses and outcomes. Standardization of practice and developing clear pathway for NIV are important for its success. The pathway should include early use of NIV in the delivery room, bedside care and checklist, and algorithm for escalation of care. A full bundle of care that includes non-respiratory elements can increase the success rate with the use of CPAP; components of the bundle could include transfusion practice, fluid management, caloric intake, ductus arteriosus management and use of caffeine [21]. Establishment of a collaborative multidisciplinary team including physicians, nurses, respiratory therapists, and speech and physical therapists, who are experienced with management of preterm infants is an important key to successful practice. Maintaining the infant's comfort during non-invasive ventilation care and frequent clinical assessment of infants reduce the incidence of complications and increase trust of the health care practitioner on the efficacy of NIV.

5. Summary and conclusions

Non invasive ventilation has been widely used in the treatment of respiratory insufficiency in preterm infants with significant improvement in neonatal outcomes compared to invasive mechanical ventilation. Multiple trials were conducted on different modes of NIV. Interestingly, the outcomes of the same mode of support differed widely among centers; that highlights the critical importance of bedside skills to successfully support an infant with NIV. Therefore, when reviewing available literature, it is important to evaluate the baseline incidence of BPD in addition to relative risks and risk reduction. The control group in one study may have significantly higher BPD incidence compared to other centers using the same mode of support which needs to be considered when interpreting results. However, general highlights of NIV include: 1) the lowest incidence of BPD were reported from centers experienced with the use bubble CPAP. The claim that all CPAP systems are equally efficacious does not have data to support it, 2) HFNC, despite its tempting ease of use, was shown repeatedly as an inferior therapy when compared to CPAP, and 3) the use of NIPPV is a better alternative than invasive mechanical ventilation in infants with significant apnea and increased work of breathing while supported with CPAP. It is considered unjustified escalation of care for stable infants who could otherwise be supported with CPAP (Table 1).

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