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Indications for and Risks of Non-invasive Respiratory Support

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Abstract

Within the last decades, therapeutic advances have significantly improved the survival of extremely preterm infants. In contrast, the incidence of major neonatal morbidities, including bronchopulmonary dysplasia has not declined. Given the well-established relationship between exposure to invasive mechanical ventilation and neonatal lung injury, neonatologists have sought for effective strategies of non-invasive respiratory support in high-risk infants. Continuous positive airway pressure has replaced invasive mechanical ventilation for the initial stabilization and the treatment of respiratory distress syndrome. Today, non-invasive respiratory support has been adopted even in the tiniest babies with the highest risk of lung injury. Moreover, different modes of non-invasive respiratory support supplemented by a number of adjunctive measures and rescue strategies have entered clinical practice with the goal of preventing intubation or re-intubation. However, does this unquestionably important paradigm shift to strategies focused on non-invasive support lull us into a false sense of security? Can we do better in (i) identifying those very immature preterm infants best equipped for non-invasive stabilization, can we improve (ii) determinants of failure of non-invasive respiratory support in the individual infant and underlying etiology and can we enhance (iii) success of non-invasive respiratory support and (iv) better prevent ultimate harm to the developing lung? With increased survival of infants at highest risk of developing lung injury and an unchanging burden of bronchopulmonary dysplasia we should question indiscriminate use of non-invasive respiratory support and address the above issues.

Keywords

Non-invasive respiratory support; preterm infant; respiratory distress syndrome (RDS); bronchopulmonary dysplasia (BPD); continuous positive airway pressure (CPAP)

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Conflict of Interest Statement

KG or CJW declare no potential conflict of interest, real or perceived.

Introduction

Bronchopulmonary dysplasia (BPD) affects nearly half of all babies born with birth weight less than 1000 grams [1]. Both exposure to, and the duration of invasive mechanical ventilation (IMV), increase the risk of developing BPD [2, 3]. To date, no optimal mode of mechanical ventilation has been identified that reliably minimizes lung injury and prevents BPD [4–6]. These realities have driven the interest in providing and optimizing non-invasive respiratory support for very immature preterm infants. Unfortunately, studies reveal high rates of failure [7, 8], with about 50% of infants initially managed on non-invasive respiratory support subsequently requiring IMV [9–11]. In light of these findings, this review addresses the question whether the main contributors to failure could be identified early and more precisely, leading to improved success. With rates of BPD remaining high in very immature infants and with growing evidence of persistent pulmonary morbidity in BPD survivors even in the post-surfactant era [12, 13], we further raise the question of long-term effects of non-invasive respiratory support in this cohort.

What is the Indication for Non-invasive Respiratory Support in Preterm Infants?

Physiologic and anatomic features unique to the preterm neonate result in a near universal requirement for respiratory support. Structural immaturity of conducting airways, combined with increased compliance of the chest wall account for an inability to maintain functional residual capacity (FRC). Subsequent low lung volume, increased airway resistance and decreased pulmonary compliance, lead to increased work of breathing and contribute to respiratory failure. Over the past 50 years, multiple solutions have been proposed to address this physiology unique to the preterm lung, culminating in the introduction of continuous positive airway pressure (CPAP) by Gregory et al in 1971 [14]. By the late 1980s, the early and aggressive use of CPAP in very low birth weight infants was associated with significantly lower rates of BPD [2, 15, 16].

While these early reports were encouraging, it was unknown whether non-invasive support would prevent lung injury in the growing numbers of surviving neonates born less mature and largely antenatal corticosteroid (ACS) exposed in the late 1990s and early 2000s [17]. In light of this, three RCTs were performed comparing early nasal CPAP with routine intubation and surfactant: COIN [9], SUPPORT [10] and the *Vermont Oxford Network Delivery Room Management Trial* (VON-DRM) [11]. These studies demonstrated that routine use of early CPAP prevents lung injury in high-risk infants, with a numbers needed to treat of 17.7 [7], 25 [18] and 35 [19]. All studies enrolled extremely low gestational age neonates (ELGAN), and rates of ACS were high (>90%). Based on these results, the American Academy of Pediatrics and the European Consensus Guidelines recommend routine CPAP and early selective surfactant over primary intubation with prophylactic surfactant for extremely preterm infants at risk for respiratory distress syndrome (RDS) [20, 21].

CPAP Failure in the Tiny Baby - Common and Preventable?

Most published data demonstrate that routine and indiscriminate use of CPAP, based on gestational age or birth weight, results in a relatively consistent and high rate of failure, with the most immature neonates failing at the highest rates [9, 22, 23]. Data from RCTs report nearly 50% failure in the first week of life [9–11], a rate similar to published observational study numbers [22, 24–27]. Furthermore, 40–70% of infants randomized to early CPAP ultimately received surfactant [9–11]. In summary, neonatologists caring for ELGANs are facing two realities: 1) routine and even indiscriminate use of CPAP in high-risk neonates may decrease the burden of BPD, and 2) the same routine and indiscriminate use is associated with high rates of failure, potentially exposing a subset of high-risk neonates to unintended harm in various respects.

Chest wall instability and subsequent inability to recruit and maintain FRC constitute a major cause of non-invasive ventilation (NIV) failure in the very tiny baby [28]. Therefore, prevention efforts have focused on effective recruitment of FRC, administration of non-invasive positive pressure, and prevention of apnea. Augmenting CPAP, different modes of NIV have been introduced, with nasal intermittent positive-pressure ventilation (NIPPV) being the alternative most frequently used to mitigate failure, in particular, in infants with poor respiratory drive (Table 1) [29–31]. Moreover, the use of sustained lung inflation, T-piece in the delivery room, optimized infant positioning, application of various interfaces and delivery devices as well as early administration of caffeine have been studied. These interventions seem to be effective to variable degrees and have been reviewed elsewhere [8, 32, 33].

What Happens when Surfactant Deficiency Complicates Preterm Lung Physiology?

The results of the first RCT using a natural porcine surfactant to treat severe RDS were published in 1988, convincingly demonstrating a reduction in air leak, death, and the combined outcome of death or BPD [34]. Additional trials helped to fine-tune surfactant therapy in the management of RDS and revealed a key thematic link between treatment and outcome: the earlier RDS was accurately diagnosed and appropriately treated with surfactant, the better the outcome. “Early” compared to “delayed surfactant” improved survival and decreased air leak in preterm infants with RDS [35]. Guiding further studies, “prophylactic surfactant use” was proved to reduce air leak and mortality in infants at highest risk of developing RDS [36–38], leading to the adoption of this approach in the US and Europe [39].

In 2021, preterm infants at highest risk of RDS and later BPD differ significantly from subjects enrolled in the surfactant trials in the 1980s and early 1990s. While the Collaborative European Multicenter Study Group had enrolled subjects averaging 28.5 weeks’ gestation [34], data from the NICHD Neonatal Research Network centers revealed increased survival from 1993 to 2012 in those born at 23, 24, 25 and 27 weeks’ gestation [17]. In this same population, rates of BPD were about 40–90% [17], indicating that the most vulnerable babies are surviving at rates higher than ever before, but with significant

morbidities. The increase in ACS exposure from 24% in 1993 to 87% in 2010 [17] may have significantly contributed to this improved survival, contrasting with even lower rates of ACS exposure (about 30–40%) in the early RCTs evaluating prophylactic surfactant [37].

In light of these fundamental changes in the NICU population, the results of the early surfactant trials might not be directly applicable to today's ACS exposed, ever increasingly less mature babies. In the 9 trials included in the Cochrane review published before 1999, prophylactic surfactant was superior to selective surfactant in terms of air leak and mortality [38]. In contrast, prophylactic surfactant provided no benefit, and perhaps increased risk of harm, when compared to routine use of CPAP in a less mature population with near universal ACS exposure [38]. However, there may be logical and biologically plausible conclusions that still apply. It is likely to be true that if an extremely preterm baby has surfactant deficiency, the earlier the diagnosis is made and appropriately treated, the better the outcome will be. Neonatologists have to balance this reality with risks associated with intubation and IMV frequently accompanying surfactant administration. In fact, the use of imprecise measures to diagnose surfactant deficiency may lead to unnecessary harm. On the other hand, indiscriminate use of CPAP in high-risk neonates may potentially delay surfactant administration in a significant proportion of infants. Less invasive surfactant administration (LISA) represents a promising strategy to overcome this dilemma [40]. Alternatively, or additively, neonatologists need to better and earlier diagnose surfactant deficiency.

Can we Discriminate Surfactant Deficiency from other Causes of CPAP Failure?

Any degree of surfactant deficiency will immediately compound the problems caused by the structural immaturity of conducting airways and the increased compliance of the chest wall. It is reasonable to hypothesize that NIV would be most successful and appropriately indicated for a patient population where chest wall instability and both recruitment and maintenance of FRC are not complicated by this condition [28]. The ability to make this diagnosis would not only allow identification of candidates with highest likelihood of being successfully managed on non-invasive support but would also allow for early and targeted diagnosis-based surfactant therapy.

Interestingly, observational data demonstrate that CPAP failure occurs early (about 8h), with incidences highly depending on the failure criteria used [22, 25, 41–43]. These data are remarkably consistent with those reported in the CURPAP and COIN trials where most babies failing CPAP (about 50%) were intubated for increasing oxygen need within the first 8h of life [9, 44]. The early timing of failure would be consistent with the hypothesis that surfactant deficiency is a significant contributor to the inability to stabilize these babies with non-invasive support.

If surfactant deficiency is a primary cause of CPAP failure in ELGANs, it would be reasonable to expect currently available diagnostic tests to support this diagnosis. However, published data regarding the relationship between RDS determined by chest radiograph and CPAP failure are less compelling. The presence of severe RDS on chest x-ray was associated

with an increased odds of CPAP failure [24, 43, 45]. However, failure is not uniform among those infants with severe RDS, occurring in 50–80% [24, 45]. Furthermore, among those failing CPAP, less than a third have radiologic evidence of severe RDS [22, 43, 45]. These data, demonstrating that not every baby with severe RDS fails CPAP and that a minority of babies failing has severe RDS on x-ray, might indicate that the contribution of surfactant deficiency to CPAP failure in this population is overestimated. If this assumption is wrong, on the contrary, and if surfactant deficiency *is* a major cause of early CPAP failure, these data demonstrate the limited accuracy and value of chest radiographs in the diagnosis of this condition.

Does Increasing Oxygen need Indicate that the Baby is not a Candidate for Non-invasive Support?

In the absence of diagnostic testing, clinical criteria, such as oxygen requirement, are used to support the diagnosis of RDS. Both in the RCTs of surfactant performed in the 1980s and 1990s and the RCTs of CPAP in the 2000s, oxygen need (FiO_2) was incorporated into the definition of “treatment failure”. In general, the early trials incorporated FiO_2 requirement of about 40% to demonstrate presence of RDS prior to randomization [46]. In contrast, the later trials of CPAP incorporated higher FiO_2 requirement (range 40–60%, Table 2). While the finding of increasing FiO_2 requirement is consistent with the diagnosis of surfactant deficiency, clarification is needed to what extent FiO_2 provides adequate sensitivity and specificity to distinguish those babies on non-invasive support that would benefit from surfactant replacement therapy. Lacking clear data, there is no consensus on what FiO_2 requirement defines threshold for intubation and subsequent surfactant administration in extremely preterm infants on CPAP. The European Guidelines recommend surfactant treatment at an FiO_2 of 0.30, Canadian Guidelines recommend 0.50, while the Committee on Fetus and Newborn of the American Academy of Pediatrics do not identify a specific level [20, 21, 47].

Fuchs et al. demonstrated how changing the FiO_2 criteria affected intubation rates of extremely preterm infants on CPAP. In this study, intubation occurred when the FiO_2 reached 0.60. By dropping the FiO_2 criteria to 0.35, 16% more infants required intubation and received surfactant, and were treated about 2.5 hours earlier [25]. Additionally, FiO_2 of 0.30 at NICU admission had a sensitivity of 60% in predicting CPAP failure. These data reveal the fundamental limitations of oxygen requirement to guide surfactant therapy. Choosing a lower threshold allows a more inclusive approach and achieves earlier treatment. Alternatively, while a higher threshold maximizes the number of babies that will ultimately be successfully managed with CPAP, this selective approach will delay surfactant administration in some babies. Complicating this issue further, there may be some babies that never reach the set threshold for surfactant therapy although they are truly surfactant deficient and would benefit from treatment. Finally, there may be some extremely preterm babies that require supplemental oxygen for reasons not related to surfactant deficiency who reach the set threshold and do not benefit from this intervention. Given the therapeutic inaccuracies dictated by the loose association between FiO_2 and surfactant deficiency, advanced diagnostic approaches are needed.

Can we Identify those that will Succeed on Non-invasive Support by Accurately Diagnosing Surfactant Deficiency?

In order to identify infants with the highest likelihood of being successfully managed on non-invasive support, accurate tests to diagnose surfactant deficiency are needed. Given what is known about the benefit of early surfactant administration, it is essential that a diagnostic test can be done early, quickly, and in extremely preterm infants. Ideally, the test would be easy to perform and non-invasive. Lung ultrasound (LUS) has been shown useful in diagnosing various conditions in pediatric patients [48, 49], and has been used to diagnose RDS in extremely preterm infants. This test can be done quickly and early, with reliable data being obtained as early as 5–10 minutes after birth [50–55]. Importantly, findings on early lung ultrasound consistent with the diagnosis of surfactant deficiency correlate well with alveolar-arterial gradient, oxygenation index and arterial-to-alveolar ratio. These relationships are more reliable in very immature infants [51]. The presence of these findings is superior to chest radiograph, and can aid in predicting CPAP failure [50–52, 54–56]. Perhaps even more importantly, published observational, quality improvement and RCT data demonstrate that use of LUS may result in earlier administration of surfactant, and decreased oxygen exposure [53, 54, 57].

While these results are promising, there is one significant limitation. In these trials, the threshold for CPAP failure in extremely preterm infants was defined as requiring $FiO_2 > 0.30$ [52–54, 56]. By using this FiO_2 level and creating a more inclusive definition of CPAP failure, whether routine use of LUS improves the ability of the clinician to identify extremely preterm infants with the highest likelihood of succeeding on non-invasive support is left unanswered. Ideally, LUS could be used to further refine and target surfactant therapy. This nuanced perspective is conceptualized by considering the “false positive” (reported at 12–50%) and “false negative” (reported at 5–23%) LUS findings [51, 52, 54–56]. Whether the “false positives” – infants that demonstrate LUS findings consistent with RDS but never reach FiO_2 of 0.30 – would benefit from surfactant therapy resulting in less oxygen exposure and lower positive pressure requirement is unknown. Alternatively, whether the “false negatives” – meaning those without LUS findings of RDS but reaching a threshold of 0.30 – could or should be managed with non-invasive support without surfactant is unanswered. Hopefully, with increased use of LUS in this population these answers will become clear.

Why we need to Fine-tune the Indication for Non-invasive Respiratory Support

Indiscriminate use of non-invasive respiratory support may cause potential harm including nasal trauma, pneumothorax and air leak syndromes, gastrointestinal distension and perforation, and barotrauma and volutrauma (Table 1). Infants randomized to CPAP showed higher rates of pneumothorax in the COIN trial (9% vs. 3% in ventilated infants) [9] and in the Colombian Neonatal Network Study (9% vs. 2% in early surfactant therapy) [58], while rates did not differ between early CPAP and mechanical ventilation in the SUPPORT trial [10]. Also, a meta-analysis covering COIN, SUPPORT, CURPAP and VON-DRM trial did not confirm this association [18]. A recent Cochrane review comparing CPAP with oxygen

treatment alone described an increased risk of pneumothorax associated with CPAP, with a number needed to treat for an additional harmful outcome of 11 [59].

Gastric distension is observed with CPAP and NIPPV, and trials have reported cases of gastrointestinal perforation and necrotizing enterocolitis (NEC) [9–11]. Moreover, concerns about increased risk of intracerebral hemorrhage were raised in early studies of CPAP in preterm infants [60]. COIN, SUPPORT and VON-DRM trial did not find significant differences in high-grade intraventricular hemorrhage, NEC, patent ductus arteriosus and severe retinopathy of prematurity, with early CPAP versus elective intubation and IMV [9–11]. Moreover, the existing meta-analysis covering these trials did not confirm any association [18]. Cochrane reviews comparing CPAP and NIPPV did not find increased risk ratio for one modality [29–31]. Nevertheless, NIV can cause all adverse effects associated with IMV apart from intubation-related risks [29–31]. Therefore, routine use of NIPPV in non-apneic infants constitutes an unjustified escalation of non-invasive support. Depending on the leakage of prongs or mask and the intrinsic resistance, on the contrary, there is the additional risk of decreased transmission of the desired distending pressure.

In nasal high-flow therapy (nHF), distending pressures are unpredictable and unmonitored [61]. Preclinical models show that high pressures can be transmitted to infants if adequate leakage or pressure-relief valves are not present [62, 63]. Vice versa, set flow, resistance and leak through nares and mouth account for little to no delivery of distending pressures in many other babies. Although increased comfort and reduced nasal trauma [61] tempt practitioners to continuously expand nHF use, potential risks need to be critically reviewed. A Cochrane review concluded that there is inadequate data on nHF use in extremely preterm infants [61].

Data on the effect of NIV on long-term outcome in preterm infants is scarce. A longitudinal follow-up of infants 28 weeks' gestation comparing three periods of respiratory management (1991–1992 vs. 1997 vs. 2005) found increased rates of BPD and worsened lung function at 8 years age in the 2005 cohort versus earlier periods, despite an increased use of NIV over time [13]. The use of postnatal steroids decreased significantly from 40% in 1991–1992 to 23% in 2005, while survival rates increased (53% vs. 65%) [13], suggesting that highest-risk infants did not survive long enough to develop BPD in the early cohort. Given the more frequent use of NIV, however, these findings raise the question of long-term effects of NIV. Respiratory follow-up of the SUPPORT study population documented fewer episodes of wheezing (28.9% vs. 36.5%, $p<0.05$), respiratory illnesses (47.7% vs. 55.2%, $p<0.05$) and physician visits for breathing problems (68.0% vs. 72.9%, $p<0.05$) in the CPAP group compared to infants randomized to intubation/surfactant at 18–22 months corrected age [64]. Moreover, the two SUPPORT study groups did not differ in the composite outcome of death/neurodevelopmental impairment (10.9% vs. 9.1%, CPAP vs. intubation/surfactant) at 18–22 months corrected age [64].

By trying to avoid IMV, neonatologists might run the risk of overdoing non-invasive support. Using higher thresholds for intubation and re-intubation will increase the number of babies managed on non-invasive support. It is critical to weigh risks of intubation against prolonged

exposure to episodes of apnea or worsening RDS. Contrariwise, care must be taken to avoid adverse hyperinflation of airways and gastrointestinal tract.

Conclusions

The widespread use of non-invasive respiratory support in very immature infants unquestionably constitutes an important paradigm shift in neonatal care. Though the physiologic basis and the non-invasive character of NIV are convincing, it is somewhat disappointing that current approaches do not result in larger short-term and long-term treatment effects. Early identification of infants that benefit most from non-invasive support versus those who need intubation and targeted surfactant therapy seems key to maximize benefit and limit harm. A “one strategy fits all” approach does not meet individual needs affected by gestational age and other determinants, and indications for non-invasive support in the absence of surfactant treatment will fail to capture the patient population that benefit most, and exclude those who do not. In this context, LISA constitutes a promising approach allowing surfactant administration without intubation. Of note, the potential benefit of this approach might be higher than assessed so far. With criteria often relying on very inclusive FiO_2 requirement, the observed effect may have been biased by including those who do not benefit from surfactant treatment, and potentially by excluding some that do. Lung ultrasound constitutes a promising tool in diagnosing RDS. Whether a combination of clinical findings, lung ultrasound, and biochemical assessment of maturation of surfactant production could further refine a more discriminate use of non-invasive support is unknown. Ultimately, strategies like these could usher in a new era of personalized neonatal medicine. Although risk of complications appears small, one cannot conclusively determine the long-term effects of non-invasive support. Proper selection of patients, modes, and instrument settings and constant re-evaluation is critical. The paucity of data on long-term outcome of high-risk infants managed with non-invasive support highlights the need for appropriate follow-up studies that take into account the shortcomings of BPD as a surrogate for pulmonary dysfunction and morbidity later in life.

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Table 1: Modes of non-invasive respiratory support in preterm infants - evidence, indications, potential risks and open questions to be addressed

Mode	Evidence	Indication	Potential risks	Issues to be addressed
Continuous positive airway pressure (CPAP)	<ul style="list-style-type: none"> Respiratory stabilization by recruitment of FCR Prevention of intubation and mechanical ventilation Prevention of post-extubation failure 	<ul style="list-style-type: none"> primary support post-extubation support 	<ul style="list-style-type: none"> Nasal trauma Pneumothorax and air leak syndromes Gastric distension and GI perforation Impediment of delivered pressure by resistance of prongs or leakage 	<ul style="list-style-type: none"> What PEEP levels are best? What strategy to wean off CPAP is most beneficial? What is the optimum duration?
Nasal high-flow therapy (nHF)	<ul style="list-style-type: none"> Inadequate data to support nHF as primary support Inadequate data to support nHF as post-extubation support 		<ul style="list-style-type: none"> Application of unpredictable and unmonitored, low-related distending pressures 	<ul style="list-style-type: none"> Is initial stabilization with nHF efficacious? Are distending pressures dangerously high or ineffective? Are we overdoing nHF?
Nasal intermittent positive-pressure ventilation (NIPPV)	<ul style="list-style-type: none"> Respiratory stabilization by recruitment of FCR Prevention of intubation and mechanical ventilation Prevention of post-extubation failure Prevention of apnea and reduction of work of breathing 	<ul style="list-style-type: none"> primary support post-extubation support 	<ul style="list-style-type: none"> Nasal trauma Pneumothorax and air leak syndromes Gastric distension and GI perforation Barotrauma and volutrauma 	<ul style="list-style-type: none"> Does NIPPV effectively prevent intubation and re-intubation in the tiniest babies? How harmful are PIP-related side-effects in the most immature infants?
Nasal high frequency oscillatory ventilation (NHFOV)	<ul style="list-style-type: none"> No data to support routine use No RCTs available Small single-center studies in very few infants 		<ul style="list-style-type: none"> Limited data regarding efficacy 	<ul style="list-style-type: none"> Efficacy yet to be determined in RCTs Risks and benefits yet to be evaluated
Neurally adjusted ventilatory assist (NAVA)	<ul style="list-style-type: none"> No data to support routine use No RCTs available Few very small studies indicating safety and feasibility, smaller PIPs and decreased work of breathing 		<ul style="list-style-type: none"> Limited data regarding efficacy Potential limitations in very immature preterm infants 	<ul style="list-style-type: none"> Efficacy yet to be determined in RCTs Risks and benefits yet to be evaluated Does NAVA improve oxygenation and decrease rates of desaturations?

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Mode	Evidence	Indication	Potential risks	Issues to be addressed
				<ul style="list-style-type: none">• Does NAVA impact short-term and long-term pulmonary outcome?

Abbreviations: FRC, functional residual capacity; GI perforation, gastrointestinal perforation; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; RCT, randomized controlled trial

Criteria defining CPAP Failure used in RCT comparing CPAP vs. Prophylactic Surfactant

Table 2:

Trial	Publication Year	CPAP Failure	
		FiO2	Oxygen Saturation Targets
COIN *	2008	>60%	not stated
SUPPORT *	2010	>50%	maintain 88%
VON (Dunn) *	2011	mandatory: >60% discretionary: 40–60%	maintain 86–94%

* we will include reference numbers for these trials to correlate with the text when the final manuscript is accepted