Non-invasive Ventilation and Exogenous Surfactant in Times of Ever Decreasing Gestational Age: How Do We Make the Most of These Tools?

Clyde J. Wright[1*], MD; Kirsten Glaser[2*], MD; Christian P. Speer[3], MD, FRCPE; Christoph Härtel[3], MD; Charles C. Roehr[4,5], MD

Affiliations:
[1]Section of Neonatology, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO

[2]Division of Neonatology, Department of Women's and Children's Health, University of Leipzig Medical Center, Leipzig, Germany

[3]Department of Pediatrics, University Hospital of Würzburg, Würzburg, Germany

[4]Southmead Hospital, North Bristol NHS Trust, University of Bristol, Dept. Paediatrics, Faculty of Health Science, Bristol, UK

[5]National Perinatal Epidemiology Unit, Nuffield Department of Population Health, Medical Sciences Division, University of Oxford, Oxford OX3 7LF, Oxfordshire, UK

* contributed equally

Address correspondence to:
Charles C. Roehr, MD
Postal address: National Perinatal Epidemiology Unit, Richard Doll Building, Old Road Campus, Headington, Oxford OX3 7LF, UK
E-mail: charles.roehr@npeu.ox.ac.uk

Key Words:
Non-invasive respiratory support, preterm infant, extreme prematurity, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), continuous positive airway pressure (CPAP), exogenous surfactant therapy

Conflict of Interest:
Clyde J. Wright and Kirsten Glaser report nothing to disclose. Christian P. Speer was consultant to Chiesi Farmaceutici Parma, Italy. Charles C. Roehr and Christoph Härtel report to have worked as a consultant to Chiesi Farmaceutici Parma, Italy.

Statement of Financial Support:
This work was supported by NIH grant R01HL132941 to CJW.

RDS and Neonatology – Forever Linked, Forever Evolving

The evolution of neonatal practice is intimately linked to our treatment of one disease - respiratory distress syndrome (RDS).[1-3] The evolution of the threshold of viability has necessitated a continual re-assessment of the application of well-studied and evidence-based treatments for this disease. Survival rates of extremely preterm neonates continue to improve,[4,5] including for those born at 22-23 weeks' gestational age (GA).[6-8] However, rates of respiratory morbidity and bronchopulmonary dysplasia (BPD) remain unacceptably high, especially among these most immature, highest risk neonates (<28 weeks' GA, and in particular <25 weeks' GA).[9] Thus, choosing the best care options is one of the central challenges to be met.

With CPAP and surfactant replacement therapy present-day neonatologists are equipped with two powerful tools. This commentary seeks to explain how our treatment of RDS has evolved over time, and how lessons learned in more mature populations may both advance and hinder respiratory care when applied to this new population of (extremely premature) neonates. It addresses the question of whether and how RDS could be identified early and more precisely in the most immature preterm infants, allowing for a more fine-tuned approach to early respiratory support for this high-risk patient population. We ask whether our inability to diagnose RDS inadvertently causes harm by delaying exogenous surfactant therapy in those destined to fail CPAP/NIV, and whether or not less/minimally invasive surfactant administration (LISA/MIST) represents both a pragmatic and beneficial approach in combining early surfactant and CPAP. Finally, we argue that it is time to distinguish high-risk very immature preterm infants (25-28 weeks' GA) from the increasing number of highest-risk, periviable preterm infants born at 22-24 weeks' GA, in order to better adapt respiratory management meeting individual needs and risk profiles.

Bronchopulmonary Dysplasia – The Reason Why Neonatologists Seek to Avoid Invasive Mechanical Ventilation

BPD remains among the most common morbidities following preterm birth, and rates are even increasing in the most immature preterm infants.[10,11] In addition to predicting long-term pulmonary dysfunction,[12] BPD increases the risk of poor neurodevelopmental outcomes.[13,14] Thus, there is an urgent need to identify strategies that minimize the risk of developing BPD, in particular, in high-risk patients. The pathogenesis of BPD is multifactorial, with main contributing factors being mostly out of the clinicians' control – including preterm birth, structurally and biochemically immature lungs, intrauterine growth restriction, prenatal and postnatal inflammation and neonatal infections.[10,15,16] However, exposure to mechanical ventilation, one of the strongest risk factors for BPD,[17-24] on the contrary, is *within* the clinicians' control. Consistent with this, large randomized controlled trials (RCTs) have convincingly demonstrated that avoiding invasive mechanical ventilation (IMV) through the routine use of CPAP is safe and prevented BPD in very immature neonates at high risk of lung injury (25-30 weeks' GA).[25-27]

CPAP and Non-Invasive Ventilation – What Do The Guidelines Say?

These data have largely convinced neonatologists that avoiding IMV is advantageous in very immature neonates. Thus, one might expect to find relatively consistent recommendations in national and international guidelines and expert consensus statements regarding (i) the use of CPAP and NIV for the initial respiratory support as well as (ii) what constitutes "CPAP failure" and when to intervene and provide exogenous surfactant to treat RDS in this cohort.[28]

Unfortunately, consensus in written guidelines regarding these issues does not exist.[29-31] Apparent inconsistencies reflect the different concepts, structures and practices of neonatal medicine as well as recommendations of academic bodies and international societies in the US,

Canada and Europe. And while each set of guidelines proclaims to be firmly based on the available evidence, regional interpretation and clinical implementation result in variability of practice based on practitioner preference. While potentially frustrating, this variability highlights gaps in and the urgent need for further improvement of evidence base of early respiratory management of preterm infants. Given today's cohort of extremely preterm, often periviable infants, the development of gestational age-specific optimal care seems inevitable.[32]

The Benefit of Early and Liberal CPAP – Applicable to the Very Tiny Baby?

When analyzing the question whether routine use of CPAP in extremely premature infants compared to routine intubation and prophylactic surfactant prevents BPD assessed at 36 weeks' postmenstrual age, it is necessary to exclusively consider subjects at the highest risk of BPD development and to enroll adequate numbers. Ideally the control group would be managed with the current standard-of-care. By the late 1990's/early 2000's, the then best available evidence supported the practice of routine intubation and prophylactic or early surfactant for babies at high risk of RDS, but this approach had not been compared to CPAP alone.[33-36] Importantly, the studies supporting prophylactic or early surfactant enrolled very few infants born at 25-28 weeks' GA, and rates of antenatal corticosteroid (ACS) exposure were much lower than seen in current practice.[35,36] Thus, changes in obstetrical practice (increased ACS) and the evolving NICU patient population (increasing survival of extremely premature neonates) created a knowledge gap.

Two RCTs performed in the late noughties – SUPPORT and the Vermont Oxford Network Delivery Room Management Trial (VON-DRM)[37,38] – demonstrated that compared to prophylactic surfactant, routine use of early CPAP in very high-risk neonates with high rates of ACS exposure, prevents BPD/death with a number needed to treat (NNT) of 17.7.[27] More inclusive meta-analyses cite a NNT of 25 and 35.[25,26] This treatment effect is encouraging for what is essentially a "de-

escalation" of therapeutic invasiveness (i.e., no intubation and no administration of exogenous surfactant), and supports broad implementation of this approach in infants at high risk of BPD development. Aiming at minimizing the exposure to IMV, these data supported the adoption of rather liberal criteria of CPAP/NIV failure – comprising higher FiO_2 as well as CPAP levels – in the Canadian and US guidelines.[29,31] However, it is reasonable to ask why the treatment effect (NNT 17.7-35) is not larger, given the known risks of exposure to IMV.

High Incidence of CPAP Failure – Does It Blunt the Treatment Effect in the Extremely Premature Infant?

One conceivable explanation of this lack of treatment effect is that CPAP/NIV does not sufficiently reduce exposure to IMV when broadly applied to a high-risk population. Stoll and colleagues reported outcomes of preterm infants born at <28 weeks' GA at Neonatal Research Network centers.[39] In 2012, and despite increased use of CPAP for initial respiratory support, over 85% of those that survived >12 hours were exposed to IMV. Consistent with these data, rates of CPAP failure in the first week approached 50% in SUPPORT and VON-DRN trials[37,38] and are similarly high in observational studies.[40-42]

While the benefits of CPAP/NIV are clear, the NIV approach when broadly applied apparently fails to adequately support over half of the target population. It is thus important to ask whether this broad application mixes two distinct patient populations, each needing a different approach. While routine or liberal use of CPAP may adequately support one subset of high-risk neonates and may effectively decrease the burden of BPD, the same approach may be associated with high rates of failure in another subset of high-risk infants. The first population – those most likely to need only NIV support – should demonstrate a greater treatment effect with targeted application. The

second population – those who ultimately will not sustain on NIV support – may suffer significant harm from delay of adequate treatment.

Surfactant Deficiency – Primary Driver of NIV Failure in the Extremely Premature Infant

It is necessary to identify the primary cause of NIV failure in order to target appropriate therapy. Data both from RCTs and observational studies depict that ~50% of infants initially supported with CPAP require IMV within the first week of life, [37,38,43] with a majority failing within the first 8 hours.[42-44] Failure is foreshown by increasing oxygen requirement, and the most immature neonates are at highest risk of not sustaining on CPAP/NIV alone.[41-45] Multiple contributing factors, ultimately leading to ineffective gas exchange and the requirement of maximal respiratory support have been identified. These include (i) surfactant deficiency, as well as (ii) unique anatomic and physiologic features in the extremely premature infant causing an inability to effectively deliver distending pressure and to maintain sufficient functional residual capacity and (iii) impaired respiratory drive. Surfactant deficiency as a major feature of pulmonary immaturity increases with decreasing gestational age. It is therefore not surprising that best estimates place surfactant deficiency, synonymously referred to as RDS, as the key driver of CPAP failure in 80% of cases of extremely premature infants.[46]

The initial trials evaluating exogenous surfactant for RDS convincingly demonstrated that the earlier the treatment administered, the greater the treatment effect in terms of air leak and pneumothorax, chronic lung disease and mortality.[47] Strategies referred to as “prophylactic surfactant use” or “early rescue surfactant” were proved to decrease air leak and improve survival of infants at highest risk of developing RDS.[36,48,49] However, it is necessary to highlight that infants enrolled in these early studies of surfactant replacement therapy were relatively mature, had lower ACS exposure rates, and were already intubated due to RDS. Nonetheless, it is reasonable to

assume that the well-proven lung protective properties of exogenous surfactant therapy should extend to the cohort of extremely premature neonates with RDS, whether supported by IMV or CPAP/NIV. The desire to capture the beneficial effects of early surfactant treatment and to avoid the potential harm of treatment delay drove the adoption of very inclusive surfactant treatment criteria (FiO_2 ≥0.3) suggested in the European Consensus Guidelines – besides critical assessment of clinical symptoms, such as increased work of breathing and sternal retractions.[30] In summary, current recommendations reflect the dilemma still present for neonatologists: RDS and its severity can only be determined clinically by judgement of progressive dyspnea and FiO_2 requirement. In line with this, signs of increased work of breathing, apnea or respiratory acidosis together with an increased oxygen need despite presumed optimized CPAP/PEEP are used as pointers towards respiratory failure.[50] In an even more immature preterm infant population in 2022 these limitations in our diagnostic repertoire and their impact on therapeutic decisions must not be underestimated. One cannot help but argue that these clinical signs are merely confirming CPAP failure, rather than providing useful information towards its prevention.

FiO_2 as Determinant of CPAP Failure – The Need to Improve Our Predictive Capacity

Indeed, FiO_2 requirement is a consistent objective marker heavily relied upon when determining CPAP failure in the extremely premature neonate. While lower FiO_2 thresholds result in earlier treatment, higher thresholds will maximize the number of babies successfully managed with CPAP alone. The impact of FiO_2 criteria on intubation rates was demonstrated by Fuchs and colleagues.[41] By lowering the intubation criteria from FiO_2 0.6 to 0.35, rates of intubation increased by 16%. Dargaville and colleagues demonstrated that FiO_2 levels in the first two hours of life had the “strongest predictive effect on CPAP failure” in neonates born at 25-28 weeks’ GA.[42] However, the need to improve this predictive capacity is clearly demonstrated by the poor positive predictive value of FiO_2 in the given study. Applying the reported sensitivity of ~85% and specificity of ~50%

of an early life (<2 hours of life) FiO_2 requirement of 0.3 to the subjects born at 25-28 weeks' GA in this dataset, we find a positive predictive value of 59% and a negative predictive value (NPV) of 82%. Thus, FiO_2 might function as a relatively good screening tool, but it is far too imprecise as a determinant for intervention. Furthermore, given the NPV of 82% in a patient population where the incidence of failure is ~50%, a significant number of patients that will ultimately fail CPAP are missed. Gulczynska and colleagues reported similar numbers, with an FiO_2 of 0.29 providing 73% sensitivity and 57% specificity for predicting CPAP failure in preterm infants at risk of RDS (i.e., no clinical or radiographic confirmation of RDS).[51] In this dataset, CPAP failure occurred in 108 of 389 subjects. Thus, using FiO_2 requirement of 0.29 alone had a positive predictive value of only 36.6% and a negative predictive value of 84.7%. Complicating this issue even more, there may be other babies who require supplemental oxygen for reasons not related to surfactant deficiency. Some of these cases may be related to functional surfactant inactivation such as infection, inflammation and edema secondary to fluid transudate that follows injury to the immature airway-capillary unit.

It has been reported that the radiographic finding of severe RDS predicts CPAP failure.[52,53] However, this finding occurs in only a subset of ~20-30% of those infants that will ultimately not sustain on CPAP. Thus, while the presence of severe RDS aids the clinician, it is absent in most of those extremely premature infants that might ultimately require more than CPAP. These data demonstrate the limitations of relying on FiO_2 and chest radiograph to guide decisions on exogenous surfactant replacement in extremely premature neonates.

If We Cannot Diagnose RDS Accurately and Early, Can We Minimize the Risks of Surfactant Administration?

The dilemma of diagnosing RDS articulated by Bancalari and Jobe in 2012 – "*There is no clinically acceptable way to securely diagnose surfactant deficiency. The RDS diagnosis is imprecise at*

best because many of these infants are intubated and ventilated shortly after birth and are given surfactant. These interventions can mask the clinical and radiographic signs of RDS." [1] – remains unchanged, a decade later, in 2022. Considering the next 100 extremely premature neonates admitted to today's NICU, it is highly likely that ~50 can be successfully managed with CPAP/NIV, while best estimates predict that ~50 of these high-risk patients will not be sustained on CPAP/NIV support alone, primarily due to RDS, in the first day of life. At best, neonatologists would be able to identify these separate cohorts and treat them appropriately – ideally offering CPAP/NIV to just those 50 infants with a high likelihood of success. By targeting NIV to only this cohort, the beneficial effect of CPAP would increase beyond the estimates provided by current RCTs. On the other hand, the ability to diagnose RDS as early as possible would provide the maximal benefit of exogenous surfactant. Targeting replacement therapy to those infants with RDS the beneficial treatment effect of exogenous surfactant would increase beyond estimates provided by RCTs, too. By appropriately cohorting these patients, and tailoring their early respiratory support, neonatologists would be able to take the best therapeutic advantage of both CPAP/NIV and exogenous surfactant. This search for individualized care approaches accounts for some of the biggest challenges in neonatal care today.

So far, the inability to accurately diagnosis surfactant deficiency as the primary reason for respiratory failure in these patients prevents targeted and timely exogenous surfactant treatment. Lacking this capacity, alternative techniques of surfactant administration aim at combining the benefits both of early surfactant *and* early CPAP. The INtubation-SURfactant-Extubation (IN-SUR-E) procedure comprises the brief insertion of an endotracheal tube (ETT) to administer surfactant, a short period of positive pressure ventilation and extubation back to CPAP.[54] In the recently published IN-REC-SUR-E trial a lung-recruitment maneuver was added to the IN-SUR-E strategy.[55] Comparing this modified approach to regular IN-SUR-E, the authors found less need for IMV within 72 hours of procedure without increasing the risk of adverse neonatal outcome.[55]

Notably, the IN-SUR-E procedure usually requires analgesia or sedation which may delay immediate extubation leading to IMV exposure in up to 17% of infants <30 weeks' GA.[38,44] Given the rapidly changing lung physiology following surfactant administration, even a limited time of IMV exposure may be harmful for the immature lung. Less invasive techniques of surfactant administration do without ETT and invasive ventilation. Among different modes, less invasive surfactant administration (LISA) or minimally invasive surfactant therapy (MIST) have emerged as a practicable approach – increasingly used for the management of RDS in preterm infants.[54,56-60] Potential advantages of LISA/MIST compared to standard surfactant via ETT – when performed by experienced proceduralists – comprise (i) avoidance of positive pressure ventilation while providing similar effectiveness of surfactant deposition as compared to ETT,[61,62] (ii) risk reduction of intubation trauma by using small diameter catheters for surfactant administration,[63,64] (iii) maintenance of physiological larynx and glottis function[65] and (iv) support of physiological adaptation after birth including lung recruitment, circulation and regional tissue oxygenation. [66-70] Of note, in units practicing LISA/MIST, the procedure is considered as *one* part of a whole *bundle* of "less intensive or less invasive support measures" further comprising delayed cord clamping, avoidance of hypothermia and discomfort, acceptance of PEEP levels ≥ 8 cm H_20 as well as early initiation of caffeine. [71-73]

Surfactant Administration to Spontaneously Breathing Infants

A recent network meta-analysis of RCTs and observational studies as well as a Cochrane review indicate that LISA/MIST compared with administration of surfactant via ETT and/or INSURE is strongly associated with a risk reduction in mechanical ventilation, BPD or the combined outcome of BPD/death.[74,75] However, very few of the studies included enrolled patients born at <28 weeks' GA at high risk of CPAP failure and lung injury. Before drawing final conclusions on safety and efficacy it is, thus, important to consider separately those trials that enrolled high-risk and highest-

risk neonates and to evaluate whether LISA/MIST hold promise to improve outcomes of the most vulnerable preterm infants.[76]

There is evidence coming from two RCTs that LISA/MIST as compared to continuation of CPAP reduces the need for IMV in these high-risk neonates within 72 hours of birth (*Avoidance of mechanical ventilation* (AMV) trial: n=220 infants 26-28 weeks' GA; RR, 0.61 [95% CI, 0.42-0.88]; and the OPTIMIST trial: n=485 infants 25-28 weeks' GA; RR, 0.50 [95% CI, 0.40 to 0.64]).[77,78] Moreover, the OPTIMIST trial documented a reduced risk of pneumothorax requiring drainage, decreased incidence of BPD in survivors to 36 weeks' GA and reduced duration of respiratory support in hospital in MIST treated infants.[77] However, neither the AMV nor the OPTIMIST trial showed a decrease in BPD/death upon LISA/MIST treatment – and it is important to ask why.

The beneficial treatment effects of this approach might be higher than assessed so far. Inclusion of subjects with a very low likelihood of treatment effect biases any beneficial effect of LISA/MIST in published trials towards the null. It is therefore likely that by targeting LISA/MIST to those preterm infants suffering from respiratory failure primarily due to surfactant deficiency would demonstrate much larger beneficial effects than currently reported. This hypothesis remains to be tested. Published data support the hypothesis that the benefit of LISA/MIST wanes as GA decreases. GA has been demonstrated as critical determinant for LISA/MIST failure.[77,79] Large-scale GNN data as well the OPTIMIST trial document significantly reduced need for IMV in the first 72 hours upon LISA/MIST in the more mature infants, in infants >25 weeks' GA and, in particular, >27 weeks' GA.[60,77,80] However, in the GNN cohort, even in infants ≤25 weeks a reduction of IMV was reported in 40% of cases. In infants born at 25-26 weeks' GA this reduction was 60% and in infants born at 27-28 weeks' GA the effect was almost 75%.[60] Risk factors for LISA/MIST failure include the absence of ACS, high FiO_2 thresholds, dose and timing of surfactant as well as practitioner and team experience.[46,79,81] A tailored approach seems to be most important in infants at the lowest gestational ages.

The Way Forward: Can We Diagnose RDS Earlier and More Accurately and Tailor Our Approach to Optimized Care or Is There a Renaissance for Prophylactic Surfactant?

In Germany, many units have adopted a strategy of CPAP-assisted spontaneous breathing and early treatment of preterm infants ≤28 weeks' GA with surfactant within the first hour of life. This strategy includes the tiniest, periviable babies.[60] This early treatment remains the only surfactant dose in more than two thirds of infants, a second dose is required in 24% and a third dose in 6% of infants, respectively (GNN, personal communication). However, published outcome data of this *quasi-prophylactic approach* are not yet available.[82] Appropriate diagnosis of surfactant deficiency, on the contrary, would allow for targeted instead of prophylactic exogenous surfactant. So far, the risk of RDS is assessed using gestational age, birth weight, and possibly ACS treatment. As stated, even incorporation of FiO_2 and chest radiograph into this assessment does not adequately cohort the extremely premature neonates into the groups that will A) succeed on NIV and benefit from avoiding exposure to IMV or will B) not sustain on CPAP/NIV support due to surfactant deficiency and, thus, benefit from early surfactant administration.

In more recent years, several approaches were made to objectify the need for higher-grade respiratory support from birth. Estimation of the endogenous surfactant pool can be performed using the stable microbubble test, lamellar body count or mass spectrometry analysis of the lecithin/sphingomyelin ratio on gastric aspirates test.[83-86] How these tools perform in the extremely premature population, and whether they can be incorporated into a diagnostic paradigm remains to be tested. Recent studies indicate that in the appropriate setting, lung ultrasound outperforms chest radiograph in diagnosing RDS and can predict CPAP failure as defined by FiO_2 >0.3.[44,46-48] However, whether lung ultrasound can help tailor exogenous surfactant therapy when less inclusive treatment criteria are used remains to be tested. In 2015 Siew at al. used a respiratory function monitor (RFM) to investigate whether objective, cot-side measurements of respiratory function (respiratory rate, tidal volumes, presence or absence of breath holds, gas flow rates,

CPAP-level and oxygen concentration) could serve to predict early CPAP failure.[87] Investigating a small cohort of very preterm infants <31 week's gestation, the authors found that infants who could not be sustained on CPAP had higher respiratory rates, lower tidal volumes and required higher CPAP pressures and FiO_2 within minutes after birth.[87] This study suggests that incomplete pulmonary transition is indeed measurable, thus predictable and potentially preventable, if counteracted appropriately. A recent meta-analysis of three RCTs investigating the use of RFMs during manual ventilation in the delivery room concluded that use of an RFM reduces the proportion of high tidal volume delivery during mask ventilation. Although the total number of patients studied was small, the meta-analysis showed a signal towards slightly improved clinical outcomes, especially less severe intraventricular hemorrhage in very low birth weight infants.[88] A further meta-analysis on the use of RFM during delivery room CPAP by the ILCOR neonatal life support task force is under way and may yield further important insights (https://costr.ilcor.org). Recently, Thandaveshwara and co-workers looked beyond the often-practiced approach of correlating CPAP failure with FiO_2 requirements.[42] The authors proposed that the saturation oxygen pressure index (SOPI), calculated as (CPAP pressure or PEEP × FiO_2)/SpO_2 = SOPI, could be used as a simple non-invasive bedside tool for monitoring CPAP failure in preterm infants with RDS. In their study in 126 preterm infants (mean GA 35 weeks) authors compared SOPI to the $AaDO_2$ values and found a high correlation between the two, reliably predicting CPAP failure in preterm infants with RDS with high sensitivity and specificity.[89] However, whilst technological advances such as routine use of RFMs have now been tested in a larger RCT[88] and their overall use might be encouraged,[90] more evidence of the clinical utility is needed.[91,92] Likewise, the encouraging results from studies investigating non-invasive and objectifiable parameters of respiratory failure do need further study in the appropriate target population of extremely preterm infants.

Limitations and Dangers of Indiscriminate Application of These Lessons – WHY WE MUST PRESS FORWARD

The inability to make the diagnosis of RDS early and accurately forces the neonatologist to treat gestational age as a disease state thus necessitating intervention. If the neonatologist equates low gestational age to BPD, universal CPAP is employed. If the neonatologist equates low gestational age to RDS, early and inclusive exogenous surfactant is employed. While both approaches provide benefit neither is without risk.

There are potential harms associated with universal application of CPAP/NIV. Short-term complications include nasal trauma and the potential of pneumothorax and air leak syndromes as well as gastrointestinal distension and perforation.[37,38,43,93,94] In light of the prevailing idea of consequent avoidance of IMV, higher thresholds for intubation may maximize the number of preterm infants managed on non-invasive support. However, it is critical to weigh the risk of intubation and IMV against prolonged exposure to worsening RDS, higher FiO_2 exposure or adverse hyperinflation of the gastrointestinal tract. Recently, Doyle and colleagues reported the 8-year respiratory function of extremely premature neonates born across three epochs (1991-92, 1997, 2005) in Victoria, Australia.[95] Despite increased use of CPAP/NIV in the most current epoch, respiratory function was not better, and in some cases worse. The mechanisms underlying this finding are unknown, but could include increased shear forces and oxygen burden, especially in those infants with RDS that could have been mitigated through early diagnosis and targeted exogenous surfactant therapy. These hypotheses remain speculative and must be tested. Of note, the data by Doyle and colleagues do not only conflict with the RCTs presented above documenting a beneficial effect of CPAP/NIV on BPD development but highlight the shortcomings of BPD as outcome parameter. Although today's widely used definition[96] gives a nuanced classification of the severity of the disease at the time of assessment, it does not allow any prediction of later and long-term lung function. A more recent definition of BPD takes changes in

respiratory management of preterm infants and prolonged exposure to NIV into account.[97] However, the given shortcomings remain. BPD is the best surrogate available for pulmonary morbidity so far, but it is not the overall predictor that we think it is.

It is worth mentioning potential risks of indiscriminate use of LISA/MIST. If the potential benefit decreases with GA, it would be particularly concerning if the exposure was associated with similarly increased risk. It has recently been reported that rates of focal intestinal perforation (FIP) increased with routine administration of LISA.[82] This signal appeared primarily in the most immature babies, affecting ~25% of those exposed to LISA at 22 weeks' GA and ~17% of those at 23 weeks' GA and ~10% of those at 24 weeks. In contrast, RCTs, such as the *Nonintubated Surfactant Application* (NINSAPP) trial and the OPTIMIST trial did not confirm a potential association with FIP.[77,80] However, additional findings from the OPTIMST trial ought to be taken into consideration: While in this cohort of 25-28 week GA neonates, mortality was not different between control and MIST exposed, in the 25-26 week GA subgroup, mortality was 8% in control compared to 17.8% in MIST exposed.[98] Although these differences were not statistically significant, if true, they would be clinically relevant.

Conclusion

A neonatologist entering the intensive care unit in 2022 faces continuously improved survival rates of very immature and even extremely immature preterm neonates, while rates of BPD and long-term respiratory dysfunction remain high. NIV and exogenous surfactant treatment are two powerful tools to avoid ventilator-associated lung injury. However, early identification of those preterm infants that benefit most from non-invasive support versus those who primarily need surfactant therapy is key for targeted respiratory care maximizing the benefits and preventing harm. A "one strategy fits all" approach does not meet the individual needs. It is clear that the time has come to divest ourselves of the habit to implement therapies primarily based on GA or

birth weight. We need to continue to develop our ability to diagnose RDS more accurately and to predict CPAP/NIV failure earlier to be able to apply more individualized care approaches. New and promising diagnostic tools include lung ultrasound, the use of respirator function monitors and calculation of saturation oxygen pressure indices.

In the absence of the ability to diagnose RDS early and accurately, identifying the safest way to administer surfactant seems critically important. Aerosolized administration seems attractive but has not yet been reported as being successful in the highest risk neonates.[99] For now, LISA/MIST represents the most promising approach combining early surfactant and early CPAP. However, more trials are needed to exclude potential harm especially in the tiniest babies. Moreover, comparative trials, including LISA/MIST and IN-SUR-E as well as lung recruitment maneuvers would be helpful to assess the best strategy for surfactant delivery in extremely preterm infants with RDS.

Finally, we still do not know whether the short-term benefits of a less invasive mode of surfactant administration improve long-term pulmonary outcomes. Making this determination is complicated by the shortcomings of BPD as a surrogate for long-term pulmonary function and overall morbidity. It is essential to conduct long-term pulmonary and neurodevelopmental follow-up to conclusively determine the impact of early life NIV exposure and the exogenous surfactant treatment in these high-risk neonates.

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