The Association of an Early Bubble CPAP Protocol Implementation on the Incidence of Death/Bronchopulmonary Dysplasia in Very Preterm Infants

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Abstract

Background: A multidisciplinary comprehensive protocol to use bubble continuous positive airway pressure (bCPAP) as the primary respiratory support in the delivery room (DR) and the neonatal intensive care unit (NICU) was introduced in 2014. This study aimed to assess the association of this change on respiratory outcomes over time.

Methods: Infants with gestational age (GA) <32 weeks and birthweight <1250g admitted between January 2012 and June 2020 were included and categorized into four periods: pre-implementation (P0: 2012-2014), and post-implementation (P1: 2014-2016, P2: 2016-2018, P3: 2018-2020). Primary outcome was rates of death/severe bronchopulmonary dysplasia (BPD), and secondary outcomes included rates of DR intubation and NICU intubation ≤7 days of age, need of surfactant and incidence of pneumothorax. Multivariate logistic regression models accounting for relevant risk factors were used to calculate the adjusted odds ratio (OR).

Results: The study included 440 infants (P0=90, P1=91, P2=128, P3=131). Over time, more infants were free of BPD ($p<0.001$), and rates of death/severe BPD decreased significantly: P1=OR 1.21 (95% CI 0.56-2.67); P2=OR 0.45 (95% CI 0.20-0.99) and P3=OR 0.37 (95% CI 0.15-0.84). DR intubation decreased from 66% (P0) to 24% (P3) in the entire cohort ($p<0.001$) and from 96% (P0) to 40% (P3) in infants <26 weeks ($p<0.001$). The need for NICU intubation was similar ($p=0.98$), with a decreased need for surfactant administration ($p=0.001$) and occurring at higher FiO_2 (P0=0.35 vs P3=0.55, $p<0.001$). Pneumothorax rates were unchanged.

Conclusion: In very preterm infants, the implementation of a comprehensive bCPAP protocol led to a significant and consistent improvement in respiratory practices and rates of death/severe BPD.

Résumé

Contexte: Un protocole complet multidisciplinaire pour utiliser la pression positive continue des voies aériennes (bCPAP) comme support respiratoire principal dans la salle de d'accouchement (SA) et l'unité de soins intensifs néonatals (USIN) a été introduit en 2014. Cette étude visait à évaluer l'impact de ce changement sur les résultats respiratoires au fil du temps.

Méthodes: Les nouveau-nés avec un âge gestationnel (AG) <32 semaines et un poids de naissance <1250g admis entre janvier 2012 et juin 2020 ont été inclus et catégorisés en quatre périodes : pré-implémentation (P0 : 2012-2014), et post-implémentation (P1 : 2014-2016, P2 : 2016-2018, P3 : 2018-2020). Les taux de décès/dysplasie bronchopulmonaire (DBP), les critères principaux d'intubation en SA, et d'intubation en USIN ≤7 jours d'âge, ont été analysés à l'aide de modèles de régression logistique multivariée tenant compte des facteurs de risque pertinents.

Résultats: L'étude a inclus 440 nourrissons (P0=90, P1=91, P2=128, P3=131). Plus de nouveau-nés étaient exempts de DBP (p<0.001) avec des taux réduits de décès/DBP sévère dans l'analyse ajustée : P1=OR 1.21 (95% CI 0.56-2.67); P2=OR 0.45 (95% CI 0.20-0.99) and P3=OR 0.37 (95% CI 0.15-0.84). L'intubation en SA est passée de 66% (P0) à 24% (P3) dans l'ensemble de la cohorte (p<0.001), et de 96% (P0) à 40% (P3) chez les nouveau-nés <26 semaines (p<0.001). Les taux d'intubation en NICU resté stable, avec une diminution d'administration de surfactant (p=0.001), et survenant à une FiO2 progressivement plus élevée (P0=0.35 vs P3=0.55, p<0,001). Les taux de pneumothorax sont restés inchangés.

Conclusion: Chez les nouveau-nés très prématurés, la mise en œuvre d'un protocole complet de bCPAP a conduit à une amélioration significative et constante des pratiques respiratoires et des taux de décès/de DBP sévère.

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Contribution of Authors

Gabriela de Carvalho Nunes conceptualized and designed the study, collected data, carried out the statistical analyses, drafted the initial thesis and all chapters, and critically reviewed and revised the thesis.

Caio Barbosa de Oliveira assisted with the conceptualization and design of the study and the design of the data collection instrument, contributed to chapters 1 and 2.

Marco Zeid, Marisa Leone, Stephanie Mardakis, Elissa Remmer, Johanne Boyer, and Elizabeth Hailu designed the protocol and assisted with its implementation.

Marc Beltempo and Wissam Shalish assisted with the study design, supervised the statistical analyses, contributed to chapters 2, and 4, and critically reviewed and revised the thesis for important intellectual content.

Gabriel Altit assisted with the patent ductus arteriosus management protocol, contributed to chapter 4 and critically reviewed and revised the thesis for important intellectual content.

Guilherme Sant'Anna designed the protocol and assisted with implementation, conceptualized and designed the study, coordinated and supervised data collection, supervised statistical analyses, and critically reviewed and revised the thesis.

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List of Abbreviations

bCPAP – bubble continuous positive airway pressure

BPD – bronchopulmonary dysplasia

BW – birthweight

CGA – corrected gestational age

CPAP – continuous positive airway pressure

DR – delivery room

FiO_2 – fraction of inspiratory oxygen

GA – gestational age

HFNC – high-flow nasal cannula

LOS – late-onset sepsis

MV – mechanical ventilation

nHFV - non-invasive high frequency ventilation

NICU – Neonatal Intensive Care Unit

NIPPV – non-invasive positive pressure ventilator

NIV-NAVA - non-invasive neurally adjusted ventilation

PDA – patent ductus arteriosus

PEEP – positive end-expiratory pressure

PIP – peak inspiratory pressure

PPROM – premature prolonged rupture of membranes

RDS – respiratory distress syndrome

1. Introduction

1.1 Prematurity, Lung Development & Disease, and Survival

The World Health Organization defines prematurity as birth before 37 weeks of gestation. Newborns can be further categorized as “very premature” when birth occurs before 32 weeks and “extremely premature” if born before 28 weeks (1). Preterm deliveries are a global concern, as a quarter of deaths in children younger than five years occurred in the neonatal period, mainly due to preterm birth complications (2). In Canada, preterm delivery accounts for 8% of live births (3), and prematurity is the second most frequent cause of infant deaths (4). For preterm infants, respiratory immaturity is a significant cause of morbidity and mortality. A North American multicentric study showed that the leading cause of death in the first month of life for infants surviving longer than 12 hours was respiratory distress syndrome (RDS). For those surviving beyond two months, it was bronchopulmonary dysplasia (BPD) (5). More importantly, those rates were stable for a ten-year period (5). Therefore, lung immaturity remains one of the main determinants of viability and long-term morbidities.

RDS is a disease intrinsically related to prematurity, with its incidence and severity being inversely proportional to gestational age (GA) at birth (6, 7). The canalicular stage of fetal lung development occurs between 16 to 26 weeks, where rudimental airways branch into respiratory bronchioles, alveolar ducts and saccules, and the cytodifferentiation of type I and II pneumocytes begins (8). Pneumocytes type II are responsible for the production of surfactant, a macroaggregate molecule that decreases the surface tension of the alveoli, lowers its opening pressure, and maintains recruitment at expiration. In the alveolar stage, the subdivision of distal airways dramatically increases the gas exchange surface as new alveoli appear (8). Preterm birth arrests lung development in its early stages, leading to alveolar hypoplasia with decreased acinar

complexity, vascular hypoplasia, and fewer structural proteins such as collagen and elastin (9, 10). While pneumocytes are present at birth after around 22 weeks, their number is significantly smaller, and the surfactant initially secreted is qualitatively inferior (11). Thus, RDS is caused by a combination of characteristics of the preterm lung, such as low lung volumes, increased chest wall compliance, and quantitative and qualitative surfactant deficiency. Progressive microatelectasis, inflammation and injury to the pulmonary epithelium (11) can lead to hypoxic respiratory failure and death (12). The respiratory course of preterm infants has changed after implementing two revolutionary interventions: antenatal glucocorticoids and exogenous surfactant administration. Prenatal exposure to glucocorticoids accelerates morphologic lung development and the synthesis of surfactant (8), reducing death and RDS (13). A few years later, the endotracheal administration of exogenous surfactant was proven to be a highly effective treatment for RDS, with robust evidence of reducing the risk of pulmonary air leak and mortality (14, 15).

Such interventions allowed for the increased survival of infants born <25 weeks GA (16) and brought changes in the pathophysiology and epidemiology of BPD. Historically, BPD was thought to be a consequence of the healing phase of RDS (17). The initial report of BPD described a four-stage disease, with chronic changes being established as early as one month of age. In end-stage disease, microscopic findings were described as severe heterogeneous lesions with emphysematous alveoli, marked hypertrophic peribronchiolar smooth muscle and alveolar septal fibrosis (17). The 32 infants included in this first report were ventilated using intermittent positive-pressure respirators with peak pressures between 20 and 40 cmH_2O, with all infants receiving a fraction of inspiratory oxygen (FiO_2) of at least 80% in the first 24 hours of life (17). Remarkably, the survivors' mean birth weight (BW) was 2234g, with a mean GA of 34 weeks (17). Authors speculated that prolonged exposure to high oxygen concentrations was the leading cause for such

changes, perhaps with some contribution of mechanical ventilation (MV) (17). Currently, the "new BPD" occurs in very preterm infants, with a recent cohort demonstrating a mean GA of 25.7 weeks and BW of 738g for infants who developed grade III BPD and 26.5 weeks for those with grades I-II (18). Microscopic findings, previously remarkable for fibrosis, now include impaired alveolarization, dysregulated vascular growth and surfactant production disruption (19, 20, 21, 22). Presently, the pathogenesis of BPD is understood as multifactorial, involving a complex interplay of prenatal risk factors, such as intrauterine growth restriction, chorioamnionitis, maternal smoking, and postnatal exposures, including inflammation, poor nutrition, and oxidative stress (9, 19, 21, 22, 23).

1.2 Invasive Mechanical Ventilation

It became clear that MV is a crucial contributor to inflammation of the respiratory airways and a significant risk factor for BPD (24). Ventilator-associated lung injury involves multiple mechanisms, such as volutrauma, atelectrauma and biotrauma (25, 26). Excessive tidal volumes lead to pulmonary tissue overdistention and disruption of alveolar small airway epithelium, a process known as volutrauma (26). Inappropriately low tidal volumes can be equally harmful, as repeated alveolar collapse and expansion also lead to lung injury (26). Atelectrauma occurs when there is a ventilation/perfusion mismatch - the atelectatic region is under-ventilated, while aerated portions are overdistended, leading to structural damage (26). Those injuries can trigger biotrauma, a complex cascade of lung injury and repair, which includes the release of pro-inflammatory cytokines and chemokines, such as interleukin-6 and interleukin-8, proteases, and macrophageal activation (22, 25, 26, 27). Changes in inflammatory markers can be present as early as one hour of MV, as demonstrated in animal and human models (28). Advancements in respiratory care techniques targeted to mitigate lung injury were accomplished, such as the widespread use of

volume-targeted mechanical ventilation, which decreased BPD compared to pressure-limited ventilation (29). Yet, with the increased survival of more immature infants, BPD incidence remains relatively unchanged (21, 30, 31).

Various modes of invasive respiratory support have emerged, such as high-frequency oscillatory and jet ventilation; however, they frequently involve high-complexity technology, and studies supporting their benefit for preterm infants have contradictory results (32, 33, 34). On the other hand, a more substantial body of evidence suggests that entirely avoiding endotracheal intubation and MV significantly reduces the incidence of BPD in extremely preterm infants (35).

1.3 Non-Invasive Respiratory Support

Many non-invasive ventilation modes have been introduced and are frequently used in Neonatology. Non-invasive positive pressure ventilation (NIPPV) generates a superimposed peak inspiratory pressure (PIP) over the continuous distending pressure. Its proposed mechanism suggests that the added PIP increases the distending pressure above the positive end-expiratory pressure, subsequently increasing the mean airway pressure (36). However, the delivery of the set pressures may not be reliable (37). The actual PIP tends to be generally lower, with occasional peaks as high as 9cm H_2O above the set value (37). These variations can be explained by factors such as mouth closure, glottic closure, and variable interface leaks, which increase at higher pressures (37). Most available ventilators offer asynchronous NIPPV, given at a set frequency irrespective of the infant's breathing. Synchronized NIPPV is a challenge in preterm infants, as interface leaks at the mouth and nose directly impact the ability of the machine to trigger a breath based on flow measures (38). Previous research proposed that synchronizing NIPPV could offer superior outcomes by reducing breathing effort and enhancing infant-ventilator interaction but failed to demonstrate a significant difference between synchronous and asynchronous modes (36,

39, 40). A recent meta-analysis indicates a modest advantage of NIPPV over CPAP in decreasing the need for endotracheal intubation and the risk of respiratory failure (39). However, caution is warranted in interpreting these findings, considering that the overall mean gestational age of infants in the included studies was 30 weeks, with the vast majority being between 28 to 32 weeks (39).

Another widely adopted mode of non-invasive respiratory support is high-flow nasal cannula (HFNC), due to its ease of use and decreased incidence of nasal trauma. Heated, humidified high-flow gas (usually 5-7 L/min) is delivered to the infant via nasal prongs, generating a continuous distending pressure in the upper airways. The laminar flow is thought to promote washout of the nasopharyngeal dead space, reduce work of breathing, and maintain functional residual capacity. Unfortunately, there are significant concerns about its use for very preterm infants. The actual distending pressure is challenging to measure and highly variable; the lack of an expiratory arm can lead to undetected and undesired high pressures (41). Previous literature indicates that the use of HFNC is associated with an increased risk of death/BPD, delayed oral feedings and prolonged hospitalization (42). A study in our center demonstrated that, in extremely preterm infants immediately after extubation, HFNC was associated with increased FiO_2 requirements and longer respiratory pauses compared to CPAP (43). Similarly, two studies comparing HFNC or CPAP as the primary mode of respiratory support for preterm infants had to be terminated early due to higher treatment failure in the HFNC groups (44, 45).

More recently, two promising methods of non-invasive ventilation have emerged: non-invasive neurally adjusted ventilation (NIV-NAVA) and non-invasive high frequency ventilation (nHFV). NIV-NAVA uses electrodes embedded in a specialized feeding tube to measure the patient's inspiratory effort, delivering synchronized pressure proportional to diaphragmatic

contraction. Yagui et al. found no difference in the need for intubation at 72h of life in infants with RDS who received NIV-NAVA or CPAP as their primary respiratory support mode (46). There is conflicting evidence on whether NIV-NAVA is superior to other non-invasive ventilation modes for preventing extubation failure (47, 48, 49). Further research is needed to establish its superiority, and there is a scarcity of direct references addressing the cost implications associated with the devices required to provide NIV-NAVA. Similar to invasive high-frequency oscillatory ventilation, nHFV delivers a continuous distending pressure with oscillations at a constant high-frequency, with an active expiratory phase (50). Limited information on its mechanism is available; most theories are extrapolations from invasive high-frequency ventilation (50). A large randomized controlled trial found that preterm infants on nHFV had a lower risk of extubation failure when compared to CPAP but no difference compared to NIPPV (51), comparable to previous reports (52). Such findings must also be carefully approached, as the highest pressure on CPAP was 8 cm H_2O, while nHFV was initiated with a minimum pressure of 10 cm H_2O; equally high pressures were allowed for infants randomized to NIPPV (51). Most current literature focuses on short-term respiratory outcomes; further research is needed regarding tolerance, interface, patient comfort, and long-term outcomes, such as BPD.

CPAP is a well-established mode of non-invasive support that provides a mixture of gas (air/oxygen) flow in a closed system, transmitting a continuous distending pressure to the airways. CPAP improves respiratory function due to various mechanisms: 1) splinting of the upper airways, preventing anatomical obstruction; 2) increase of the diaphragmatic tone and contractility; 3) reduction of airway resistance; 4) improvement in lung compliance due to the stabilization of alveoli during expiration and reduction in lower airway resistance (53, 54). Interest in the early use of CPAP as the initial respiratory support for premature infants has increased over the last

decades, fueled by a growing body of evidence supporting its positive outcomes (55, 56, 57, 58). Its use in neonates, however, is not novel. In 1975, an initial publication by Dr Jen-Tien Wung described a new device for nasal CPAP, successfully used at Columbia University's Neonatal Intensive Care Unit (NICU) to treat infants with RDS (59). In 1988, they reported impressive results on premature infants with signs of RDS who received CPAP as the initial mode of respiratory support: the survival rates at 28 days and survival at 28 days with no oxygen therapy were the highest among eight academic centers, persisting after adjustment for possible confounders (60). Avery et al. identified their use of bubble CPAP as early as the delivery room (DR) as a potential explanation for the significant site differences in the risk-adjusted incidence of BPD (60).

Two large randomized controlled trials were crucial to shift the pendulum towards favouring CPAP on very preterm infants. In 2010, the SUPPORT trial randomized extremely preterm infants to receive either nasal CPAP in the DR or early surfactant followed by conventional MV (56). Although there were no differences in the primary outcome, infants who received any CPAP had better secondary outcomes, which included shorter ventilation days and decreased need for postnatal corticosteroids for BPD or MV (56). Similarly, the COIN trial compared different types and strategies of nasal CPAP or early intubation and surfactant in the delivery room in infants born between 25 and 28 weeks GA. While there was no statistically significant difference in death/BPD, infants who received CPAP had a decreased risk of death or need for oxygen at 28 days (55). More importantly, these trials established CPAP as a safe alternative to early respiratory care for extremely preterm infants (55, 56). Two meta-analyses that included both trials reinforced the positive outcomes of early CPAP (61, 62). Schmolzer et al. found that CPAP in the DR, when compared to intubation and MV, led to a reduction in the incidence of death/BPD with a number

needed to treat of 25 (61). These findings were corroborated by a more recent Cochrane review, demonstrating that CPAP in DR effectively decreased rates of BPD, death/BPD and reduced need for MV when compared to intubation (62). It is important to note that the COIN and SUPPORT trials are the main drivers of both meta-analyses; the critical difference is that the latter excluded studies that involved other interventions, such as prophylactic surfactant (61, 62). Unfortunately, results can be challenging to interpret and replicate due to the large variability of CPAP interfaces and systems. Also, reports vary widely on indications for CPAP initiation, definitions of failure, routine daily care, and weaning strategies (7, 63, 64, 65, 66, 67, 68, 69, 70, 71). This may partially explain why rates of DR intubation, CPAP failure and death/severe BPD remain an issue, especially in infants with BW <1250g (63, 64, 66, 72).

1.4 The Bubble CPAP

Among the many devices currently available for CPAP therapy in preterm infants, the bubble CPAP (bCPAP) offers additional benefits compared to ventilator-derived options (73, 74). In the bCPAP system, the expiratory limb is submersed in water, with its depth determining the continuous pressure (53, 75) (**Figure 1**). The continuous flow of the gas generates oscillations of the water level at a high frequency, which is transmitted to the lungs via low-resistance bi-nasal prongs (**Figure 1**, **Figure 2**) (53, 73, 75). The oscillatory bubbling is dynamic and can change based on lung characteristics (**Figure 3**) (73, 75). In a low-compliance lung with high airway opening pressures, such as in RDS, more flow is directed to the water seal, increasing pressure amplitude and frequency of the bubbling, which is then transmitted to the infant respiratory system (73, 76). Once lung compliance improves, the increase in flow directed to the airways will decrease bubbling, thus offering less oscillatory pressure at lower frequencies (73). The oscillatory pressure amplitudes are in the order of 2 - 4 cmH_2O around the set CPAP level, with a frequency ranging

from 15 to 30 Hz (74, 75, 76). In an experimental study, bCPAP was superior to ventilator-derived CPAP when using the same CPAP level (75). In intubated preterm lambs, bCPAP improved CO_2 clearance and arterial oxygen levels, increased oxygen extraction, and more effectively stabilized lung volumes at lower pressures (73). Two small studies compared short-term outcomes using bCPAP or other devices: one used a continuous-flow ventilator CPAP (77), while the other used a variable-flow CPAP (78). Despite no difference in work of breathing, one study reported that infants on bCPAP had a significant increase in transcutaneous oxygen measurements (better oxygenation), which is especially notable as outcomes were recorded only 5 minutes after therapy initiation (77). The second study did not observe significantly worse results for infants on bCPAP, contrary to their initial hypothesis (78); their findings led to speculation that bCPAP might offer advantages compared to continuous-flow CPAP (78).

The proposed physiologic effects of bCPAP are summarized in **Table 1**. One of its main proposed mechanisms is the stochastic resonance effect. The noise produced by the bubbling superimposes the generated peak pressures (pressure amplitude) at high frequencies, enhancing its effect and promoting better lung recruitment and oxygenation (75). Another hypothesis is that these increases in oscillatory frequency and pressure would be directed to airways with increased opening pressures in a similar way to which high-frequency oscillatory invasive ventilation works, improving areas of atelectasis while protecting regions that are well-ventilated (73, 74, 75). Additionally, Lee et al. highlighted that the physiological effects of bCPAP may decrease fatigue, as it decreases minute ventilation and respiratory rate while maintaining adequate gas exchange (74).

Subsequent reports from Columbia University NICU continued to demonstrate remarkable results on respiratory outcomes achieved by implementing early bCPAP therapy (63, 67, 79).

Maintaining constant practice made their results sustainable and continuously improved (63, 67). Other centers have also reported improvement in respiratory morbidities after establishing the "Columbia bCPAP approach" as the primary respiratory support, such as decreased need and duration of MV (64, 68, 80, 81, 82, 83), decreased rates of chronic lung disease (68, 81), and reduced postnatal steroid use (80). In addition, other publications demonstrated positive outcomes by combining bCPAP with other therapies, such as administration of surfactant via minimally-invasive technique (66, 84) or immediate extubation post surfactant administration (85).

1.5 Protocols and Standardization in Neonatal Respiratory Care

Variations in respiratory care practices are frequent across centers (86) and can be a significant source of morbidity, especially in extremely premature infants (87, 88). One study found respiratory care was the third most frequent cause of adverse events in the NICU (87). The misuse, underuse, and overuse of resources are commonly identified as root causes for patient safety events, often stemming from gaps between evidence-based practice and clinical practice (89, 90, 91). Implementing multidisciplinary protocols as part of quality improvement initiatives is a key approach to address these challenges. Protocols improve adherence to evidence-based strategies, leading to better patient outcomes and reduced variability in care delivery (92, 93, 94). Beyond standardization, clinical protocols contribute to the broader and active involvement of healthcare practitioners in care, as demonstrated by the success of a registered respiratory therapist-driven weaning protocol (92). Additionally, protocols can offer valuable guidance and reassurance to junior staff members (95).

In our unit, a comprehensive protocol establishing bCPAP as the initial ventilation mode was implemented in 2014, aiming to decrease the need for endotracheal intubations in the delivery room and reduce variation in respiratory practices. A first informal review of the impact of the

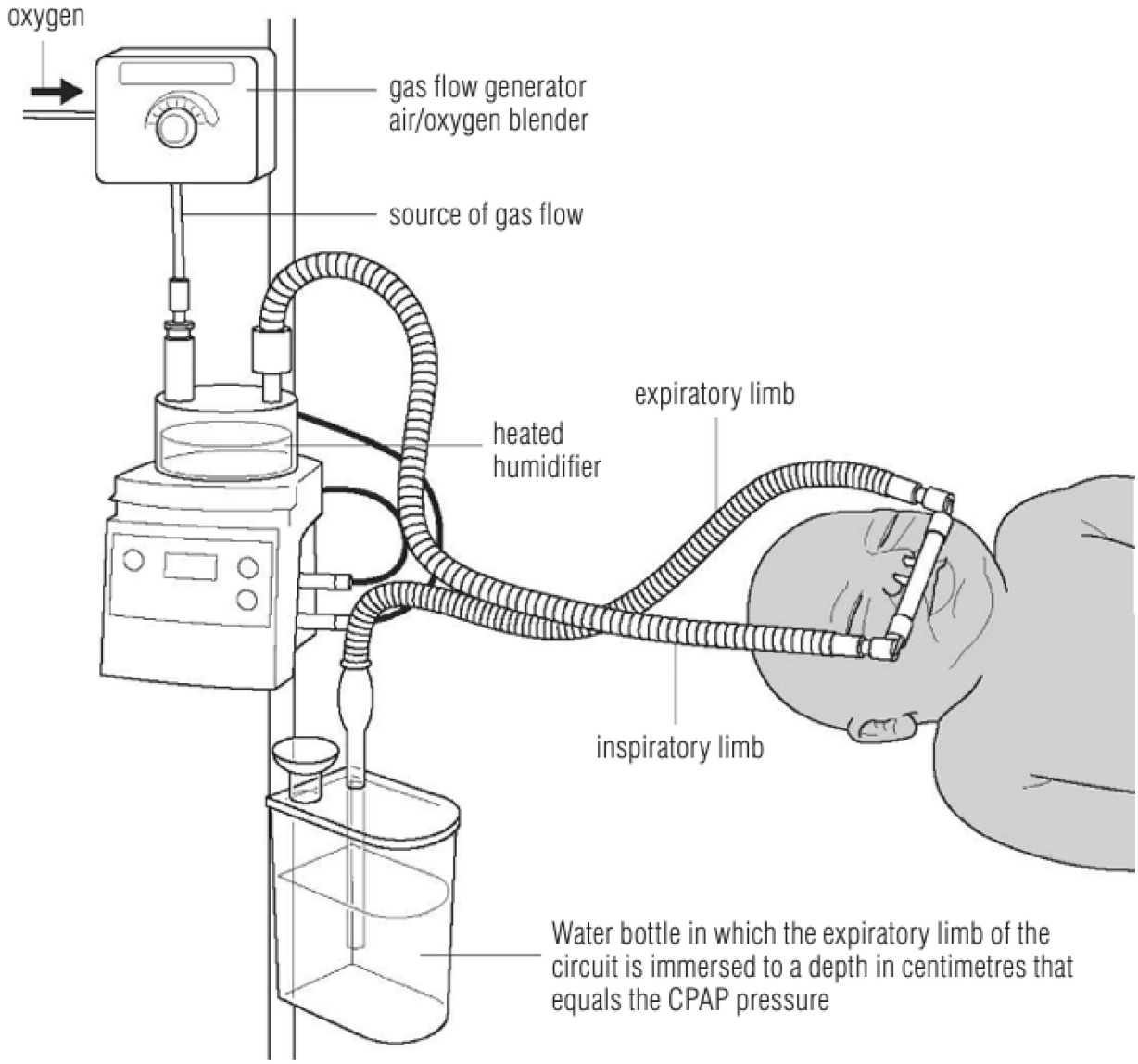
protocol implementation was performed between 2016 and 2018 with encouraging results. The annual Canadian Neonatal Network data review also noted improvements in overall respiratory outcomes at our center. However, we perceived an important gap in knowledge when comparing our results to recent literature. Studies have numerous definitions for bCPAP therapy failure, different criteria for endotracheal administration, and rescue MV strategies (56, 66, 68, 81, 82, 83, 84, 85). Furthermore, evolving definitions of BPD have made the comparison of results challenging, as reports use different BPD classifications or criteria that are no longer compatible with the increased survival of infants at the extreme of viability (56, 66, 68, 81, 82, 83, 84, 85).

1.6 Thesis Objectives

Our data provides a unique opportunity to contribute to current knowledge for multiple reasons: 1) the use of a comprehensive, reproducible protocol focused on a single intervention using only one CPAP system and type of interface; 2) clear criteria for bCPAP failure and discontinuation; 3) a contemporary cohort with a large number of very preterm infants, the majority born <29 weeks; and 4) the use a more recent BPD definition, allowing for accurate assessment of incidence of death/severe BPD in extremely preterm infants.

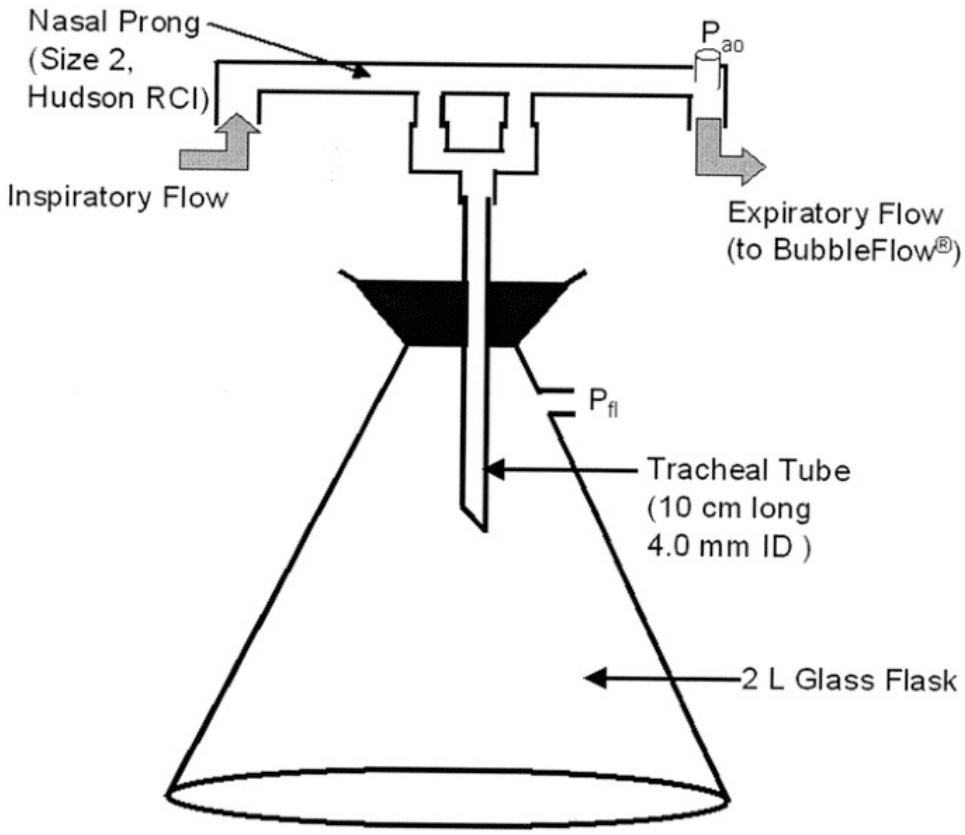
The objective of this study was to evaluate the impact of the implementation of an early, comprehensive bCPAP protocol on rates of death/severe BPD in very preterm infants.

Figure 1. Bubble CPAP Circuit



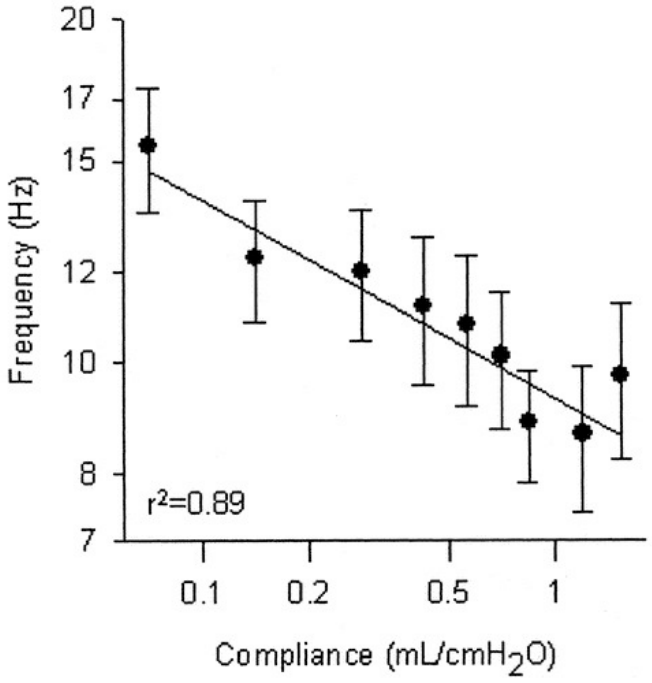
Legend: CPAP = continuous positive airway pressure. Diagram of a commercially available bubble continuous positive airway pressure set-up. Reprinted from "Oxygen therapy for children," by the World Health Organization, 2016.

Figure 2. Bubble CPAP system adapted to an in vitro lung model



Legend: In vitro lung model. Compliance was varied by filling the glass flask with known volumes of water. Reprinted from "Bubble CPAP: Is the noise important? An in vitro study," by Pillow J et al., 2005, Pediatric Research, 57(6), 826-830. Copyright 2005 by Springer Nature.

Figure 3. Effect of lung compliance on dominant frequencies transmitted to lung during Bubble CPAP



Legend: The graph demonstrates the mean frequency of spectral components at which power was > 75% of maximum power within a representative measurement at each compliance and a flow of 6 L/min. Reprinted from "Bubble CPAP: Is the noise important? An in vitro study," by Pillow J et al., 2005, Pediatric Research, 57(6), 826-830. Copyright 2005 by Springer Nature. Reprinted with permission.

Table 1. Proposed Effects and Mechanisms of Bubble CPAP

Physiological effect	Proposed mechanism
Upper airway stabilization*	Continuous positive distending pressure has a splinting effect on upper airways, preventing anatomical obstruction
Reduction in lower airway resistance*	
Increased minute-volume ventilation*	Increase in diaphragmatic tone and contractility
Improved lung compliance	Conservation of surfactant function on alveolar surfaces* and promotion of surfactant production
Improved oxygenation and CO2 clearance	Noisy pressure waveforms superimposed on pressure fluctuations, enhancing compliance and gas exchange
	Vibrations similar to high-frequency ventilation promote better gas exchange via facilitated diffusion
	Frequency of oscillatory bubbling changes based on lung compliance
Improved functional residual capacity	Pressure fluctuations promote airway opening events and lung volume recruitment
	Stabilization of alveoli during expiration and reduction in lower airway resistance
Decreased work of breathing	Improved oxygenation leads to reduced respiratory rate and decreased fatigue
Recruitment of areas of atelectasis	Oscillatory pressure is directed to airways with increased opening pressures, similar to high-frequency ventilation
Decreased lung inflammation	Avoidance of early intubation and exposure to high tidal volumes
	Prevention of atelectasis
	Decreased neutrophil recruitment into the lungs
Improvement in lung growth	Prolonged exposure to oscillatory pressures generates variable mechanical strain, promoting alveolarization and lung growth

Legend: *effects and mechanisms common to ventilator-derived CPAP and bubble CPAP.

2. Methods

2.1 The Bubble CPAP Protocol

A multidisciplinary group of neonatologists, respiratory therapists, and nursing leaders was formed in January 2013 to streamline the use of non-invasive respiratory support. The team identified an opportunity to decrease rates of DR and NICU intubations as an internal review noted substantial variability of non-invasive respiratory support practices, including the use of different interfaces and types of ventilator-derived CPAP, HFNC and NIPPV. Thus, the group decided on the need for a comprehensive CPAP protocol using the bubble system to decrease DR and NICU and, subsequently, the rates of death/severe BPD (**Appendix A**). The protocol established bCPAP as the primary respiratory support for infants <32 weeks with spontaneous breathing in the DR, using a single interface (short binasal prongs) and system (Infant Bubble CPAP®, Fisher Paykel). The initial CPAP pressure was set as 5 cmH_2O, with the option to escalate to a maximum of 7 cmH_2O at the discretion of the attending Neonatologist. Therapy failure and NICU intubation were considered if the infant met any of the following criteria: a) respiratory failure (consistent increase (1-2h) in oxygen requirement above 50% or severe respiratory acidosis - PCO_2 above 65 mmHg with a pH < 7.20 in two consecutive blood gases); b) severe apneas (1-2 episodes of apnea requiring bag and mask ventilation due to failure to resume spontaneous breathing) or c) frequent episodes of apnea and/or bradycardia (more than six episodes in 6 hours), with apnea defined as a respiratory pause longer than 20 seconds, or less than that but associated with desaturation (SpO_2 < 88%) and/or bradycardia (<100 bpm). If the infant met the criteria for respiratory failure, surfactant was administered after the infant was intubated.

The protocol also specified criteria for discontinuation, requiring all of the following criteria to be present: a) minimum corrected gestational age of 32 weeks; b) PEEP of 5 cmH_2O and on

room air; c) no episodes of bradycardia (<80 bpm) and desaturations (<88%); d) no episodes of apnea requiring stimulation; e) no tachypnea (RR > 60 bpm); and e) no respiratory distress (mild or moderate sub-sternal and/or suprasternal retractions).

After a review of the evidence and multiple meetings, the protocol was developed and presented to all healthcare professionals working in the units. A final version was circulated by email and placed on the hospital intranet for easy consultation and feedback. Respiratory therapist leaders ensured that all team members became aware and received training on using the protocol directives. “Champions” were identified to promote its dissemination, offering further training on the system fixation by using a mobile cart with a mannikin that circulated on random day/night shifts in the NICU. Portable bCPAP systems became available 24h/day in the DR. Moreover, regular interdisciplinary workshops and presentations were held at local conferences and divisional meetings. The comprehensive bCPAP protocol was officially adopted in April 2014.

2.2 Respiratory Management Practices and Changes Over Time

Before protocol implementation, intubation in the DR followed the Neonatal Resuscitation Program algorithm, but local culture preconized early intubation for infants born at the extreme of gestational age (GA). Other unit practices included surfactant administration if FiO_2 >0.3 with infants remaining intubated after the procedure, as trials on minimally invasive techniques had not yet been performed and published. Caffeine administration was a standard of practice for all infants ≤28 weeks. Assisted controlled volume guaranteed ventilation started in 2011, and the SpO_2 target was between 88-92% as the standard of care, all premature infants were ventilated using a permissive hypercapnia strategy ($PaCO_2$: 45-55 mmHg for the first 72h and 55-65 mmHg afterwards if pH >7.20) with the following extubation criteria: a) BW <1000 g: mean airway pressure ≤7 cmH_2O and FiO_2 ≤0.3; or b) BW ≥1000g: mean airway pressure ≤8 cmH_2O and

FiO_2 ≤0.3. In 2015, all ventilators changed to VN500® (Dräger); in 2017, the SpO_2 range changed to 91-95%(96).

2.3 Study Design

Inborn infants admitted to the Royal Victoria Hospital and Montreal Children's Hospital NICUs between January 2012 and June 2020 were identified using a local Canadian Neonatal Network database. Infants born with GA <32 weeks and BW <1250g were included; outborn infants and those with major congenital anomalies or genetic syndromes were excluded. As initial training and protocol implementation occurred between January and March 2014, this interval was considered a "washout period." To allow for comparable numbers and reasonable sample sizes, infants were divided into four periods of approximately 24 months: pre-protocol (P0: January 2012 to December 2013), period 1 (P1: April 2014 to June 2016), period 2 (P2: July 2016 to June 2018) and period 3 (P3: July 2018 to June 2020).

Initially, infants were born at the Royal Victoria Hospital and treated at a level III NICU with 26 beds divided into four open bays. In May 2015, this unit merged with the Montreal Children's Hospital NICU into a new level IV facility with 52 individual rooms under the care of a large team of nurses, respiratory therapists, and neonatologists. The number of inborn preterm infants increased after that due to increased capacity/volume of high-risk pregnancies.

Electronic medical records were retrospectively reviewed, and the following data collected: maternal characteristics, GA (weeks) and BW (g), sex, Apgar score at 1 and 5 minutes, small for GA (BW <10^{th} percentile in Fenton's growth chart), reason for intubation, early onset sepsis (positive blood and/or cerebrospinal fluid culture drawn ≤72 hours of life), late-onset sepsis (positive blood and/or cerebrospinal fluid culture drawn >72 hours of life), necrotizing

enterocolitis (stage 2 or worse (97)), severe intraventricular hemorrhage (grade III or worse (98)) and length of stay.

The primary outcome was the composite death before 36 weeks of corrected gestational age (CGA) and severe BPD. To address the considerable heterogeneity in respiratory support methods during P0, P1 and P2, BPD was defined based on the 2018 National Institute of Child Health and Human Development criteria, with severe BPD defined as defined as the use of CPAP, NIPPV or HFNC (flow >3L/min) with FiO2 ≥ 30%, MV with FiO2 > 21% or death between 14 days of postnatal age and 36(21). Secondary outcomes were DR and NICU intubation (≤7 days among infants not intubated in the DR), survival with no or mild BPD, death or mild/moderate BPD, incidence of pneumothorax in infants successfully treated with CPAP in the DR (diagnosed by chest radiography), time to first intubation (hours of age), days on MV, NIPPV, HFNC and low flow nasal cannula, need for MV at 36 weeks of CGA, sepsis (early and late onset), use of postnatal steroids, necrotizing enterocolitis, and severe intraventricular hemorrhage.

2.4 Statistical Analysis

Unadjusted analysis was done using Chi-square or Fisher's exact tests for categorical data and ANOVA for continuous data for the overall population and three pre-specified groups: <26 weeks, 26 to 28 weeks and ≥29 weeks GA. Adjusted analysis was done by using multivariate logistic regression. Two models were used based on known risk factors for developing BPD(99): Model 1 – for long-term respiratory outcomes and rates of death/severe BPD analysis was adjusted for GA, SGA, Apgar <7 at 10 minutes of life and male sex, and late-onset sepsis (LOS). Model 2 – for short-term respiratory outcomes of interest, such as DR/NICU intubations, analysis was adjusted for GA, SGA, Apgar <7 at 10 minutes of life and male sex. Odds ratio and 95% confidence intervals were calculated to compare P0 with P1, P2 and P3. Time to intubation in the

NICU was compared using a Cox proportional hazards model, adjusted for GA, SGA, Apgar score <7 at 10 minutes, and male sex. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were done using RStudio (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, USA). The Review Ethics Board of McGill University Health Centre approved this study.

3. Research findings

A total of 440 infants were included (**Figure 4**). Maternal and neonatal characteristics are presented in **Table 2**.

3.1 Primary Outcome

3.1.2 - Rates of Death/Severe BPD

The number of infants free of any BPD increased from 55% to 60%, with lower rates of severe BPD in P3 (12% to 6%; **Table 3**). Death/severe BPD rates decreased over time (**Figure 5**), with a statistically significant and progressive OR reduction noted at P2 and P3 (**Table 4**).

3.2 Secondary Outcomes

3.2.1 - DR and NICU Intubation (≤ 7 days)

DR intubation decreased over time for the overall population (**Figure 5**, **Table 5**) and in infants <29 weeks GA (**Table 6**). Furthermore, the logistic regression model showed a significant decrease in the OR for DR intubation over time (**Figure 6**). Since NICU intubation remained stable (**Figure 5**, **Table 4, Table 5**, **Table 6**), the adjusted OR for DR/NICU intubation significantly decreased after protocol implementation (**Table 4**). Thus, the number of infants not requiring any intubation within the first seven days of age increased from 19% to 41% (p=0.004). Reasons for NICU intubations were similar, most frequently increased FiO_2 within the first 24h of age (**Table 5**). Pneumothorax rates were unchanged (**Table 5**).

Time to intubation in the NICU demonstrated a consistent increase, with the most extended interval noted in P3 (**Figure 6**; Hazard's ratio -0.82, 95% CI 0.23-0.86). Consistent with the protocol adherence, increased bCPAP use and duration were observed (**Table 5**), with a concomitant decrease in HFNC and NIPPV days. There were no differences in MV duration,

postnatal steroids, length of hospitalization, or death. Patent ductus arteriosus (PDA) treatment and LOS also decreased over time (**Table 7**).

3.3 Subgroup Analysis

3.3.1 - Gestational Age

Infants born at <26 weeks had the most marked reduction in DR intubations, from 96% (P0) to 40% (P3) (**Table 6**), with no impact on NICU intubations. The need for surfactant administration showed a marked decrease across all gestational groups (**Table 6**). Infants with GA 26 to 28 weeks were the main drivers for respiratory outcomes improvements, including reduced need for any intubation (**Table 3**) and decreased BPD rates, both overall and in severity (**Table 6**). Endotracheal intubations in infants with GA ≥29 weeks were infrequent at baseline and became even more unusual (P0: 32%, P3: 5%) (**Table 6**).

3.3.2 - Infants Intubated in the DR

Infants requiring DR intubation were predominantly the smallest and most immature, with a mean birth weight of 810g ± 185g in P0 and 784g ± 235g in P3, and a mean gestational age of 26.5 ± 2 weeks in P0 and 25.7 ± 2 weeks in P3 (**Table 8**, **Table 9**). These values showed a decreasing trend across the periods (**Table 9**) and were significantly lower when compared to infants who received CPAP in DR (**Table 8**). Apgar at 5min was considerably lower (P0: 7 [6-8], P3: 5[3-6]). Although a higher percentage of infants who were intubated in DR were diagnosed with any degree of BPD (P0: 45%, P3: 62%), this difference was not statistically significant. Furthermore, no differences were observed in the length of MV, exposure to postnatal steroids, and early death or death/severe BPD (**Table 9**).

3.3.4 - Infants Successfully Treated with CPAP in DR

The mean GA and BW consistently decreased (**Table 8**, **Table 10**). The duration of MV for infants who failed CPAP therapy and required NICU intubation remained unchanged, as did the length of admission. Significantly fewer infants were categorized as severe BPD (P0: 10%, P3: 1%), with no statistical difference in death/severe BPD.

Figure 4. Patient Flowchart

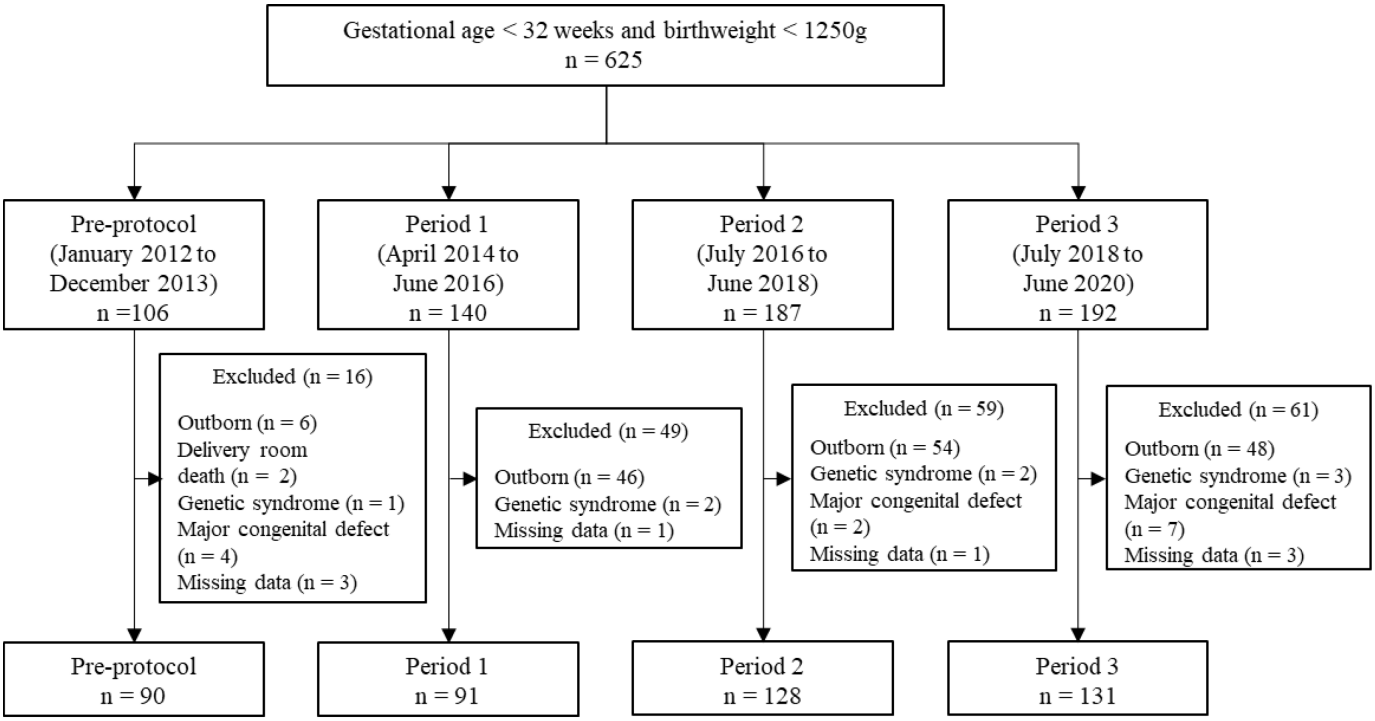
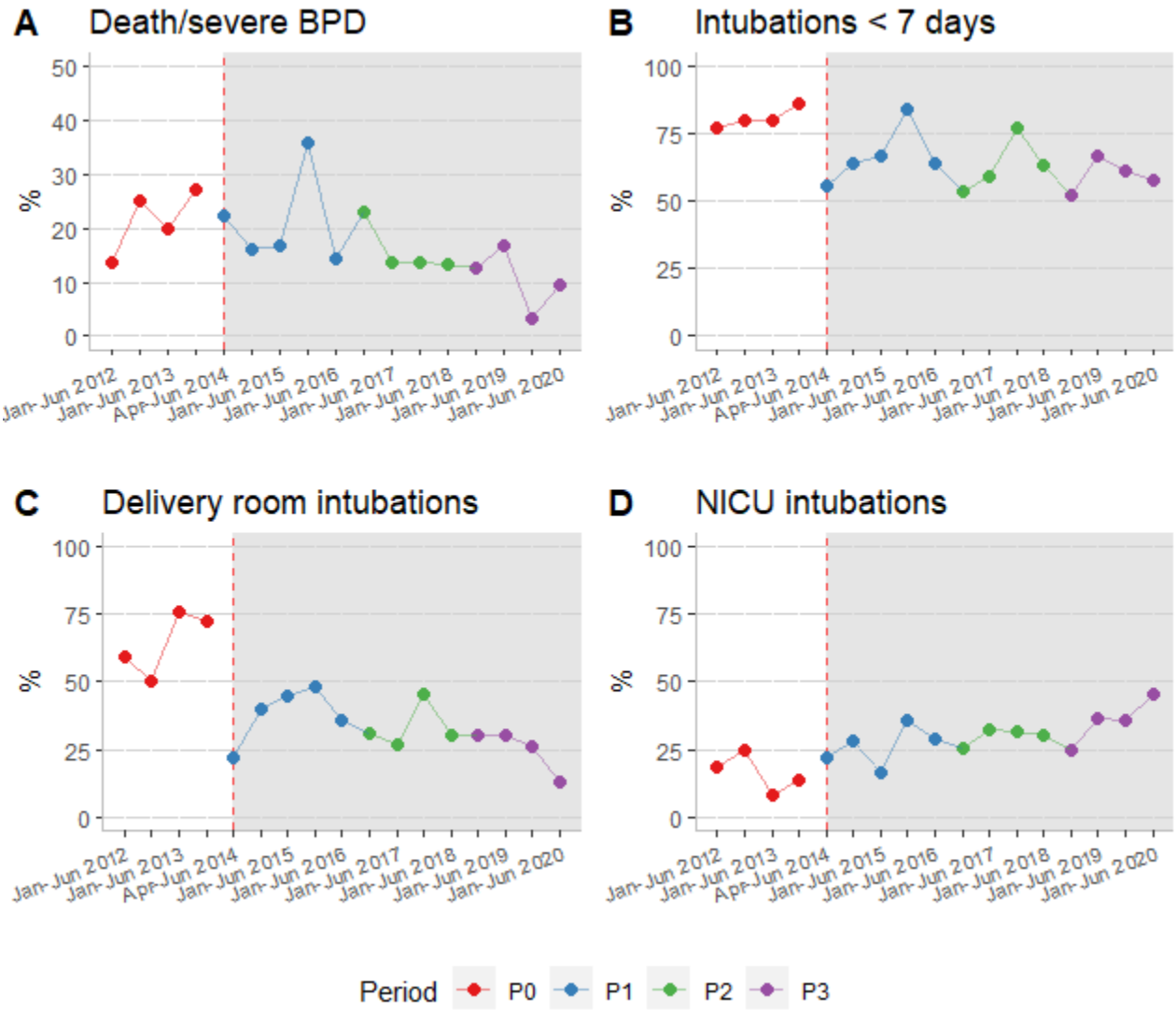
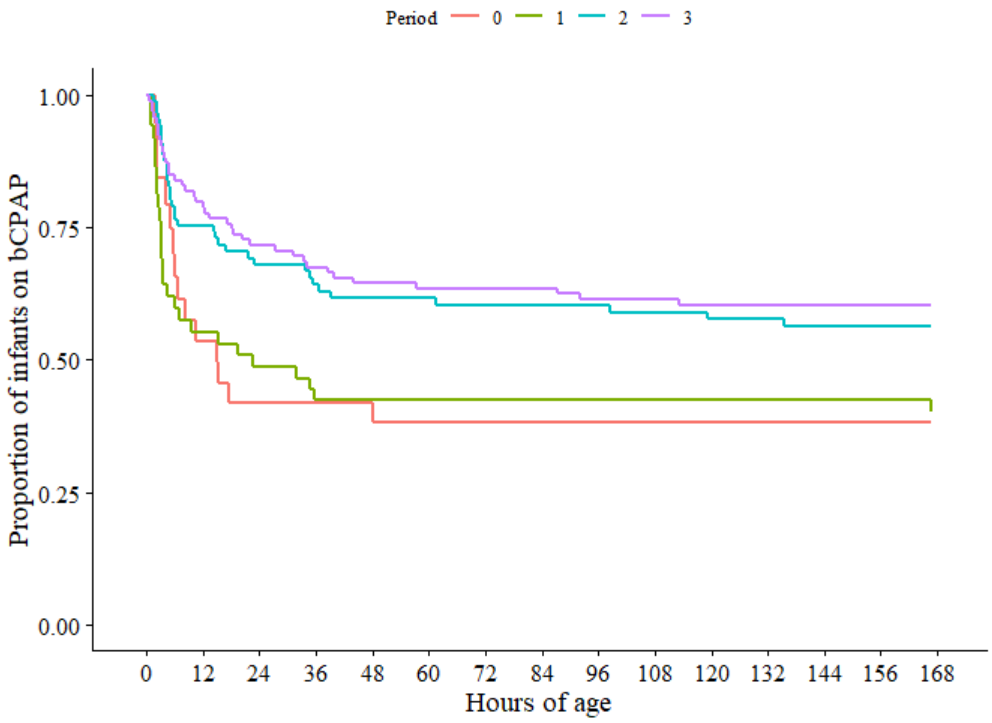


Figure 5. Primary Outcome and Early Intubations



Legend: BPD = bronchopulmonary dysplasia; NICU = neonatal intensive care unit. Circles represent the percentage of the outcomes for each 6-month period, and the connecting lines show the trend. The vertical red dotted line indicates bubble CPAP protocol implementation, and post-protocol implementation periods are shaded in light gray. NICU intubations were computed only for infants successfully managed with bubble CPAP in the delivery room. BPD was defined according to the 2018 National Institute of Child Health and Human Development Workshop.

Figure 6. Time to NICU intubation (≤ 7 days)



Legend: Cox regression curve representing the proportion of patients remaining on CPAP over time (not intubated), based on each period and accounting for gestational age, small for gestational age, Apgar < 7 at 10min and male sex. Log rank test, P < 0.001.

Table 2. Maternal and Neonatal Characteristics

	Period 0 (n = 90)	Period 1 (n = 91)	Period 2 (n = 128)	Period 3 (n = 131)	P-value
Prenatal					
Maternal age, years	31 ± 6	32 ± 6	32 ± 5	32 ± 6	0.84
Cesarian delivery	64 (71)	63 (69)	92 (72)	92 (70)	0.98
Complete antenatal steroids	78 (87)	68 (75)	110 (86)	97 (74)	0.06
Preeclampsia	24 (27)	24 (26)	30 (23)	23 (18)	0.32
Gestational diabetes	7 (8)	11 (12)	8 (6)	17 (13)	0.23
PPROM	39 (43)	34 (37)	59 (46)	47 (36)	0.32
Neonatal					
Gestational age, weeks	27.3 ± 2.2	27.3 ± 2	26.4 ± 2.2	26.9 ± 2	**0.006**
< 26	25 (28)	23 (25)	59 (46)	43 (33)	
26 to 28	43 (48)	46 (50)	49 (38)	69 (53)	
≥ 29	22 (24)	22 (24)	20 (16)	19 (15)	
Birth weight, grams	876 ± 202	929 ± 202	831 ± 212	895 ± 216	**0.006**
< 750	26 (29)	20 (22)	53 (41)	34 (26)	
750 – 999	35 (39)	31 (34)	42 (33)	50 (38)	
1000 – 1249	29 (32)	40 (44)	33 (26)	47 (36)	
Small for gestational age	18 (20)	9 (10)	18 (14)	10 (8)	**0.04**
Singleton	49 (54)	49 (54)	72 (56)	97 (74)	**0.003**
Male	45 (50)	44 (48)	67 (52)	65 (50)	0.95
Apgar at 1min	5 [3-6]	4 [2-6]	3 [2-5]	4 [2-6]	**<0.001**
Apgar at 5min	7 [6-8]	7 [5-7]	6 [5-7]	7 [6-8]	**<0.001**

Legend: PPROM = premature prolonged rupture of membranes. Results are presented as mean ± standard deviation, n (%) or median [IQR]. Small for gestational age was defined as birthweight less than the 10th percentile in the Fenton Growth chart.

Table 3. Respiratory Outcomes

	Period 0 (n = 90)	Period 1 (n = 91)	Period 2 (n = 128)	Period 3 (n = 131)	P-value
All infants					
Death/Severe BPD	19 (21)	20 (22)	21 (16)	14 (11)	0.09
Death < 14 days	9 (10)	8 (9)	14 (11)	6 (5)	0.27
Death 14 d to 36 weeks CGA*	2 (2)	3 (3)	1 (1)	3 (2)	
BPD classification	**n = 81**	**n = 83**	**n = 114**	**n = 125**	
No BPD	44 (55)	32 (39)	41 (36)	75 (60)	**< 0.001**
Mild BPD	17 (21)	27 (33)	44 (39)	30 (24)	
Moderate BPD	10 (12)	12 (14)	22 (19)	12 (10)	
Severe BPD*	10 (12)	12 (14)	7 (6)	8 (6)	
Composite Outcomes					
Survival with No or Mild BPD	61 (68)	59 (65)	85 (66)	105 (80)	**0.03**
Death/Moderate or Severe BPD	29 (32)	32 (35)	43 (34)	26 (20)	**0.03**
< 26 weeks	**n = 25**	**n = 23**	**n = 59**	**n = 43**	
Death/Severe BPD	9 (36)	10 (43)	15 (25)	9 (21)	0.20
Death < 14 days	7 (28)	4 (17)	9 (15)	4 (9)	0.24
Death - 14 d to 36 weeks CGA*	0	3 (13)	1 (2)	2 (5)	
BPD classification	**n = 18**	**n = 19**	**n = 50**	**n = 39**	
No BPD	8 (44)	2 (10)	8 (16)	13 (33)	**0.02**
Mild BPD	5 (28)	8 (42)	19 (38)	14 (36)	
Moderate BPD	3 (17)	3 (16)	17 (34)	7 (18)	
Severe BPD*	2 (11)	6 (32)	6 (12)	5 (13)	
Composite Outcomes					
Survival with No or Mild BPD	13 (52)	10 (43)	27 (46)	27 (63)	0.31
Death/Moderate or Severe BPD	12 (48)	13 (57)	32 (54)	16 (37)	0.31
26 to 28 weeks	**n = 43**	**n = 46**	**n = 49**	**n = 69**	
Death/Severe BPD	8 (19)	9 (20)	5 (10)	4 (6)	0.09
Death < 14 days	2 (5)	4 (9)	4 (8)	2 (3)	0.49
Death - 14 d to 36 weeks CGA*	2 (5)	0	0	1 (1.5)	
BPD classification	**n = 41**	**n = 42**	**n = 45**	**n = 67**	
No BPD	18 (44)	17 (40)	20 (45)	48 (72)	**0.002**
Mild BPD	10 (24)	14 (33)	19 (42)	13 (19)	
Moderate BPD	7 (17)	6 (14)	5 (11)	4 (6)	
Severe BPD*	6 (15)	5 (12)	1 (2)	2 (3)	
Composite Outcomes					
Survival with No or Mild BPD	28 (65)	31 (67)	39 (80)	61 (88)	**0.01**
Death/Moderate or Severe BPD	15 (35)	15 (33)	10 (20)	8 (12)	**0.01**
≥ 29 weeks	**n = 22**	**n = 22**	**n = 20**	**n = 19**	
Death/Severe BPD	2 (9)	1 (4)	1 (5)	1 (5)	0.92
Death < 14 days	0	0	1 (5)	0	0.36
Death - 14 d to 36 weeks CGA*	0	0	0	0	
BPD classification	**n = 22**	**n = 22**	**n = 19**	**n = 19**	
No BPD	18 (82)	13 (59)	13 (68)	14 (74)	0.28
Mild BPD	2 (9)	5 (23)	6 (32)	3 (16)	
Moderate BPD	0	3 (14)	0	1 (5)	
Severe BPD*	2 (9)	1 (4)	0	1 (5)	
Composite Outcomes					
Survival with No or Mild BPD	20 (91)	18 (82)	19 (95)	17 (89)	0.57
Death/Moderate or Severe BPD	2 (9)	4 (18)	1 (5)	2 (11)	0.57

Legend: BPD = bronchopulmonary dysplasia, MV = mechanical ventilation, CGA = corrected

gestational age. Results are presented as n (%). Unadjusted univariate analysis. BPD was defined according to the 2018 National Institute of Child Health and Human Development Workshop. * severe BPD includes deaths between 14 days and 36 weeks of CGA owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (21).

Table 4. Primary and Secondary Respiratory Outcomes Adjusted Odds Ratio

	Period 0 (N = 90)	**Period 1 (n = 91)**			**Period 2 (n = 128)**			**Period 3 (n = 131)**		
	n (%)	n (%)	AOR [95% CI]	p-value	n (%)	AOR [95% CI]	p-value	n (%)	AOR [95% CI]	p-value
Primary										
Death < 14 days	9 (10)	8 (9)	0.82 [0.31-2.14]	0.64	14 (11)	0.43 [0.17-1.05]	0.06	6 (5)	0.27 [0.10-0.72]	**0.01**
Severe BPD	10/81 (12)	12/83 (14)	1.43 [0.53-3.98]	0.49	7/114 (6)	0.36 [0.11-1.14]	0.08	8/125 (6)	0.60 [0.20-1.77]	0.35
Death/Severe BPD	19 (21)	20 (22)	1.21 [0.56-2.67]	0.62	21 (16)	0.45 [0.20-0.99]	**0.05**	14 (11)	0.37 [0.15-0.84]	**0.02**
Secondary										
Mild BPD	17/81 (21)	27/83 (33)	1.76 [0.86-3.67]	0.12	44/114 (39)	2.10 [1.08-4.23]	0.03	30/125 (24)	1.04 [0.52-2.13]	0.89
Moderate BPD	10/81 (12)	12/83 (14)	1.15 [0.45-2.99]	0.75	22/114 (19)	1.32 [0.57-3.21]	0.52	12/125 (10)	0.66 [0.26-1.70]	0.38
Survival with No or Mild BPD	61 (68)	59 (65)	0.77 [0.39-1.53]	0.46	85 (66)	1.32 [0.69-2.53]	0.39	105 (80)	2.2 [1.12-4.39]	**0.02**
Death/Moderate or Severe BPD	29 (32)	32 (35)	1.29 [0.65-2.56]	0.46	43 (34)	0.75 [0.39-1.44]	0.39	26 (20)	0.45 [0.23-0.89]	**0.02**
DR intubation	59 (66)	37 (41)	0.25 [0.12-0.51]	**< 0.001**	41 (32)	0.07 [0.03-0.14]	**< 0.001**	32 (24)	0.06 [0.13-0.13]	**< 0.001**
NICU intubation	14/31 (45)	25/54 (46)	0.88 [0.34-2.27]	0.80	38/87 (44)	0.48 [0.19-1.28]	0.11	46/99 (46)	0.58 [0.14-1.42]	0.23
DR/NICU intubation	73 (81)	62 (68)	0.46 [0.21-0.98]	**0.05**	79 (62)	0.20 [0.09-0.41]	**< 0.001**	78 (60)	0.21 [0.19-0.41]	**< 0.001**

Legend: AOR = adjusted odds ratio, BPD = bronchopulmonary dysplasia, DR = delivery room, NICU = neonatal intensive care unit. Results are presented as n (%) or odds ratio [95% confidence interval]. Denominators are the number of infants with available data. BPD was defined according to the 2018 National Institute of Child Health and Human Development Workshop. Logistic regression model 1 was used for primary outcome/BPD, adjusting for gestational age, small for gestational age, Apgar < 7 at 10min of life, male sex, and late-onset sepsis. Model 2 was used for DR and NICU intubation, adjusting for gestational age, small for gestational age, Apgar < 7 at 10min of life and male sex.

Table 5. Respiratory Management

	Period 0 (n = 90)	Period 1 (n = 91)	Period 2 (n = 128)	Period 3 (n = 131)	P-value
Delivery room					
Endotracheal intubation	59 (66)	37 (41)	41 (32)	32 (24)	**< 0.001**
bCPAP	31 (34)	54 (59)	87 (68)	99 (76)	**< 0.001**
Time to intubation (h)	0.1 [0.1-0.2]	0.2 [0.1-3.0]	2.1 [0.1-6.1]	2.6 [0.1-18.0]	**0.003**
NICU (≤ 7 days)					
NICU intubation	14/31 (45)	25/54 (46)	38/87 (44)	46/99 (46)	0.98
< 24h of life	13/31 (42)	22/54 (41)	32/87 (37)	35/99 (35)	
24-72h of life	1/31 (3)	3/54 (6)	4/87 (5)	3/99 (3)	
72h to ≤7 days	-	-	2/87 (2)	8/99 (8)	
Reason for intubation					0.09
Increased FiO_2	13/14 (93)	23/25 (92)	33/38 (87)	34/46 (74)	
Apnea	1/14 (7)	2/25 (8)	4/38 (11)	11/46 (24)	
Pneumothorax	-	-	1/38 (3)	1/46 (2)	
FiO_2 at intubation (%)	35 [32-43]	45 [37-50]	50 [45-60]	55 [38-65]	**0.003**
Time to intubation (h)	6.3 [4.2-13.8]	3.5 [2.2-13.7]	5.5 [3.4-22.8]	12.2 [3.8-34.0]	0.30
Respiratory care in the NICU					
Surfactant	70 (78)	57 (63)	73 (57)	68 (52)	**0.001**
MV (days)	7 [3-21]	7 [2-15]	16 [4-31]	11 [3-27]	0.11
bCPAP (days)	22 [11-30]	19 [11-28]	28 [15-38]	37 [29-47]	**< 0.001**
NIPPV (days)	4 [0-17]	6 [0-15]	0 [0-7]	0 [0-7]	**< 0.001**
HFNC (days)	0 [0-3]	6 [0-16]	5 [0-12]	0 [0-7]	**< 0.001**
Pneumothorax^	2 (2)	0	4 (3)	2 (2)	0.20
Postnatal steroids	43 (48)	28 (31)	54 (42)	45 (34)	0.06

Legend: bCPAP = bubble continuous airway pressure; FiO_2 = fraction of inspired oxygen; HFNC = high flow nasal cannula; NICU = neonatal intensive care unit; MV = mechanical ventilation; NIPPV = non-invasive positive pressure ventilation. Results are presented as mean ± standard deviation, n (%) or median [IQR]. ^Pneumothorax in infants who received bCPAP in the delivery room.

Table 6. Respiratory Management by Gestational Age Group

Gestational age (weeks)	Period 0	Period 1	Period 2	Period 3	P-value
< 26 weeks	**n = 25**	**n = 23**	**n = 59**	**n = 43**	
DR intubation	24 (96)	20 (87)	29 (49)	17 (40)	**< 0.001**
bCPAP in the delivery room	1 (4)	3 (13)	30 (51)	26 (60)	**< 0.001**
NICU intubation	-	2/3 (67)	22/30 (73)	18/26 (69)	0.45
< 24 hours of life	-	2/3 (67)	19/30 (63)	12/26 (46)	
24-72 hours of life	-	-	2/30 (7)	1/26 (4)	
72 hours to 7 days	-	-	1/30 (3)	5/26 (19)	
FiO_2 at intubation (%)	-	49 [48-49]	53 [50-65]	60 [36-67]	0.86
Surfactant administration	24 (96)	22 (96)	50 (85)	30 (70)	**0.004**
Never intubated	1 (4)	0	7 (12)	8 (19)	0.08
MV (days)	14 [6-23]	14 [7-30]	28 [9-41]	26 [12-35]	0.30
26 to 28 weeks	**N = 43**	**N = 46**	**N = 49**	**N = 69**	
DR intubation	28 (65)	14 (30)	10 (20)	14 (20)	**< 0.001**
bCPAP in the delivery room	15 (35)	32 (70)	39 (80)	55 (80)	**< 0.001**
NICU intubation	10/15 (67)	17/32 (53)	15/39 (38)	22/55 (40)	0.18
< 24 hours of life	10/15 (67)	15/32 (47)	13/39 (33)	21/55 (38)	
24-72 hours of life	-	2/32 (6)	2/39 (5)	-	
72 hours to 7 days	-	-	-	1/55 (2)	
FiO_2 at intubation (%)	34 [32-41]	46 [37-55]	45 [44-55]	55 [42-63]	**0.004**
Surfactant administration	37 (86)	29 (63)	23 (47)	34 (49)	**<0.001**
Never intubated	5 (12)	15 (33)	23 (47)	33 (48)	**<0.001**
MV (days)	7 [2-22]	5 [2-13]	7 [3-18]	6 [3-12]	
≥ 29 weeks	**N = 22**	**N = 22**	**N = 20**	**N = 19**	
DR intubation	7 (32)	3 (14)	2 (10)	1 (5)	0.15
bCPAP in the delivery room	15 (68)	19 (86)	18 (90)	18 (95)	0.15
NICU intubation	4/15 (27)	6/19 (31)	1/18(6)	6/18 (33)	0.13
< 24 hours of life	3/15 (20)	5/19 (26)	-	2/18 (11)	
24-72 hours of life	1/15 (7)	1/19 (5)	-	2/18 (11)	
72 hours to 7 days	-	-	1/18 (6)	2/18 (11)	
FiO_2 at intubation (%)	39 [33-43]	42 [35-45]	21	31 [21-48]	0.40
Surfactant administration	9 (41)	6 (27)	0	4 (21)	**0.02**
Never intubated	11 (50)	13 (59)	16 (80)	12 (63)	0.26
MV (days)	2 [1-4]	1 [1-4]	2 [2-6]	3 [2-7]	0.40

Legend: bCPAP = bubble continuous airway pressure; DR = delivery room; FiO_2 = fraction of inspired oxygen; NICU = neonatal intensive care unit; MV = mechanical ventilation. Results are presented as mean ± standard deviation, n (%) or median [IQR].

Table 7. Other Neonatal Outcomes

	Period 0 (n = 90)	Period 1 (n = 91)	Period 2 (n = 128)	Period 3 (n = 131)	P-value
Severe IVH (grade III or IV)	13 (14)	10 (11)	22 (17)	20 (15)	0.65
NEC (stage IIa or worse)	7 (8)	13 (14)	8 (6)	7 (5)	0.11
PDA	81 (90)	68 (75)	100 (78)	74 (56)	**<0.001**
PDA treatment	38 (42)	10 (11)	0	4 (3)	**<0.001**
Early onset sepsis	4 (4)	3 (3)	8 (6)	2 (1)	0.23
Late-onset sepsis	29 (32)	32 (35)	30 (23)	22 (17)	**0.002**
Length of NICU stay (days)	98 [64-133]	93 [46-113]	96 [76-123]	86 [66-111]	0.95
CGA at discharge	41 [38-45]	40 [34-42]	40 [38-43]	39 [37-41]	0.74

Legend: CGA = corrected gestational age; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; NICU = neonatal intensive care unit. Results are presented as mean ± standard deviation, n (%) or median [IQR]. Length of stay and CGA were calculated among infants who survived to discharge.

Table 8. Infant Characteristics and Outcomes Based on Respiratory Support in the Delivery Room

	Period 0			Period 1			Period 2			Period 3		
	CPAP (n = 31)	Intubation (n = 59)	*p*	CPAP (n = 54)	Intubation (n = 37)	*p*	CPAP (n = 87)	Intubation (n = 41)	*p*	CPAP (n = 99)	Intubation (n = 32)	*p*
Gestational age	29 ± 2	26 ± 2	***	28 ± 2	26 ± 2	***	27 ± 2	25 ± 2	***	27 ± 2	26 ± 2	***
Birthweight	1003±174	810 ± 185	***	1002 ±176	823 ± 192	***	902 ± 205	681 ±137	***	931 ± 197	784 ± 235	***
SGA	8 (26)	10 (17)		8 (15)	1 (3)		11 (13)	7 (17)		7 (7)	3 (9)	
Apgar at 5min	8 [7-8]	7 [6-8]	***	7 [6-8]	5 [4-7]	***	6 [6-8]	4 [3-6]	***	7 [6-8]	5 [3-6]	***
MV (days)	5 [2-9]	8 [3-22]		7 [2-14]	8 [2-24]		15 [4-29]	18 [5-42]	*	11 [3-25]	13 [3-29]	
Postnatal steroids	8 (26)	35 (59)	**	12 (22)	16 (43)	*	30 (34)	24 (59)	*	27 (27)	18 (56)	**
Death < 14 days	0	9 (15)		1 (2)	7 (19)		4 (5)	10 (24)		1 (1)	5 (16)	
No BPD	20 (65)	24/50 (48)		23/53 (44)	9/30 (30)		35/83 (42)	6/31 (19)	***	66/98 (67)	9/27 (33)	***
Mild BPD	6 (19)	11/50 (22)		15/53 (28)	12/30 (40)		34/83 (41)	10/31 (32)		20/98 (20)	10/27 (37)	
Moderate BPD	2 (6)	8/50 (16)		9/53 (17)	3/30 (10)		13/83 (16)	9/31 (30)		9/98 (9)	3/27 (11)	
Severe BPD	3 (10)	7/50 (14)		6/53 (11)	6/30 (20)		1/83 (1)	6/31 (19)		3/98 (1)	7/27 (19)	
Death/Severe BPD	3 (10)	16 (27)		7 (13)	13 (35)	*	5 (6)	16 (39)	***	4 (4)	10/27 (31)	***

Legend: BPD = bronchopulmonary dysplasia; MV = mechanical ventilation; SGA = small for gestational age. Results are presented as mean ± standard deviation, n (%) or median [IQR]. BPD was defined according to the 2018 National Institute of Child Health and Human Development Workshop, with severe BPD categorized as grade III and IIIa. Small for gestational age was defined as birthweight less than the 10th percentile in the Fenton Growth chart. * P-value < 0.05; ** P-value < 0.01; *** P-value < 0.001

Table 9. Characteristics and outcomes of infants who were intubated in DR

	Period 0 (n = 59)	**Period 1 (n = 37)**	**Period 2 (n = 41)**	**Period 3 (n = 32)**	**P-value**
Gestational age	26 ± 2	26 ± 2	25 ± 2	26 ± 2	**0.009**
Birthweight	810 ± 185	823 ± 192	681 ±137	784 ± 235	**0.003**
SGA	10 (17)	1 (3)	7 (17)	3 (9)	0.14
Apgar at 5min	7 [6-8]	5 [4-7]	4 [3-6]	5 [3-6]	**< 0.001**
MV (days)	8 [3-22]	8 [2-24]	18 [5-42]	13 [3-29]	0.13
Postnatal steroids	35 (59)	16 (43)	24 (59)	18 (56)	0.43
Death < 14 days	9 (15)	7 (19)	10 (24)	5 (16)	0.67
No BPD	24/50 (48)	9/30 (30)	6/31 (19)	9/27 (33)	0.21
Mild BPD	11/50 (22)	12/30 (40)	10/31 (32)	10/27 (37)	
Moderate BPD	8/50 (16)	3/30 (10)	9/31 (30)	3/27 (11)	
Severe BPD	7/50 (14)	6/30 (20)	6/31 (19)	7/27 (19)	
Death/Severe BPD	16 (27)	13 (35)	16 (39)	10/27 (31)	0.63

Legend: BPD = bronchopulmonary dysplasia; MV = mechanical ventilation; SGA = small for gestational age. Results are presented as mean ± standard deviation, n (%) or median [IQR]. BPD was defined according to the 2018 National Institute of Child Health and Human Development Workshop, with severe BPD categorized as grade III and IIIa. Small for gestational age was defined as birthweight less than the 10th percentile in the Fenton Growth chart.

Table 10. Characteristics and outcomes of infants who received CPAP in DR

	Period 0 (n = 31)	**Period 1 (n = 54)**	**Period 2 (n = 87)**	**Period 3 (n = 99)**	**P-value**
Gestational age	29 ± 2	28 ± 2	27 ± 2	27 ± 2	**< 0.001**
Birthweight	1003±174	1002 ±176	902 ± 205	931 ± 197	**0.007**
SGA	8 (26)	8 (15)	11 (13)	7 (7)	**0.05**
Apgar at 5min	8 [7-8]	7 [6-8]	6 [6-8]	7 [6-8]	**< 0.001**
MV (days)	5 [2-9]	7 [2-14]	15 [4-29]	11 [3-25]	0.45
Postnatal steroids	8 (26)	12 (22)	30 (34)	27 (27)	0.43
Death < 14 days	0	1 (2)	4 (5)	1 (1)	0.29
No BPD	20 (65)	23/53 (44)	35/83 (42)	66/98 (67)	**0.001**
Mild BPD	6 (19)	15/53 (28)	34/83 (41)	20/98 (20)	
Moderate BPD	2 (6)	9/53 (17)	13/83 (16)	9/98 (9)	
Severe BPD	3 (10)	6/53 (11)	1/83 (1)	3/98 (1)	
Death/Severe BPD	3 (10)	7 (13)	5 (6)	4 (4)	0.18

Legend: BPD = bronchopulmonary dysplasia; MV = mechanical ventilation; SGA = small for gestational age. Results are presented as mean ± standard deviation, n (%) or median [IQR]. BPD was defined according to the 2018 National Institute of Child Health and Human Development Workshop, with severe BPD categorized as grade III and IIIa. Small for gestational age was defined as birthweight less than the 10th percentile in the Fenton Growth chart. MV was calculated for infants who required NICU intubation.

4. Discussion

The protocol promoted the initiation of bCPAP in the DR and a comprehensive approach in the NICU, including its original design, fundamental principles, and short binasal curved prongs as the interface (100). The protocol implementation positively impacted important respiratory outcomes and, most importantly, improved rates of death/severe BPD. Notably, DR and NICU intubations decreased consistently and significantly, particularly in infants born between 26 to 28 weeks.

4.1 Death/Severe BPD

BPD imposes a substantial long-term burden on patients and their families. The need for MV at 36 weeks CGA was associated with an increase in moderate/severe neurodevelopmental impairment and a 2-fold increase in the rates of death and need for tracheostomy or supplemental O_2 at two years of age in a recent cohort (101). Similarly, Canadian data demonstrated that the need for supplemental O_2 or respiratory support at 36 weeks CGA was highly predictive of severe respiratory morbidity (multiple rehospitalizations, need for tracheostomy, need for respiratory monitoring at home and prolonged need for respiratory support) and neurosensory impairment (102). Accordingly, there is immense interest in finding strategies to prevent BPD; however, its incidence has remained stable. Several trials have reported a significant decrease in DR and NICU intubation (<72h of age) without major improvements in death/BPD (55, 56). In our cohort, the overall rates of BPD initially increased from 47% to 62%, mainly driven by infants with GA <29 weeks. This could be attributed to the increased survival of infants <26 weeks from 68% to 86% or the learning curve required to implement such a comprehensive bCPAP protocol (67). Indeed, rates of BPD subsequently decreased, mainly in infants at the extreme of GA, and more importantly, severe BPD significantly declined from 13% to 6%. The improvement in respiratory

morbidity is evident, with several potential contributing factors. Decreasing endotracheal intubation rates in the DR is associated with reduced risk of BPD and decreased need for MV during admission (35, 61), which was successfully achieved in our centre. Intubations in the DR and subsequent manual ventilation can lead to variations in peak inspiratory pressures (when using flow/self-inflating bags) and inspiratory times (when using a T-piece ventilator or flow/self-inflating bags) (103). Such variability increases the likelihood of providing excessive tidal volumes during positive pressure ventilation, which has been associated with hemodynamic instability and volume-induced lung injury (103). The proposed physiologic effects of bCPAP may have also played a role by multiple proposed routes: 1) decreasing biotrauma by improving lung recruitment, 2) preventing or decreasing the harmful effects of atelectrauma, and 3) possibly reducing inflammation, as animal models demonstrated that lambs treated with bCPAP had decreased alveolar protein content when compared to ventilator-derived CPAP (73), as well as decreased neutrophil recruitment into the lungs (80). Furthermore, even stable infants were kept on prolonged bCPAP therapy as outlined in the protocol (**Appendix A**). Prolonged exposure to CPAP may enhance lung remodelling and growth and decrease the number of respiratory events such as apnea/bradycardia and intermittent hypoxemia (104, 105). This effect could potentially be optimized by the oscillatory pressure amplitudes generated by the bCPAP, exposing the lung to higher distending pressures in brief periods. In our cohort, prolonged bCPAP exposure was not translated into increased length of stay or CGA at discharge. However, larger trials of extended CPAP in extremely preterm infants are necessary to determine the benefits and risks of this strategy.

BPD has changed in epidemiology, pathophysiology, and management (21, 106). Survival of extremely preterm infants increased, leading to evolving care practices to address their specific

needs, including a greater variety of respiratory support modalities (21, 102, 106). In response to these advancements, the initial definitions of BPD have been reviewed numerous times to incorporate these changes. The ideal definition should be an accessible benchmarking tool and offer some prognostic insight to clinicians and families (102). Our center identified the 2018 NICHD definition (21) as an accessible, suitable option for our population for many reasons. Before protocol implementation and during its uptake, there was significant heterogeneity in the choice of non-invasive respiratory support (NIPPV, HFNC, CPAP and low-flow nasal cannula), which is well captured by the 2018 NICHD definition and allows for a fair comparison of infants across periods. Another important strength is the combination of respiratory support mode and FiO_2 needs (21). In keeping with the strict discontinuation criteria, some infants remained on bCPAP at 36 weeks CGA for other reasons, such as poor growth or apneic events, the vast majority requiring FiO_2 0.21. As such, the need for continued respiratory support reflected immaturity rather than lung disease. Furthermore, although the 36-week CGA is used as a cutoff point, this definition encompasses early deaths attributable to respiratory causes, denoted as IIIa – an aspect often overlooked by other classifications. We recognize that benchmark trials using early CPAP intervention have utilized the 2001 BPD definition (55, 56), making comparison with other studies more difficult. Although the 2018 definition could be wrongly perceived as supporting using nasal cannulas for premature infants, our results show otherwise. Our data demonstrates that the best results occurred during P3, a period characterized by a significant reduction in nasal cannula usage (**Table 5**). Recent studies highlight a correlation between the 2018 definition of severe BPD and a spectrum of adverse neonatal outcomes, including significant neonatal morbidities, in-hospital mortality, and the use of supplemental respiratory support at discharge (18, 107). Further literature corroborates the 2018 definition's alignment with critical prognostic factors, such as

neurodevelopmental impairment and respiratory outcomes observed at five years of corrected age (108). Moreover, comparative evaluations demonstrate that the 2018 and 2001 definitions had similar discriminative performance on long-term neurodevelopmental and respiratory outcomes at 2, 5, and 7-8 years of corrected age (107, 108).

4.2 Delivery Room Intubation

Recent data from the Canadian Neonatal Network showed that 34% of infants with GA <31 weeks and 68% of <26 weeks required intubation in the DR (16). In a recent large trial evaluating an optimized use of minimally invasive surfactant treatment, 46% of infants between 25 to 28 weeks of GA were intubated in the DR and could not be enrolled (109). In our center, a quick and sustained shift in practice was noted, leading to decreased rates of DR intubation from 65% to 24%, primarily driven by infants born at <29 weeks. A mobile bCPAP system facilitated the DR initiation and maintenance during transport, avoiding unnecessary changes upon NICU admission. This improvement was similar to that reported by other cohort studies and quality improvement projects using bCPAP protocols (63, 67, 79, 80, 110) and a bundle of care allowing spontaneous breathing after tactile stimulation and initiation of different types of CPAP (66).

4.3 NICU Intubations (≤ 7 days)

Among infants GA <29 weeks not intubated in the DR, published CPAP failure rates have varied between 38% and 67%, likely due to differences in population demographics and definitions of failure (25). Although most studies consider "failure" to be the need for MV, different thresholds of maximum CPAP level, FiO_2, and clinical events to trigger intubation have been described (56, 66, 68, 81, 82, 83, 84, 85, 111). A recent systematic review and meta-analysis demonstrated a lower incidence of intubation ≤7 days of life with bCPAP compared to other types of CPAP (112). Unfortunately, the included studies were small single-center trials with significant bias,

downgrading the level of evidence (112). We observed that during the six years following protocol implementation, rates of NICU intubation remained unchanged, likely because of the higher number of more immature infants successfully treated in the DR and admitted to the NICU on bCPAP. Indeed, during P3, 60% of infants <26 weeks and 95% of infants ≥29 weeks were successfully treated with bCPAP in the DR. The adjusted analysis, accounting for GA, demonstrated that the odds of DR and NICU intubation consistently decreased with an increased absolute number of preterm infants never intubated during the first week of life (**Figure 6**). Furthermore, the time interval between birth and NICU intubation increased almost 2-fold, from 6.3h in P0 (IQR 4.2-13.8) to 12.2h in P3 (IQR 3.8-34h), comparable to previous reports with a mean time of intubation at 7.9h (IQR 3.8-19h) for infants between 25-28 weeks, and 18h (IQR 6.9-34h) for those between 29-32 weeks (113). We observed that the delay in intubation and surfactant administration did not negatively impact lung disease or other neonatal outcomes such as rates of pneumothorax, postnatal steroids or severe IVH.

4.4 Protocols and Practice Standardization

Standardization contributes to enhanced patient safety by minimizing the potential for errors that may arise from inconsistent practices (63, 93). In the context of respiratory care, this becomes particularly critical, especially given the vulnerability of extremely premature infants. The reduced variability in care delivery resulting from standardized practices translates to a more reliable and predictable healthcare environment, fostering better outcomes for preterm infants. While guidelines and protocols are vital elements of implementing evidence-based practices in the NICU, the active engagement of the multidisciplinary team is equally important (90). Previous literature underscores the efficacy of active knowledge dissemination (such as workshops) in facilitating the implementation of new policies, proving more effective than passive dissemination alone (90). In

our unit, major interventions were done before and during protocol launch. Over the years, the volunteer “champions” maintained bedside teaching initiatives with colleagues and bedside nurses. Neonatologists and trainees frequently discussed the use of bCPAP during rounds. The protocol was made available within the hospital’s computers, and bCPAP training became part of the orientation process for newly hired professionals, ensuring continuous exposure to the guidelines and equipment.

Similar to other reports (67), we observed that the improvement in respiratory outcomes was consistent and increased over time. While the observed results in our study can be attributed to the physiologic effects of bCPAP itself (73, 75), consistent adherence to protocol is a crucial factor contributing to its longevity and success (63). This positive trend is likely a result of the growing expertise of the staff with the intervention and a substantial transformation in the unit's culture, embracing a "gentle ventilation" approach. Another essential aspect of our protocol is emphasizing a single intervention rather than combined interventions that may require additional skills or resources. Our unit prioritized addressing every detail involved in caring for infants on bCPAP, including suctioning and positioning. These characteristics ensure the reproducibility of our protocol in diverse settings, which can be particularly important to low-resource NICUs.

4.5 Other NICU-specific Confounders

Although PDA has been associated with BPD in observational studies, trials of drugs used to accelerate ductal closure have failed to demonstrate improvements in outcomes (114). In fact, in a recent randomized controlled trial, preterm infants treated with acetaminophen had the worst combined outcomes, driven mainly by severe BPD (115). Despite a conservative policy towards PDA management in our NICU, BPD rates have decreased, and a previous report done by our group demonstrated that spontaneous closure occurred in most infants (116).

4.6 Limitations

The retrospective data collection is a limitation; however, our study describes a large contemporary cohort of very premature infants, the majority born <29 weeks and the 8-year observational period (2 years before and six years after the bCPAP protocol implementation) allowed for analysis over an extended timeframe. Furthermore, the multidisciplinary protocol established clear criteria for bCPAP initiation, failure and discontinuation and focused on a single intervention with consistent use and maintenance of the system.

5. Conclusion

In very preterm infants, the implementation of an early bCPAP protocol led to decreased rates of death/severe BPD over time. The unique characteristics of our data, including a contemporary cohort of very preterm infants and the use of a comprehensive protocol, underscore the study's significance.

The observed positive trend highlights the feasibility of implementing bCPAP as the initial mode of respiratory support for very preterm infants, emphasizing its role in mitigating the need for more invasive interventions. Our findings reveal a significant positive impact on the primary respiratory outcomes, with reduced DR and NICU intubations, particularly in infants between 26 and 28 weeks. The rapid reduction in DR intubation rates, from 66% to 24%, reflects a successful shift in clinical practice. Despite the higher number of more immature infants treated with bCPAP in the DR, NICU intubation rates remained stable. Other secondary outcomes, such as severe IVH, remained unchanged, underlining the protocol's safety and effectiveness. The results were sustained over time, showing protocol adherence and a significant transformation in the unit's culture.

By disseminating our comprehensive protocol and best practices, our goal is to promote the replicability of our findings. This ensures that our success extends beyond our NICU and becomes a valuable resource to other units, contributing to establishing a culture centred around standardized, evidence-based care. Our study is a practical guide for bCPAP implementation, providing a tested pathway to enhance respiratory outcomes of very preterm infants. It lays the foundation for improving this fragile population's overall quality of care.

Future research could focus on evaluating the cost-effectiveness of bCPAP compared to newer modalities of non-invasive respiratory support and compare their impact on respiratory outcomes of very preterm infants. Additionally, considering that some infants will invariably require endotracheal intubation as a life-saving measure, future studies could determine which infants are more likely to need this intervention. This knowledge would significantly contribute to refining our understanding of respiratory care in preterm infants, particularly those born before 28 weeks. Such insights could guide clinicians in making more informed decisions about the appropriate respiratory support for each infant, optimizing care strategies and outcomes.

6. References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.
2. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151-61.
3. Irvine B, Dzakpasu S, León J. Report Summary - Perinatal Health Indicators 2013: a Surveillance Report by the Public Health Agency of Canada's Perinatal Surveillance System. Health Promotion and Chronic Disease Prevention in Canada. 2015;35(1):23-4.
4. Statistics Canada. Table 13-10-0395-01 Leading causes of death, infants [Data table]. 2022.
5. Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, et al. Causes and Timing of Death in Extremely Premature Infants from 2000 through 2011. N Engl J Med. 2015;372(4):331-40.
6. Hiles M, Culpan A-M, Watts C, Munyombwe T, Wolstenhulme S. Neonatal respiratory distress syndrome: Chest X-ray or lung ultrasound? A systematic review. Ultrasound. 2017;25(5):80-91.
7. Ammari A, Suri M, Milisavljevic V, Sahni R, Bateman D, Sanocka U, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. The Journal of Pediatrics. 2005;147(3):341-7.
8. Polin RA, Abman SH, Rowitch DH, Benitz WE, Fox WW. Fetal and neonatal physiology. Fifth edition ed. Philadelphia, PA: Elsevier; 2017.
9. Coalson JJ. Pathology of new bronchopulmonary dysplasia. Semin Neonatol. 2003;8(1):73-81.
10. Jobe AH. The Amazing Premature Lung. Am J Perinatol. 2019;36(S 02):S1-S3.
11. Ueda T, Ikegami M, Jobe AH. Developmental changes of sheep surfactant: in vivo function and in vitro subtype conversion. J Appl Physiol. 1994;76(6):2701-6.
12. Warren JB, Anderson JDM. Core concepts: Respiratory distress syndrome. NeoReviews. 2009;10(7):351-61.
13. McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020(12):CD004454.
14. Polin RA, Carlo WA, Committee On Fetus and Newborn, American Academy of Pediatrics. Surfactant Replacement Therapy for Preterm and Term Neonates With Respiratory Distress. Pediatrics. 2014;133(1):156-63.
15. Wood AJJ, Jobe AH. Pulmonary Surfactant Therapy. N Engl J Med. 1993;328(12):861-8.
16. Shah PS, Yoon E, Chan P, Members of the Annual Report Review Committee. Canadian Neonatal Network 2021 Annual Report http://www.canadianneonatalnetwork.org/portal/Portals/0/Annual%20Reports/2021%20CNN%20annual%20report%20final_amended.pdf: Canadian Neonatal Network; 2022.
17. Northway WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med. 1967;276(7):357-68.
18. Jensen EA, Edwards EM, Greenberg LT, Soll RF, Ehret DEY, Horbar JD. Severity of Bronchopulmonary Dysplasia Among Very Preterm Infants in the United States. Pediatrics. 2021;148(1).
19. Jobe AJ. The New BPD: An Arrest of Lung Development. Pediatr Res. 1999;46(6):641-3.
20. Tracy MC, Cornfield DN. Bronchopulmonary Dysplasia: Then, Now, and Next. Pediatric Allergy Immunology and Pulmonology. 2020;33(3):99-109.
21. Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, et al. Bronchopulmonary Dysplasia: Executive Summary of a Workshop. The Journal of Pediatrics. 2018;197:300-8.
22. McEvoy CT, Jain L, Schmidt B, Abman S, Bancalari E, Aschner JL. Bronchopulmonary dysplasia: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases. Annals of the American Thoracic Society. 2014;11 Suppl 3(Suppl 3):S146-53.

23. Jobe AH, Ikegami M. Lung Development and Function in Preterm Infants in the Surfactant Treatment Era. Annu Rev Physiol. 2000;62(1):825-46.
24. Philip AGS. Oxygen Plus Pressure Plus Time: The Etiology of Bronchopulmonary Dysplasia. Pediatrics. 1975;55(1):44-50.
25. Glaser K, Bamat NA, Wright CJ. Can we balance early exogenous surfactant therapy and non-invasive respiratory support to optimise outcomes in extremely preterm infants? A nuanced review of the current literature. Arch Dis Child Fetal Neonatal Ed. 2023;108(6):554-60.
26. Keszler M, Sant'Anna G. Mechanical Ventilation and Bronchopulmonary Dysplasia. Clin Perinatol. 2015;42(4):781-96.
27. Wright CJ, Polin RA, Kirpalani H. Continuous Positive Airway Pressure to Prevent Neonatal Lung Injury: How Did We Get Here, and How Do We Improve? The Journal of Pediatrics. 2016;173:17-24.e2.
28. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723-9.
29. Klingenberg C, Wheeler KI, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in neonates. Cochrane Database Syst Rev. 2017;2017(10).
30. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA. 2015;314(10):1039-51.
31. Lui K, Lee SK, Kusuda S, Adams M, Vento M, Reichman B, et al. Trends in Outcomes for Neonates Born Very Preterm and Very Low Birth Weight in 11 High-Income Countries. The Journal of Pediatrics. 2019;215:32-40.e14.
32. Bhuta T, Henderson-Smart DJ. Elective high frequency jet ventilation versus conventional ventilation for respiratory distress syndrome in preterm infants. Cochrane Database Syst Rev. 1998.
33. Carpi MF. High-Frequency Jet Ventilation in Preterm Infants: Is There Still Room for It? Respir Care. 2017;62(7):997-8.
34. Ethawi YH, Abou Mehrem A, Minski J, Ruth CA, Davis PG. High frequency jet ventilation versus high frequency oscillatory ventilation for pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev. 2016;2016(5):CD010548.
35. Fischer HS, Bührer C. Avoiding Endotracheal Ventilation to Prevent Bronchopulmonary Dysplasia: A Meta-analysis. Pediatrics. 2013;132(5):e1351-e60.
36. Dumpa V, Bhandari V. Non-Invasive Ventilatory Strategies to Decrease Bronchopulmonary Dysplasia—Where Are We in 2021? Children. 2021;8(2):132.
37. Owen LS, Morley CJ, Davis PG. Pressure variation during ventilator generated nasal intermittent positive pressure ventilation in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2010;95(5):F359-64.
38. Klotz D, Schneider H, Schumann S, Mayer B, Fuchs H. Non-invasive high-frequency oscillatory ventilation in preterm infants: a randomised controlled cross-over trial. Arch Dis Child Fetal Neonatal Ed. 2018;103(4):F1-F5.
39. Lemyre B, Deguise MO, Benson P, Kirpalani H, Ekhaguere OA, Davis PG. Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants. Cochrane Database Syst Rev. 2023;7(7):CD005384.
40. Dumpa V, Katz K, Northrup V, Bhandari V. SNIPPV vs NIPPV: does synchronization matter? J Perinatol. 2012;32(6):438-42.
41. Kubicka ZJ, Limauro J, Darnall RA. Heated, Humidified High-Flow Nasal Cannula Therapy: Yet Another Way to Deliver Continuous Positive Airway Pressure? Pediatrics. 2008;121(1):82-8.
42. Taha DK, Kornhauser M, Greenspan JS, Dysart KC, Aghai ZH. High Flow Nasal Cannula Use Is Associated with Increased Morbidity and Length of Hospitalization in Extremely Low Birth Weight Infants. The Journal of Pediatrics. 2016;173:50-5.e1.
43. Kanbar LJ, Shalish W, Latremouille S, Rao S, Brown KA, Kearney RE, et al. Cardiorespiratory behavior of preterm infants receiving continuous positive airway pressure and high flow nasal cannula post extubation: randomized crossover study. Pediatr Res. 2020;87(1):62-8.

44. Roberts CT, Owen LS, Manley BJ, Frøisland DH, Donath SM, Dalziel KM, et al. Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants. N Engl J Med. 2016;375(12):1142-51.
45. Murki S, Singh J, Khant C, Swarup, Tejo, Joy P, et al. High-Flow Nasal Cannula versus Nasal Continuous Positive Airway Pressure for Primary Respiratory Support in Preterm Infants with Respiratory Distress: A Randomized Controlled Trial. Neonatology. 2018;113(3):235-41.
46. Yagui AC, Meneses J, Zólio BA, Brito GMG, Da Silva RJ, Rebello CM. Nasal continuous positive airway pressure (NCPAP) or noninvasive neurally adjusted ventilatory assist (NIV-NAVA) for preterm infants with respiratory distress after birth: A randomized controlled trial. Pediatr Pulmonol. 2019;54(11):1704-11.
47. Shin SH, Shin SH, Kim SH, Song IG, Jung YH, Kim EK, et al. Noninvasive Neurally Adjusted Ventilation in Postextubation Stabilization of Preterm Infants: A Randomized Controlled Study. The Journal of Pediatrics. 2022;247:53-9.e1.
48. Yonehara K, Ogawa R, Kamei Y, Oda A, Kokubo M, Hiroma T, et al. Non-invasive neurally adjusted ventilatory assist versus nasal intermittent positive-pressure ventilation in preterm infants born before 30 weeks' gestation. Pediatr Int. 2018;60(10):957-61.
49. Latremouille S, Bhuller M, Shalish W, Sant'Anna G. Cardiorespiratory measures shortly after extubation and extubation outcomes in extremely preterm infants. Pediatr Res. 2023;93(6):1687-93.
50. De Luca D, Dell'Orto V. Non-invasive high-frequency oscillatory ventilation in neonates: review of physiology, biology and clinical data. Arch Dis Child Fetal Neonatal Ed. 2016;101(6):F565-F70.
51. Zhu X, Qi H, Feng Z, Shi Y, De Luca D. Noninvasive High-Frequency Oscillatory Ventilation vs Nasal Continuous Positive Airway Pressure vs Nasal Intermittent Positive Pressure Ventilation as Postextubation Support for Preterm Neonates in China: A Randomized Clinical Trial. JAMA Pediatrics. 2022;176(6):551-9.
52. Mukerji A, Sarmiento K, Lee B, Hassall K, Shah V. Non-invasive high-frequency ventilation versus bi-phasic continuous positive airway pressure (BP-CPAP) following CPAP failure in infants <1250 g: a pilot randomized controlled trial. J Perinatol. 2017;37(1):49-53.
53. Gupta S, Donn SM. Continuous positive airway pressure: Physiology and comparison of devices. Seminars in Fetal and Neonatal Medicine. 2016;21(3):204-11.
54. Sahni R, Schiaratura M, Polin RA. Strategies for the prevention of continuous positive airway pressure failure. Seminars in fetal & neonatal medicine. 2016;21(3):196-203.
55. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet J-M, Carlin JB. Nasal CPAP or Intubation at Birth for Very Preterm Infants. N Engl J Med. 2008;358(7):700-8.
56. Finer N, Carlo W, Walsh M, Rich W, Gantz M, Laptook A, et al. Early CPAP versus Surfactant in Extremely Preterm Infants. N Engl J Med. 2010;362(21):1970-9.
57. Van Marter LJ, Allred EN, Pagano M, Sanocka U, Parad R, Moore M, et al. Do Clinical Markers of Barotrauma and Oxygen Toxicity Explain Interhospital Variation in Rates of Chronic Lung Disease? Pediatrics. 2000;105(6):1194-201.
58. Hatch LD, Clark RH, Carlo WA, Stark AR, Ely EW, Patrick SW. Changes in Use of Respiratory Support for Preterm Infants in the US, 2008-2018. JAMA Pediatrics. 2021;175(10):1017-24.
59. Wung J-T, Driscoll JM, Jr., Epstein RA, Hyman AI. A new device for CPAP by nasal route. Crit Care Med. 1975;3(2).
60. Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics. 1987;79(1):26-30.
61. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ. 2013;347(oct17 3):f5980-f.
62. Subramaniam P, Ho JJ, Davis PG. Prophylactic or very early initiation of continuous positive airway pressure (CPAP) for preterm infants. Cochrane Database Syst Rev. 2021(10):CD001243.
63. Aly H, Mohamed MA. An experience with a bubble CPAP bundle: is chronic lung disease preventable? Pediatr Res. 2020;88(3):444-50.

64. Kakkilaya V, Jubran I, Mashruwala V, Ramon E, Simcik VN, Marshall M, et al. Quality Improvement Project to Decrease Delivery Room Intubations in Preterm Infants. Pediatrics. 2019;143(2):e20180201.
65. Kakkilaya V, Tang A, Wagner S, Ridpath J, Ibrahim J, Brown LS, et al. Discontinuing Nasal Continuous Positive Airway Pressure in Infants ≤32 Weeks of Gestational Age: A Randomized Control Trial. The Journal of Pediatrics. 2021;230:93-9.e3.
66. Kakkilaya VB, Weydig HM, Smithhart WE, Renfro SD, Garcia KM, Brown CM, et al. Decreasing Continuous Positive Airway Pressure Failure in Preterm Infants. Pediatrics. 2021;148(4):e2020014191.
67. Aly H. Does the Experience With the Use of Nasal Continuous Positive Airway Pressure Improve Over Time in Extremely Low Birth Weight Infants? Pediatrics. 2004;114(3):697-702.
68. Miller TA, Li J, Riddell S, Barkley SC. Decreasing Chronic Lung Disease Associated with Bubble CPAP Technology: Experience at Five Years. Pediatric Quality and Safety. 2020;5(2):e281.
69. Patel RM, Zimmerman K, Carlton DP, Clark R, Benjamin DK, Smith PB. Early Caffeine Prophylaxis and Risk of Failure of Initial Continuous Positive Airway Pressure in Very Low Birth Weight Infants. The Journal of Pediatrics. 2017;190:108-11.e1.
70. Kakkilaya V, Wagner S, Mangona KLM, Steven Brown L, Jubran I, He H, et al. Early predictors of continuous positive airway pressure failure in preterm neonates. J Perinatol. 2019;39(8):1081-8.
71. Mukerji A, Shah PS, Shivananda S, Yee W, Read B, Minski J, et al. Survey of noninvasive respiratory support practices in Canadian neonatal intensive care units. Acta Paediatr. 2017;106(3):387-93.
72. Dargaville PA, Gerber A, Johansson S, De Paoli AG, Kamlin CO, Orsini F, et al. Incidence and Outcome of CPAP Failure in Preterm Infants. Pediatrics. 2016;138(1):e20153985.
73. Pillow JJ, Hillman N, Moss TJM, Polglase G, Bold G, Beaumont C, et al. Bubble Continuous Positive Airway Pressure Enhances Lung Volume and Gas Exchange in Preterm Lambs. Am J Respir Crit Care Med. 2007;176(1):63-9.
74. Lee K-S, Dunn MS, Fenwick M, Shennan AT. A Comparison of Underwater Bubble Continuous Positive Airway Pressure with Ventilator-Derived Continuous Positive Airway Pressure in Premature Neonates Ready for Extubation. Neonatology. 1998;73(2):69-75.
75. Pillow JJ, Travadi JN. Bubble CPAP: Is the Noise Important? An In Vitro Study. Pediatr Res. 2005;57(6):826-30.
76. Kahn DJ, Courtney SE, Steele AM, Habib RH. Unpredictability of Delivered Bubble Nasal Continuous Positive Airway Pressure: Role of Bias Flow Magnitude and Nares-Prong Air Leaks. Pediatr Res. 2007;62(3):343-7.
77. Courtney SE, Kahn DJ, Singh R, Habib RH. Bubble and ventilator-derived nasal continuous positive airway pressure in premature infants: work of breathing and gas exchange. J Perinatol. 2011;31(1):44-50.
78. Liptsen E, Aghai ZH, Pyon KH, Saslow JG, Nakhla T, Long J, et al. Work of Breathing During Nasal Continuous Positive Airway Pressure in Preterm Infants: A Comparison of Bubble vs Variable-Flow Devices. J Perinatol. 2005;25(7):453-8.
79. Aly H, Massaro AN, Patel K, El-Mohandes AA. Is it safer to intubate premature infants in the delivery room? Pediatrics. 2005;115(6):1660-5.
80. Narendran V, Donovan EF, Hoath SB, Akinbi HT, Steichen JJ, Jobe AH. Early Bubble CPAP and Outcomes in ELBW Preterm Infants. J Perinatol. 2003;23(3):195-9.
81. De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. J Paediatr Child Health. 2001;37(2):161-7.
82. Nowadzky T, Pantoja A, Britton JR. Bubble Continuous Positive Airway Pressure, A Potentially Better Practice, Reduces the Use of Mechanical Ventilation Among Very Low Birth Weight Infants With Respiratory Distress Syndrome. Pediatrics. 2009;123(6):1534-40.
83. Pelligra G, Abdellatif MA, Lee SK. Nasal continuous positive airway pressure and outcomes in preterm infants: A retrospective analysis. Paediatrics and Child Health. 2008;13(2):99-103.

84. Tapia JL, Urzua S, Bancalari A, Meritano J, Torres G, Fabres J, et al. Randomized Trial of Early Bubble Continuous Positive Airway Pressure for Very Low Birth Weight Infants. The Journal of Pediatrics. 2012;161(1):75-80.e1.
85. Friedman CA, Menchaca RC, Baker MC, Rivas CK, Laberge RN, Rios EH, et al. Bubble Nasal CPAP, Early Surfactant Treatment, and Rapid Extubation Are Associated With Decreased Incidence of Bronchopulmonary Dysplasia in Very-Low-Birth-Weight Newborns: Efficacy and Safety Considerations. Respir Care. 2013;58(7):1134-42.
86. Beltempo M, Isayama T, Vento M, Lui K, Kusuda S, Lehtonen L, et al. Respiratory Management of Extremely Preterm Infants: An International Survey. Neonatology. 2018;114(1):28-36.
87. Kugelman A, Inbar-Sanado E, Shinwell ES, Makhoul IR, Leshem M, Zangen S, et al. Iatrogenesis in Neonatal Intensive Care Units: Observational and Interventional, Prospective, Multicenter Study. Pediatrics. 2008;122(3):550-5.
88. Dunbar AE, Sharek PJ, Mickas NA, Coker KL, Duncan J, McLendon D, et al. Implementation and Case-Study Results of Potentially Better Practices to Improve Pain Management of Neonates. Pediatrics. 2006;118(Supplement_2):S87-S94.
89. Fischer HR, Stewart DL. Quality Improvement and Safety in the Neonatal Intensive Care Unit. NeoReviews. 2017;18(4):e201-e8.
90. Shah V, Warre R, Lee SK. Quality Improvement Initiatives in Neonatal Intensive Care Unit Networks: Achievements and Challenges. Acad Pediatr. 2013;13(6):S75-S83.
91. Payne NR, Finkelstein MJ, Liu M, Kaempf JW, Sharek PJ, Olsen S. NICU Practices and Outcomes Associated With 9 Years of Quality Improvement Collaboratives. Pediatrics. 2010;125(3):437-46.
92. Hermeto F, Bottino MN, Vaillancourt K, Sant'Anna GM. Implementation of a Respiratory Therapist-Driven Protocol for Neonatal Ventilation: Impact on the Premature Population. Pediatrics. 2009;123(5):e907-e16.
93. Sant'Anna GM, Keszler M. Developing a neonatal unit ventilation protocol for the preterm baby. Early Hum Dev. 2012;88(12):925-9.
94. Germain A, Nouraeyan N, Claveau M, Leone M, Sant'Anna G. Optimal surfactant delivery protocol using the bovine lipid extract surfactant: a quality improvement study. J Perinatol. 2021;41(1):17-23.
95. Blackwood B, Alderdice F, Burns K, Cardwell C, Lavery G, O'Halloran P. Use of weaning protocols for reducing duration of mechanical ventilation in critically ill adult patients: Cochrane systematic review and meta-analysis. BMJ. 2011;342(jan13 2):c7237-c.
96. Askie LM, Brocklehurst P, Darlow BA, Finer N, Schmidt B, Tarnow-Mordi W. NeOProM: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. BMC Pediatr. 2011;11(1).
97. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187(1):1-7.
98. Papile L-A, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. The Journal of Pediatrics. 1978;92(4):529-34.
99. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110(2 Pt 1):285-91.
100. Falk M, Gunnarsdottir K, Baldursdottir S, Donaldsson S, Jonsson B, Drevhammar T. Interface leakage during neonatal CPAP treatment: a randomised, cross-over trial. Arch Dis Child Fetal Neonatal Ed. 2021;106(6):663-7.
101. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. Am J Respir Crit Care Med. 2019;200(6):751-9.

102. Isayama T, Lee SK, Yang J, Lee D, Daspal S, Dunn M, et al. Revisiting the Definition of Bronchopulmonary Dysplasia: Effect of Changing Panoply of Respiratory Support for Preterm Neonates. JAMA Pediatrics. 2017;171(3):271-9.
103. de Medeiros SM, Mangat A, Polglase GR, Sarrato GZ, Davis PG, Schmölzer GM. Respiratory function monitoring to improve the outcomes following neonatal resuscitation: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2022;107(6):589-96.
104. Zhang S, Garbutt V, McBride JT. Strain-induced growth of the immature lung. J Appl Physiol. 1996;81(4):1471-6.
105. Lam R, Schilling D, Scottoline B, Platteau A, Niederhausen M, Lund KC, et al. The Effect of Extended Continuous Positive Airway Pressure on Changes in Lung Volumes in Stable Premature Infants: A Randomized Controlled Trial. The Journal of Pediatrics. 2020;217:66-72.e1.
106. Jobe AH, Steinhorn R. Can We Define Bronchopulmonary Dysplasia? The Journal of Pediatrics. 2017;188:19-23.
107. Doyle LW, Ranganathan S, Mainzer RM, Cheong JLY. Relationships of Severity of Bronchopulmonary Dysplasia with Adverse Neurodevelopmental Outcomes and Poor Respiratory Function at 7-8 Years of Age. The Journal of Pediatrics. 2024;269:114005.
108. Katz TA, van Kaam AH, Schuit E, Mugie SM, Aarnoudse-Moens CSH, Weber EH, et al. Comparison of New Bronchopulmonary Dysplasia Definitions on Long-Term Outcomes in Preterm Infants. The Journal of Pediatrics. 2023;253:86-93.e4.
109. Dargaville PA, Kamlin COF, Orsini F, Wang X, De Paoli AG, Kanmaz Kutman HG, et al. Effect of Minimally Invasive Surfactant Therapy vs Sham Treatment on Death or Bronchopulmonary Dysplasia in Preterm Infants With Respiratory Distress Syndrome: The OPTIMIST-A Randomized Clinical Trial. JAMA. 2021;326(24):2478-87.
110. Tagliaferro T, Bateman D, Ruzal-Shapiro C, Polin RA. Early radiologic evidence of severe respiratory distress syndrome as a predictor of nasal continuous positive airway pressure failure in extremely low birth weight newborns. J Perinatol. 2015;35(2):99-103.
111. Alarcon-Martinez T, Latremouille S, Kovacs L, Kearney RE, Sant'Anna GM, Shalish W. Clinical usefulness of reintubation criteria in extremely preterm infants: a cohort study. Arch Dis Child Fetal Neonatal Ed. 2023;108(6):643-8.
112. Shruti KB, Abdullah A, Laura B, Sourabh D, Amit M. Bubble versus other continuous positive airway pressure forms: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2020;105(5):526.
113. Dargaville PA, Aiyappan A, De Paoli AG, Dalton RG, Kuschel CA, Kamlin CO, et al. Continuous positive airway pressure failure in preterm infants: incidence, predictors and consequences. Neonatology. 2013;104(1):8-14.
114. Benitz WE. Patent ductus arteriosus: to treat or not to treat? Arch Dis Child Fetal Neonatal Ed. 2012;97(2):F80-2.
115. Hundscheid T, Onland W, Kooi EMW, Vijlbrief DC, De Vries WB, Dijkman KP, et al. Expectant Management or Early Ibuprofen for Patent Ductus Arteriosus. N Engl J Med. 2022;388(11):980-90.
116. De Carvalho Nunes G, Wutthigate P, Simoneau J, Beltempo M, Sant'Anna GM, Altit G. Natural evolution of the patent ductus arteriosus in the extremely premature newborn and respiratory outcomes. J Perinatol. 2021;42(5):642-8.

Appendix A – Protocol for Installation, Maintenance and Weaning of Bubble Nasal Continuous Positive Airway Pressure Therapy – for the Delivery Room and Neonatal Intensive Care Unit

1. **Purpose**
   - To harmonize routine care of a patient on bCPAP therapy by assuring proper indication, installation, proper maintenance of the interface and system, and weaning & discontinuation.

2. **Indications:**

1. Spontaneously breathing premature infants < 32 weeks of gestational age (GA).
2. Any newborn showing signs of respiratory distress defined as:
   - Oxygen needs > 21% to maintain appropriate SpO_2 as per Neonatal Resuscitation Program (NRP) or NICU Guidelines (OWL protocol).
   - Increased work of breathing defined as the presence of tachypnea (>80bpm), moderate sub-sternal and/or suprasternal retractions, grunting, and/or nasal flaring.

Contraindications (includes but not limited to):

- Congenital diaphragmatic hernia before surgical repair
- Orofacial and upper airway abnormalities, such as bilateral choanal atresia,

Relative contraindications: untreated GI pathologies such as atresia, malrotation, and volvulus.

3. **POSSIBLE COMPLICATIONS**
   - Irritation, bleeding, infection, or chronic inflammation of the nasal mucosa or skin
   - Nasal obstruction from secretions or improper position of the nasal prongs
   - Pressure necrosis of the nasal septum
   - Abdominal distension ("CPAP belly") and feeding intolerance.
   - Progressive Respiratory Failure – may be caused by natural disease progression or improper airway care.
   - Pneumothorax - especially during the acute phase of RDS
   - Misshaping of the head

4. **PROCEDURE FOR bCPAP INSTALLATION**

   a. Place and position the head bonnet.
   b. Use the Nasal Sizing Guide to determine best size of nasal prong for infant. The nasal prongs should fill the nares as much as possible to avoid leak.
   c. Place prongs curved side DOWN and hold it in place with 2 fingers.
   d. Turn the heater ON and verify that is operating correctly as per manufacturer's instructions.

e. Initiate at a flow rate between 5 to 8 liters/minute. Do not exceed 10 liters/minute or provide less than 5 liters/minute. **NOTE:** Increasing the flow too much to compensate for leaks increases expiratory resistance and is not advised.
f. Set the bCPAP pressure to the prescribed pressure.
g. Set FiO_2 as per OWL Guideline.
h. Occlude the prongs to ensure that bubbles are created in the water, confirming no leaks in the delivery system.
i. Apply the Velcro around the prongs and both limbs of the bCPAP system (inspiratory and expiratory).
j. Apply the *Cannulaide*® to assure a good nasal seal during CPAP therapy. It is sized to fit all nasal cannulas and helps maintain the prongs straight and well positioned in the nares.

Cannulaide® - Attention:

- Do not use *Cannulaide*® to reduce the prong size. Remember that babies are nose breathers and therefore, it is very important the adequate prong size is used since small prongs with small *Cannulaide*® will significantly increase respiratory resistance.
- The *Cannulaide*® does NOT prevent septum injury. The ONLY way to protect the septum from injury is by preventing the prongs from touching it.
- In preterm infants with GA < 29 weeks of gestation, the *Cannulaide*® will only be placed once in the NICU, at the first full assessment after admission (at 4-6 hours of life) to prevent removal of the bCPAP system as much as possible.

k. Keep infant in supine position, with head elevated about 30° and neck supported with a small roll.

NOTE: Careful observation of the position of the prongs is essential. Excessive blanching may injure the skin and internal structures of the nose. When the appropriate size is selected, blanching of the nares is not uncommon. When it occurs, wait 30 seconds, and reassess. If it is still present, consider a smaller size of prong.

l. Ensure Consistent Bubbling. However, it is important to note that some intermittent bubbling may occur. If there is no bubbling at all, then the infant is not receiving effective bCPAP therapy. A system which is not bubbling has a pressure leak, which must be resolved.
m. If the source is thought to be an open mouth a chinstrap can be utilized but it should not be too tight that prevents the infant from yawning or crying.
n. Positioning of prongs may also create a leak or even blockage. Prongs should never sit completely up against the septum of the nares. Additionally, the joints of

the BCPAP circuit can be turned slightly to achieve optimum positioning, and thus ensure bubbling.

5. PROCEDURE FOR CARE DURING bCPAP TREATMENT

Care while on bCPAP is aimed at optimizing respiratory status, decrease work of breathing, and minimize FiO_2 required. For this reason, disconnecting infants from bCPAP during routine care should be avoided as much as possible. Patients should be weighed with their bCPAP interface and bonnet in place, and head massages without the bonnet should be done while maintaining prongs in the nares. If Cannulaide ® change is necessary, it should be done as quickly as possible (especially in the first 72 hours of life in extremely preterm infants) to prevent decruitment.

1. All care should be bundled to prevent unnecessary handling of the infant.
2. Perform equipment checks and proper documentation.
3. Check the bubbler every 2 hours and remove excess water in the container.
4. Change the dual heated circuit and bubbler every 28 days.
5. Change the interface every 7 days, and prongs must be changed when dirty or need for upsize.
6. Aspirate air from OG tube prior to feeds and, if possible, leave it vented at least an hour in between feeds to avoid abdominal distention
7. Perform hourly visualization of the infant, the interface, and the circuit.
8. Perform and document a full respiratory assessment including auscultation, work of breathing, SpO_2, $TcPCO_2$ (if available), and respiratory rate with each care.
9. Suction infant with each care period (see below), and document intervention.
10. Perform skin check with each care, and document intervention.
11. Optimize opening of airway by appropriate positioning of the patient with each care
12. Increase or decrease FiO_2 as per OWL guidelines.
13. Optimize positioning of circuit to ensure infant's comfort.
14. Remove water condensation from the circuit.
15. Hourly documentation of heart rate, respiratory rate, SpO_2, FiO_2, $TcPCO_2$ (if available) & pressure setting of bCPAP.
16. Every 2h documentation of equipment and pressure on Respiratory Therapy Non-Invasive Ventilation Order/ Flow sheet

<u>Daily bCPAP care</u>

A) Suctioning

Nares should be suctioned to avoid malfunctioning and therapy failure due to secretions. **Suctioning may be <u>required</u> every 1 to 4 hours, depending on each case**. Discuss frequency of suctioning with the team and establish a plan for each patient every day. Signs of airway obstruction are increased O_2 needs, episodes of apnea/desaturations and increased work of

breathing. It is recommended that 2 health care professionals are present when suctioning for extremely preterm infants, especially in the first 72 hours.

A. Ensure suction pressure is set at 80-100 mmHg.
B. Cover patients' eyes with gauze or clean wipe as per infection control guidelines to prevent conjunctivitis. (The bonnet should NOT be used to cover eyes as it may be already contaminated with droplets.)
C. Suction oropharynx:

a. Using oral suction device, suction both sides of oropharynx.

D. Suction nasopharynx:
    a. Use 8 Fr suction catheter. Use a 6 Fr catheter only if unable to pass a number 8 Fr. A

smaller catheter may pass or slide more easily but is less effective at removing secretions.

    b. Lubricate suction catheter with small amount of water-soluble lubricant.
    c. Remove one prong from one nare only (most easily achieved using tweezers) and pinch this prong. (The other prong should remain in the other nare to maintain some pressure

during the procedure)

    d. Suction should not exceed 5-10 seconds per pass.
    e. Repeat procedure only if large thick secretions are obtained.
    f. Replace prong and allow infant to recover.
    g. Repeat the same procedure on the other side.

B) Skin care

Redness can become skin breakdown / necrosis in a matter of hours, and it is generally caused by inadvertent pressure on the skin. The bonnet, prongs, and chin strap can also be sources of skin pressure.

A. **Head** – once per shift:
    a. Remove infant's bonnet, while maintaining prongs in nares manually.
    b. Inspect the head and ears for skin breakdown. Particular attention should be brought to the area behind the ears, where wetness, redness, irritation, and skin breakdown can hide.
    c. Perform a gentle head massage to promote blood flow to the area.
    d. Ensure skin is dry and free of compromise before re-applying bonnet. If skin breakdown is noted, consult with MD/NNP. If bonnet is creating pressure points, measure head circumference again and choose appropriate size.

B. **Nares/nasal septum** – with each care:

a. During suctioning, perform a thorough visual check of the patient's nose/septum. Use penlight to assess inside condition of nares if redness is present.
b. Ensure the nasal prongs/cannula are away from the nasal septum by always maintaining a distance between the bridge of the nasal cannula and the nasal septum.
c. Change Cannulaide® only if it no longer adheres to the skin. If so, assess areas usually covered by Cannulaide ® for skin breakdown or compromise.
d. Consult MD/NNP if redness or breakdown is noted. In addition, reposition the prongs away from the septum and allow the area to recover.

C. **Chin strap** – with each care:
a. Remove chin strap and visualize skin under strap.
b. Consult MD/NNP if redness or breakdown noted.
c. Ensure skin is dry and free of compromise before reapplying chin strap.

C) Positioning

a. Change the position of the infant every 4-6 hours. Position changes improve homogeneity of ventilation.
b. Supine position - place a roll should behind the infant's neck/shoulder to keep it slightly extended to keep airway open. Preterm infants have prominent occiput.
c. Prone or lateral - small "pillows" of clean wipes or blankets may be needed to help keep the head supported without applying pressure on the bCPAP interface.

NOTE: Repositioning of any extremely preterm infant should always be done by 2 skilled professionals to ensure that the prongs stay in place during procedure, and to ensure smooth position changes for the baby.

D) Holding / Kangaroo Care

An infant on bubble BCPAP therapy may be held or given Kangaroo Care (KC) if the baby is considered stable by the medical team and oxygen requirement is less than 50%.

a. It is recommended to have two members of the NICU team to help transfer the infant to KC.
b. Be as gentle as possible to avoid trauma or irritation of the nostrils/face of the infant.
c. Ensure the weight of the circuit is gently supported to reduce tension on the CPAP system.

6. EMERGENCY MEASURES

In case of prolonged drop in SpO_2 (< 88%) or heart rate (< 80 bpm) the infant should be stimulated and FiO_2 should be increased. The following steps should be taken:

1. Check if the system is bubbling. If not, there may be a leak in the system. In this case, check if the prongs are in place or need to be repositioned. After that, check again if the system is now bubbling.
2. Important questions: Is there is a significant leak from the mouth? Is the flow on? Are there any chest / abdominal movement (apnea)?
3. Check for nasal or upper airway obstruction due to secretions or positioning of the neck/head. Consider suction of the nares and nasopharyngeal area. If the baby recovers and has good spontaneous effort, place him/her back on bCPAP.
4. If the infant does not improve, call for help, remove the nasal interface, and start bagging using the mask interface. If apnea persists despite mask/bag, discuss with the medical team the possibility of changing to NIPPV or intubation.

7. bCPAP FAILURE

1. **Respiratory Failure**: a) consistent increase (1-2h) in oxygen requirement above 50 % or b) severe respiratory acidosis - PCO_2 above 65 mmHg with a pH < 7.20 in two consecutive blood gases.
2. **Severe apneas**: 1-2 episodes of apnea requiring bag and mask ventilation due to failure to resume spontaneous breathing.
3. **Frequent episodes of apnea and/or bradycardia** (more than 6 episodes in 6 hours). Apnea defined as a respiratory pause longer than 20 seconds, or less than that but associated with desaturation (SpO_2 < 88%) and/or bradycardia (<100 bpm).

Infants who meet one of these criteria may require escalation of respiratory support, defined as either initiation of non-invasive positive pressure ventilation **(**NIPPV) or endotracheal intubation and mechanical ventilation. MD/NNP should be advised immediately if any of the above criteria is present.

NIPPV can be delivered via a ventilator. If the patient is switched to NIPPV with a ventilator the prong interface should still be used.

Table 1. Size of the bonnet.

Bonnet Size	Body Weight	Head Circumference
1	Up to 750 grams	12 – 18 cm
2	650 to 900 grams	15 – 21 cm
3	800 to 1600 grams	18 – 23 cm
4	1500 to 2500 grams	22– 28 cm

Table 2. Nasal Prongs (NP) size chart.

Kit	NP Size	Approximate Body Weight	Kit	NP Size	Approximate Body Weight
Small	0	< 700 grams	Large	4	2000 to 3000 grams
Small	1	< 700 grams	Large	5	> 3000 grams
Small	2	700 to 1250 grams	Large	6	> 3000 grams
Small	3	1250 to 2000 grams	Large	7	> 3000 grams

Table 3. Cannulaide ® seize chart.

Size of Cannulaide®	Body Weight
0	< 700 g
1	700g- 1250 g
2	1250g-2000 g
3	2000g- 3000g
4	> 3000g

8. bCPAP Weaning and discontinuation

Continue on bCPAP system until the infant is at ≥ 32 weeks of GA for possible improvement of lung growth and remodeling. Consider removal of CPAP if all criteria are present:

a. bCPAP of 5 cmH_2O and on room air
b. no episodes of bradycardia (<80 bpm) and desaturations (<88%)
c. no episodes of apnea requiring stimulation
d. no tachypnea (RR > 60 bpm)
e. no respiratory distress (mild or moderate sub-sternal and/or suprasternal retractions)

Remove from bCPAP to room air. Do not use high or low flow nasal canula to wean from bCPAP. If the infant start presenting one of the above criteria within 24h (quick failure) after removal re-start bCPAP at 5 cmH_2O and try again between 72 to 120 hours. If the infant start

presenting one of the above criteria between 24 to168h (late failure) after removal re-start bCPAP at 5 cmH_2O. An infant that remains well for longer periods off bCPAP is almost ready to be removed. Thus, try to remove the bCPAP again within 24-48h.