Changes in Respiratory Management and the Impact on Bronchopulmonary Dysplasia

Jane Chung[1], Anjali Iyengar[2], Laura Santry[3], Eric Swanson[3], Jonathan M Davis[4], and Mary Ann Volpe[2]

[1]UCLA
[2]Tufts Medical Center
[3]Tufts University School of Medicine
[4]The Floating Hospital for Children at Tufts Medical Center

November 2, 2021

Abstract

Objective: Non-invasive respiratory support has reduced the need for mechanical ventilation and surfactant administration in very premature neonates. We sought to determine how the increased use of non-invasive ventilation and less surfactant instillation has impacted the development of bronchopulmonary dysplasia (BPD) and compared BPD outcome applying four currently used definitions. Study Design: This is a retrospective, single center cohort study of neonates born at less than 28 weeks gestation between 2010 and 2018. A respiratory practice change (less surfactant and more non-invasive ventilation) occurred in 2014 following participation in the SUPPORT trial. Therefore, patients were divided into 2 epochs to compare postnatal respiratory and clinical course and BPD outcomes across four currently relevant definitions (VON, NICHD, Canadian, NRN). Results: Clinical and demographic variables were similar between epochs. Despite significant differences in maternal and infant characteristics and clinical course, the incidence of BPD was not significantly different between the 2 epochs regardless of the BPD definition utilized. There was a wide range in the incidence of BPD depending on the definition used. Conclusions: Despite decreased use of invasive mechanical ventilation and surfactant administration between the two epochs, the incidence of BPD did not change and there was wide variation depending on the definition used. A better understanding of the risk factors associated with BPD and a consensus definition is urgently needed in order to facilitate the conduct of clinical trials and the development of novel therapeutic interventions to improve outcome.

Changes in Respiratory Management and the Impact on Bronchopulmonary Dysplasia

Jane Chung, MD[1,2]; Anjali Iyengar, MD[1,2]; Laura Santry, MD[1]; Eric Swanson, MD[1];

Jonathan M. Davis[1,2,], MD; MaryAnn Volpe, MD[1,2]

[1]Pediatrics/Newborn Medicine, Tufts Children's Hospital, [2]Tufts University School of Medicine, Boston, MA

Address for Correspondence:

MaryAnn Volpe, MD

Newborn Medicine

Tufts Medical Center

800 Washington Street, Boston, MA 021111

Tel: 617 636 5000

E-mail: mvolpe1@tuftsmedicalcenter.org

Conflict of Interest: The authors have no conflict of interest and nothing to declare

Keywords: bronchopulmonary dysplasia; prematurity; surfactant; mechanical ventilation

Short running title (<12 words): Clinical Practice Change and BPD

Abstract:

Objective: Non-invasive respiratory support has reduced the need for mechanical ventilation and surfactant administration in very premature neonates. We sought to determine how the increased use of non-invasive ventilation and less surfactant instillation has impacted the development of bronchopulmonary dysplasia (BPD) and compared BPD outcome applying four currently used definitions.

Study Design: This is a retrospective, single center cohort study of neonates born at less than 28 weeks gestation between 2010 and 2018. A respiratory practice change (less surfactant and more non-invasive ventilation) occurred in 2014 following participation in the SUPPORT trial. Therefore, patients were divided into 2 epochs to compare postnatal respiratory and clinical course and BPD outcomes across four currently relevant definitions (VON, NICHD, Canadian, NRN).

Results: Clinical and demographic variables were similar between epochs. Despite significant differences in maternal and infant characteristics and clinical course, the incidence of BPD was not significantly different between the 2 epochs regardless of the BPD definition utilized. There was a wide range in the incidence of BPD depending on the definition used.

Conclusions: Despite decreased use of invasive mechanical ventilation and surfactant administration between the two epochs, the incidence of BPD did not change and there was wide variation depending on the definition used. A better understanding of the risk factors associated with BPD and a consensus definition is urgently needed in order to facilitate the conduct of clinical trials and the development of novel therapeutic interventions to improve outcome.

Introduction:

Bronchopulmonary Dysplasia (BPD) is a complex, multifactorial disease that can lead to significant long-term respiratory morbidity and neurodevelopmental complications [1-3]. BPD is the only complication of neonatal intensive care that is increasing in frequency [4, 5]. A shift in respiratory management using more non-invasive respiratory support immediately after birth (without surfactant instillation) is associated with reduction in the mechanical ventilation [6-8]. However, the advantages of this practice on long-term respiratory outcome has been questioned [9]. Therefore, further investigation is urgently needed to determine the best respiratory care practices for very premature neonates.

While respiratory practice has changed, so has the pathology of BPD, now characterized by decreased alveolar septation and microvascular development [10]. Accordingly, BPD definitions have evolved to capture this changing pulmonary pathology. Oxygen use at 36 weeks post-menstrual age (PMA) is the most widely adopted BPD definition used [11]. The National Institutes of Health (NIH) National Institute of Child Health and Human Development (NICHD) and the National Heart, Lung, and Blood Institute (NHLBI) developed a severity scale definition based on: 1) the need for O_2 for 28 days or more, 2) type of respiratory support, and 3) degree of O_2 dependence at 36 weeks PMA [12]. The Canadian network suggested that evaluating infants at 40 wks PMA may be more predictive of respiratory outcome [13]. The study published by Jensen et al and the NICHD Neonatal Research Network (NRN) proposed to define BPD by focus on the mode of respiratory support and not the need for supplemental oxygen in order to predict respiratory morbidity at 18-26 months of age [14]. Evaluating practice changes in the context of all established definitions allows for comparisons between studies to better inform clinical practice and planning of interventional studies.

Given the concurrent evolution in respiratory care practices and BPD definitions, we sought to examine the impact of less surfactant use and and more non-invasive respiratory support on the incidence and severity of BPD in premature infants born at less than 28 weeks gestation from 2010-2018, using four current definitions of BPD to comprehensively examine how the incidence of BPD has changed over time.

Methods:

Study Population : A retrospective cohort study was conducted examining premature neonates born at less than 28 weeks gestation from 2010-2018 at a single center. The study was approved by the Tufts Health Sciences Institutional Review Board at Tufts Medical Center. In Epoch 1 (2010-2014), the clinical practice in our center had been to routinely intubate these infants in the delivery room and administer early surfactant therapy. Following participation in the SUPPORT trial which demonstrated the benefits of early continuous positive airway pressure (CPAP) instead of surfactant administration in the delivery room [6], respiratory care practice changed and early intubation only occurred with poor respiratory effort or apnea, increased oxygen requirement on CPAP of 5-6cmH_2O, or significant hypercarbia. To more clearly define this practice change, the clinical database was queried for all neonates born at less than 28 0/7 weeks without significant congenital anomalies for each year from 2010-2018. Between 2014 and 2015, a sharp decrease in intubation/surfactant instillation was noted in both the delivery room and in the first 24 hours of life (Table 1). Decision was made to limit subject enrollment to the end of 2018 given that 1) our mode of CPAP delivery had changed from ventilator-derived and VIASYS Infant Flow driver apparatuses to bubble CPAP and 2) Common Rule statutes on retrospective human subject research limited further enrollment. No other significant respiratory practice changes were made during this period, including caffeine use and oxygen saturation targets, nor did we use Vitamin A in our ELBW population. All infants in our center are started on caffeine on admission to NICU immediately after birth. The number of deaths, presence or absence of BPD based on these 4 definitions, and the composite outcome of death or BPD were compared between Epochs 1 and 2.

Maternal, Infant and Postnatal Characteristics : Maternal, neonatal, and postnatal characteristics known to influence the development of BPD were compared between Epochs 1 and 2, including antenatal steroids, mode of delivery, any pregnancy and labor complications, and any postnatal conditions that may have contributed to neonatal illness severity and potential confounders that could influence outcome of BPD [15-18].

BPD Definitions: The presence or absence of BPD was defined by: 1) O_2 use at 36 weeks PMA (VON Definition) [11], 2) NIH consensus severity-based definition [12], 3) the Canadian Neonatal Network criteria of O_2 use at 40 weeks PMA [13], and 4) Jensen-NRN criteria (henceforth referred to as NRN criteria) identifying mode of ventilation irrespective of O_2 use at 36 weeks PMA [14].

Clinical Factors Impacting BPD Severity : Further analyses of pre- and postnatal factors influencing BPD severity were performed comparing those neonates who developed moderate/severe BPD using the NIH severity-based definition in Epoch 1 versus 2. Given the more severe spectrum of clinical disease that these infants possessed, and the knowledge that they would likely have a greater utilization of medical resources and a guarded long-term prognosis, we sought to understand the differences in their hospital course between Epochs 1 and 2.

Statistics: Univariate analyses were performed to examine differences in demographic and clinical variables between epochs and between neonates who did and did not develop BPD. Continuous variables were compared between groups using students two-tailed t-test and categorical variables were compare using chi-square tests. All statistical testing was two-sided with alpha=0.05. A logistic regression model was performed for the composite outcome of BPD (based on VON definition and NIH moderate to severe definition) and death, adjusting for each of the potential confounders as predictors, including chorioamnionitis, mode of delivery, multiple births, sex, inborn/outborn status.

Results:

Study Population : Three hundred seventy-nine neonates born less than 28 weeks gestation were indentified during the 2010-2018 time period for the retrospective review. A sharp decline was detected in the use of intubation and surfactant administration in the delivery room/or at < 24 hrs of age between 2014 and 2015 (Table 1).

Maternal, Infant and Postnatal Characteristics : Table 2 compares maternal and neonatal characteristics between Epoch 1 and Epoch 2. There were significantly fewer mothers with chorioamnionitis, C-sections, multiple gestations, and male infants in Epoch 2 compared to Epoch 1 (Table 2). There were no other differences in gestational age, birth weight, or percentage of out-born neonates between the two epochs. There were no significant differences in rates of PDA, early sepsis, pneumothorax, NEC/SIP, severe IVH, and ROP between the two groups (Table 3). There were more neonates given postnatal steroids in Epoch 2 compared to Epoch 1 (Table 3), but the incidence of postnatal steroid use is low in both Epochs (6% Epoch 1 vs. 17% Epoch 2), with most infants not receiving postnatal steroids in either EPOCH. When postnatal steroids are administered in our center the DART Protocol is followed [19].

BPD Definitions: There were no statistically significant differences in the incidence of death, BPD, or composite outcome of death or BPD between Epochs 1 and 2 regardless of definition utilized (Table 4). Logistic regression model for the composite of BPD and death controlling for potential confounders in Table 2 and 3 showed no significant associations between any of the variables and the outcome of BPD (Table 4). However, BPD incidence varied widely depending on what definition was applied. In Epoch 1, the incidence of BPD was: 1) 32% at 36 weeks PMA; 2) 68% by the NIH severity definition; 3) 16% at 40 week PMA and; 4) 41% using the NRN ventilation definition. This represents a 3-4 fold difference in incidence depending on the applied definition. In Epoch 2, the incidence again ranged from 35%, 58%, 22% and 49%, between the 4 definitions, respectively.

Clinical Factors Impacting BPD Severity: Maternal and neonatal characteristics of infants who developed moderate/severe BPD via the NIH definition in Epochs 1 and 2 were analyzed separately (Tables 5 and 6). Despite significant decreases important co-morbidities such as sepsis and NEC (Table 5) and in early intubation, mechanical ventilation, surfactant administration (Table 6), there were no significant changes in the rates of BPD. Birth weight (Table 5) was higher in Epoch 2 (782 ± 20g) compared to Epoch 1 (752 ± 16g), but the biologic significance of this difference is unclear. Further, all infants in both Epochs received caffeine therapy from birth making our study different than the study by Vliegenthart et al. where differences in delivery room intubation were accompanied by differences in caffeine use and other respiratory stimulants between the Epochs [20].

Discussion:

In this retrospective cohort study, the incidence of BPD was compared before and after a significant clinical practice change of less surfactant administration and less invasive mechanical ventilation using four different definitions of BPD. In contrast to other studies that have either looked at a practice change or assessed differences in BPD incidence based on multiple definitions, our study simultaneously assessed a practice change in the context of all currently available BPD definitions [20-22]. Additionally, this study investigated an isolated practice change of less delivery room intubation and surfactant instillation in two consecutive time periods, in contrast to other studies that have evaluated multiple practice changes in multiple centers over time[20-22]. This makes our research data interpretable and more generalizable in comparison to recently published studies examining similar questions.

Our practice change followed from institutional participation in the SUPPORT trial and the results of other trials where less surfactant was administered within the first 24 hours of life due to increased use of non-invasive ventilation [7, 23]. Prior to 2014, the majority of premature neonates born at less than 28 weeks gestation were intubated and given surfactant in the delivery room or within the first 24 hours of life. More recently, very premature neonates received a trial of non-invasive ventilation with intubation, mechanical ventilation, and surfactant administration reserved for neonates who failed to adequately respond. Despite this change, there was no effect on the incidence of BPD or death, or the composite outcome of death or BPD

across varying definitions. Additionally, we did not find a difference in the incidence and severity of BPD between Epochs 1 and 2 despite fewer males, C-sections, multiple gestations, maternal chorioamnionitis, and less intubation and surfactant administration in Epoch 2, situations and characteristics expected to decrease BPD incidence [15-18, 24-26].

There are likely multiple explanations for the findings. Our population is also notable for high rates of prenatal steroid course, which may have also impacted incidence of BPD in both Epochs. Second, with a limited sample size, genetic predispositions could have accounted for BPD propensity among subjects with twin studies demonstrating that genetic factors may explain up to 80% of the variance in susceptibility to moderate/severe BPD [27]. Also, genome-wide sequencing studies have identified potential variants and novel molecular pathways that are linked to increased risk of developing BPD [28, 29]. Third, while surfactant improves respiratory status in RDS, it has not been shown to impact the incidence of BPD which occurs months after surfactant administration [30]. Fourth, the existence of different BPD phenotypes (e.g. pulmonary hypertension) [27, 31, 32] were not addressed in the current study. Fifth, prior to 2010, we began incorporating the RAM Cannula interface for non-invasive ventilation in the ELGAN population as an alternative when skin breakdown was imminent. Thus, multiple different interfaces (including Fisher & Paykel FlexiTrunk mask and prongs) with varying abilities to deliver pressure were utilized in our unit during the study period. Interestingly, we identified an increased use of postnatal steroid use (DART protocol reference) in Epoch 2. It is important to note that postnatal steroids were administered at more mature post-conceptional ages, so that the same clinical scenarios that drove the diagnosis of BPD likely drove the use of postnatal steroid use (inability to wean ventilator support and oxygen need). As a result, this was determined to be an association in our study and cause-and-effect or lack thereof, could not be discerned. Lastly, examination of moderate/severe BPD in Epochs 1 and 2 illustrate a significant increase in CPAP utilization and decreased mechanical ventilation which may indicate a negative impact of CPAP on lung development. This is consistent findings of Doyle et al who found that neonates receiving non-invasive ventilation for more than 30 days had more airway obstruction when tested at 8 years of age [9]. This study questioned whether less invasive respiratory support is actually beneficial long-term.

Another important finding from our study is demonstrating the wide variability using the four definitions of BPD (Table 4). While inconsistency across definitions is not surprising, it is very concerning because it highlights the lack of specificity among current BPD definitions despite being applied within a single institution. As a result, BPD pharmaceutical development has been hampered, as most clinical trials have shown no impact, most likely due to the outcome measures chosen and not the drug/biologic itself. It also highlights the inability to compare BPD outcomes from different trials or studies that do not use the same BPD definition. Our data supports the currently evolving strategy adopted by researchers, sponsors, and the Food and Drug Administration, which is to assess for direct evidence of chronic respiratory morbidity (e.g. hospital admissions, wheezing/coughing from asthma, use of respiratory medications) at one year corrected age–a more accurate and a clinically meaningful outcome for parents, families, and regulators [36].

While our data are consistent with that of COIN, SUPPORT, and CURPAP randomized trials, our patient population represents a more recent cross-section of patients exposed to the more current respiratory care practices [6, 7, 33]. Additionally, strengths of our study include a large sample size with an abrupt change in practice patterns along with comparisons of outcomes across four current BPD definitions.

A further unique aspect of our population in both Epochs is the large percentage of inborn infants and the ability to follow infants for prolonged periods to use the applications of the different definitions (ie the 40 wk definition). Despite this regionalization and uniformity of care in both Epochs, once again the incidence of BPD remained relatively constant.

In summary, BPD is a clinically meaningful outcome as it potentially designates infants who require closer pulmonary follow-up and because it can impact long-term pulmonary and neurodevelopmental outcomes. However, the wide variability in the incidence of BPD in our data reflects the difficulty with using these definitions to optimally plan postnatal follow-up and there remains no consensus that these current definitions represent the most appropriate clinical or research outcome measure [34] [35]. It is essential to identify

predictive criteria early in postnatal life and standardize a BPD definition to develop the next generation of novel therapies. Identifying appropriate, at-risk infants for researchers and continuing to better understand BPD phenotypes and the pathophysiology of acute and chronic lung injury will ultimately enable clinicians to change the course of prematurity-related respiratory outcomes.

Abbreviations: BPD- Bronchopulmonary Dysplasia, PMA – Postmenstrual Age, VON – Vermont Oxford Network, NIH - National Institutes of Health, NRN - Neonatal Research Network, CPAP - Continuous Positive Airway Pressure, non-invasive positive pressure ventilation.

Acknowledgements: We would like to thank Jamon Foster and Ariel Scalise for assistance with data collection and Samantha Kumarasena and Andrea Clapp with data organization. We would also like to thank Drs. Turcu, Jassar, and Brazauskas for their valuable input during the course of the research and Janis Breeze who assisted with data analysis.

References:

1. Jobe, A.J., *The new BPD: an arrest of lung development.*Pediatr Res, 1999. **46** (6): p. 641-3.

2. Jobe, A.H. and M. Ikegami, *Mechanisms initiating lung injury in the preterm.* Early Hum Dev, 1998. **53** (1): p. 81-94.

3. Jobe, A.H., *Mechanisms of Lung Injury and Bronchopulmonary Dysplasia.* Am J Perinatol, 2016. **33** (11): p. 1076-8.

4. Schmidt, B., et al., *Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms.* JAMA, 2003. **289** (9): p. 1124-9.

5. Stoll, B.J., et al., *Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012.* JAMA, 2015.**314** (10): p. 1039-51.

6. Morley, C.J., et al., *Nasal CPAP or intubation at birth for very preterm infants.* N Engl J Med, 2008. **358** (7): p. 700-8.

7. Network, S.S.G.o.t.E.K.S.N.N.R., et al., *Early CPAP versus surfactant in extremely preterm infants.* N Engl J Med, 2010.**362** (21): p. 1970-9.

8. Flannery, D.D., et al., *Continuous Positive Airway Pressure versus Mechanical Ventilation on the First Day of Life in Very Low-Birth-Weight Infants.* Am J Perinatol, 2016. **33** (10): p. 939-44.

9. Doyle, L.W., et al., *Ventilation in Extremely Preterm Infants and Respiratory Function at 8 Years.* N Engl J Med, 2017.**377** (4): p. 329-337.

10. Bancalari, E. and D. Jain, *Bronchopulmonary Dysplasia: Can We Agree on a Definition?* Am J Perinatol, 2018. **35** (6): p. 537-540.

11. Shennan, A.T., et al., *Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period.* Pediatrics, 1988. **82** (4): p. 527-32.

12. Jobe, A.H. and E. Bancalari, *Bronchopulmonary dysplasia.* Am J Respir Crit Care Med, 2001. **163** (7): p. 1723-9.

13. Isayama, T., et al., *Revisiting the Definition of Bronchopulmonary Dysplasia: Effect of Changing Panoply of Respiratory Support for Preterm Neonates.* JAMA Pediatr, 2017. **171** (3): p. 271-279.

14. Jensen, E.A., et al., *The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach.* Am J Respir Crit Care Med, 2019. **200** (6): p. 751-759.

15. Ballard, A.R., et al., *Chorioamnionitis and subsequent bronchopulmonary dysplasia in very-low-birth weight infants: a 25-year cohort.* J Perinatol, 2016. **36** (12): p. 1045-1048.

16. Jensen, E.A. and B. Schmidt, *Epidemiology of bronchopulmonary dysplasia.* Birth Defects Res A Clin Mol Teratol, 2014. **100** (3): p. 145-57.

17. Trembath, A. and M.M. Laughon, *Predictors of bronchopulmonary dysplasia.* Clin Perinatol, 2012. **39** (3): p. 585-601.

18. Du, Z., et al., *Relevance of clinical features in the prognosis of bronchopulmonary dysplasia in premature infants.* Exp Ther Med, 2017. **14** (4): p. 3433-3440.

19. Doyle, L.W., et al., *Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial.* Pediatrics, 2006. **117** (1): p. 75-83.

20. Vliegenthart, R.J.S., et al., *Restricted Ventilation Associated with Reduced Neurodevelopmental Impairment in Preterm Infants.* Neonatology, 2017. **112** (2): p. 172-179.

21. Gagliardi, L., et al., *Do differences in delivery room intubation explain different rates of bronchopulmonary dysplasia between hospitals?* Arch Dis Child Fetal Neonatal Ed, 2011. **96** (1): p. F30-5.

22. Kim, F., et al., *Revisiting the definition of bronchopulmonary dysplasia in premature infants at a single center quaternary neonatal intensive care unit.* J Perinatol, 2021. **41** (4): p. 756-763.

23. Bhandari, V., *The potential of non-invasive ventilation to decrease BPD.* Semin Perinatol, 2013. **37** (2): p. 108-14.

24. Watterberg, K.L., et al., *Chorioamnionitis and early lung inflammation in infants in whom bronchopulmonary dysplasia develops.*Pediatrics, 1996. **97** (2): p. 210-5.

25. De Felice, C., et al., *Histologic chorioamnionitis and severity of illness in very low birth weight newborns.* Pediatr Crit Care Med, 2005. **6** (3): p. 298-302.

26. Hartling, L., Y. Liang, and T. Lacaze-Masmonteil,*Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: a systematic review and meta-analysis.* Arch Dis Child Fetal Neonatal Ed, 2012. **97** (1): p. F8-F17.

27. Lavoie, P.M., C. Pham, and K.L. Jang, *Heritability of bronchopulmonary dysplasia, defined according to the consensus statement of the national institutes of health.* Pediatrics, 2008.**122** (3): p. 479-85.

28. Carrera, P., et al., *Exome sequencing and pathway analysis for identification of genetic variability relevant for bronchopulmonary dysplasia (BPD) in preterm newborns: A pilot study.* Clin Chim Acta, 2015. **451** (Pt A): p. 39-45.

29. Ambalavanan, N., et al., *Integrated genomic analyses in bronchopulmonary dysplasia.* J Pediatr, 2015. **166** (3): p. 531-7 e13.

30. Bancalari, E. and T. del Moral, *Bronchopulmonary dysplasia and surfactant.* Biol Neonate, 2001. **80 Suppl 1** : p. 7-13.

31. Li, J., et al., *Exome Sequencing of Neonatal Blood Spots and the Identification of Genes Implicated in Bronchopulmonary Dysplasia.*Am J Respir Crit Care Med, 2015. **192** (5): p. 589-96.

32. Bhandari, V., et al., *Familial and genetic susceptibility to major neonatal morbidities in preterm twins.* Pediatrics, 2006.**117** (6): p. 1901-6.

33. Sandri, F., et al., *The CURPAP study: an international randomized controlled trial to evaluate the efficacy of combining prophylactic surfactant and early nasal continuous positive airway pressure in very preterm infants.* Neonatology, 2008. **94** (1): p. 60-2.

34. Steinhorn, R., et al., *Chronic Pulmonary Insufficiency of Prematurity: Developing Optimal Endpoints for Drug Development.* J Pediatr, 2017. **191** : p. 15-21 e1.

35. Higgins, R.D., et al., *Bronchopulmonary Dysplasia: Executive Summary of a Workshop.* J Pediatr, 2018. **197** : p. 300-308.

Hosted file

Jane Chung Tables BPD.docx available at https://authorea.com/users/444127/articles/543936-changes-in-respiratory-management-and-the-impact-on-bronchopulmonary-dysplasia