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Duration of Noninvasive Respiratory Support and Risk for Bronchopulmonary Dysplasia or Death

Samuel J Gentle, MD[1], **Benjamin Carper, MS**[2], **Matthew M Laughon, MD**[3], **Erik A Jensen, MD**[4], **Austin Williams, PhD**[2], **Colm P Travers, MD**[1], **Namasivayam Ambalavanan, MD**[1], **Charitharth V Lal, MD**[1], **Waldemar A Carlo, MD**[1], **NICHD Neonatal Research Network**

[1]Department of Pediatrics, The University of Alabama at Birmingham

[2]Statistics and Epidemiology Unit, RTI International

[3]Department of Pediatrics, University of North Carolina

[4]Department of Pediatrics, Children's Hospital of Philadelphia

Abstract

Objective: To determine whether the duration of noninvasive respiratory support exposure is associated with bronchopulmonary dysplasia (BPD) or death in preterm infants.

Methods: Multicenter, retrospective study of infants born at <29 weeks' gestation. The association between days on noninvasive respiratory support and BPD or death was determined using instrumental variable techniques and generalized propensity score matching to account for potential confounding by illness severity.

Results: Among 6,268 infants 36% developed BPD or died. The median duration of noninvasive respiratory support was 18 days. There was inconsistency in the association between noninvasive support and BPD or death when analyzed by instrumental variable techniques (Average Marginal

Address correspondence to: Samuel Gentle, Department of Pediatrics, The University of Alabama at Birmingham, 1700 6th Ave S., Birmingham, AL 35233, sjgentle@uabmc.edu, Office: 205-934-6450, Fax: 205-934-3100.

Contributors' Statement Page

Samuel J. Gentle conceptualized and implemented this study, performed initial analyses, drafted the manuscript, and reviewed and revised the manuscript.

Benjamin Carper conceptualized the study, conducted the statistical analyses, and reviewed and revised the manuscript.

Matthew M Laughon assisted with analyses, conceptualization of the study, and reviewed and revised the manuscript.

Erik A Jensen assisted with analyses, conceptualization of the study, and reviewed and revised the manuscript.

Austin Williams conducted the statistical analyses, assisted with analyses, conceptualization of the study, and reviewed and revised the manuscript.

Colm P Travers assisted with analyses, conceptualization of the study, and reviewed and revised the manuscript.

Namasivayam Ambalavanan assisted with analyses, conceptualization of the study, and reviewed and revised the manuscript.

Charitharth V Lal assisted with analyses, conceptualization of the study, and reviewed and revised the manuscript.

Waldemar A. Carlo assisted with analyses, conceptualization of the study, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Effect −0.37; 95% CI −1.23 to 0.50) and generalized propensity score matching (Average Marginal Effect 0.46; 95% CI 0.33 to 0.60).

Conclusion: Findings on the association between duration of exposure to noninvasive respiratory support and the development of BPD or death were inconclusive.

INTRODUCTION

Noninvasive respiratory support, including nasal intermittent positive pressure ventilation and continuous positive airway pressure, is an alternative, initial support mode to mechanical ventilation for preterm infants with respiratory distress syndrome (RDS).[1, 2] While noninvasive respiratory support maintains functional residual capacity thereby promoting gas exchange,[3] it increases the risk of complications including air leak syndromes (when compared to mechanical ventilation alone at higher positive end expiratory pressures[2, 4] or less invasive techniques of surfactant administration[5]) and nasal septum injury.[6] Therefore, subsequent to improvement in RDS symptoms, the duration of noninvasive respiratory support exposure must balance the benefits and risks of therapy. Furthermore, it is uncertain whether prolonging exposure improves pulmonary outcomes in preterm infants.

As mechanical strain may improve postnatal lung growth,[7] it has been hypothesized that noninvasive respiratory support exposure may improve pulmonary function. In a randomized controlled trial (N=44) in which preterm infants with RDS were exposed to two additional weeks of continuous positive airway pressure (CPAP) or room air, infants exposed to prolonged CPAP had increased functional residual capacity at study completion.[8] In contrast, in a randomized controlled trial comparing gradual to immediate weaning from CPAP, infants weaned immediately from CPAP to room air had less total CPAP exposure and lower rates of bronchopulmonary dysplasia (BPD) compared to those infants gradually weaned off CPAP.[9] Other studies of rapid weaning from CPAP also indicate better or no difference in outcomes.[10] Therefore, the duration of noninvasive respiratory support needed to improve pulmonary outcomes in preterm infants with RDS is unclear. We hypothesized that in preterm infants < 29 weeks' gestation alive and on noninvasive respiratory support at seven days after birth, duration of noninvasive respiratory support would be associated with a lower incidence of BPD or death after adjustment for confounding by illness severity.

METHODS

Study Design and Patient Population

This was a secondary analysis of prospectively collected data from the NICHD Neonatal Research Network (NRN) Generic Database for infants born between April 1, 2011 and December 31, 2018. Approval was obtained by each institutions' review board. Included infants were < 29 weeks' gestational age and on noninvasive respiratory support on postnatal day seven defined as either nasal cannula, oxyhood, CPAP, or nasal intermittent positive pressure ventilation documented as the highest mode of support. Given that mechanical ventilation exposure is common, occurring in 67.1% of infants in the SUPPORT Trial randomized to CPAP,[1] postnatal day seven was chosen to maintain generalizability of study outcomes while constraining the impact of mechanical ventilation exposure days on study

outcomes. If on postnatal day seven infants were exposed to conventional or high-frequency ventilation, off respiratory support, or had died, infants were excluded. Infants exposed to conventional or high-frequency ventilation within the first postnatal seven days were included if on noninvasive respiratory support at postnatal day seven.

Outcome Definitions

The primary outcome was BPD or death by 36 weeks' postmenstrual age. BPD was defined as moderate or severe BPD at 36 weeks' postmenstrual age as treatment with supplemental oxygen or respiratory support.[11] Death was defined as death prior to 36 weeks' postmenstrual age. Other outcomes included BPD alone, death alone, growth failure, and postmenstrual age at discharge. Growth failure was defined as weight less than 10th percentile at 36 weeks' postmenstrual age using sex-specific growth curves as previously described.[12]

Exposure Classifications

For the primary outcome, the rates of BPD or death were analyzed using days of noninvasive respiratory support exposure as a continuous variable, excluding days within the first postnatal week. The risks for adverse outcomes were analyzed using discrete groups for the duration of exposure to noninvasive respiratory support (e.g. 1–7 days) in order to assess differences in baseline characteristics. Discrete exposure durations may also provide clinical applicability and further examine whether specific durations of exposure were associated with lower rates of BPD or death. Exposure was additionally grouped by discrete percentages of hospital days on noninvasive respiratory support (e.g. 0–10%) to account for early death (as infants with early death would have fewer days on noninvasive respiratory support but a higher percentage of hospital days on noninvasive respiratory support). The rate of BPD alone was also analyzed by days of noninvasive respiratory support, whereas death alone was analyzed by percentage of hospitals days of exposure to account for infants with early death.

Instrumental Variable Analysis and Propensity Score Matching

We examined the association between noninvasive respiratory support exposure and study outcomes using two analytical techniques to account for measured and unmeasured confounders: instrumental variable analysis and propensity score matching. Instrumental variables analysis was used to analyze whether the duration of exposure to noninvasive respiratory support may be related to center specific practices rather than disease severity as has previously been reported in clinician surveys.[13] For example, noninvasive respiratory support may be continued for a predefined period of time (e.g. until 32 weeks postmenstrual age)[14] irrespective of disease severity or support may be discontinued upon meeting stability criteria used in randomized trials.[10] We defined the instrument as the average days on noninvasive respiratory support at the patient's study center to predict the patient's support days. We expected average number of support days to vary by study center and indicate differences in physician practices, but not be related to individual patient outcomes other than through its influence on support days, conditional on other covariates. Therefore, the instrumental variables technique allows isolation of variation in the treatment variable unlikely to be related to unobserved confounders. Outcomes were reported as an odds ratio

or marginal effects (the change in probability of the outcome with a one-unit change in the treatment) such as the effect of one additional day of support on the outcome of BPD. A negative marginal effect indicates an inverse relationship (i.e. an additional exposure duration is associated with a decrease in the probability of developing the outcome).

We used generalized propensity score matching to explore whether certain exposure durations may have non-linear associations with BPD or death, BPD alone, or death alone. Analogous to traditional propensity score methods, generalized propensity score matching adjusts for confounding caused by differences in the distribution of covariates across treated and untreated patients, or between treated patients at different treatment doses. We matched on the following variables: gestational age, birth weight, sex, race, chorioamnionitis, length of hospital stay, total days of mechanical ventilation, highest FiO_2 on postnatal day seven, medical or surgical treatment for a PDA, postnatal steroids for BPD, early onset sepsis, late onset sepsis, and study year. As the postnatal timing of certain covariates may have preceded noninvasive respiratory support exposure, a sensitivity analysis was conducted excluding PDA, length of stay, and late onset sepsis.

These analyses were reported both as an average marginal effect and the marginal effect at the mean treatment. The average marginal effect estimates on average how an infants' risk for BPD or death changes with an increase in the percentage of hospital days an infant is exposed to noninvasive respiratory support. The marginal effect at the mean estimates the change in probability of BPD or death from an additional unit (percentage, day) increase in noninvasive respiratory support when starting at the *mean* level of noninvasive respiratory support in the sample. These effects differ because of the non-linear relationship between the treatment and outcome. For example, increasing from 0% to 10% of days on noninvasive respiratory support may have a different impact on the risk of BPD or death than an increase from 50% to 60% of days on noninvasive respiratory support. We used generalized propensity score matching to then estimate dose response curves demonstrating the rates of BPD alone or death alone associated with the percentage of days on noninvasive respiratory support.

Power Calculation

For power estimates, we estimated that 85–90% of infants from the study period (n=14,830) would be alive at postnatal day seven of which ~50% of infants would not be on mechanical ventilation. These estimates were based on historical data from the NRN Generic Database and data from the SUPPORT trial wherein 49% of infants randomized to intubation/surfactant and 55% of infants randomized to CPAP were alive and off mechanical ventilation at seven days.[1] By using noninvasive respiratory support exposure days as a continuous variable, a baseline likelihood of developing BPD or death of 36% in this cohort, and using an alpha value of 0.05, we estimated that this analysis will have >0.80 power to detect a 10% difference in the outcome of BPD or death corresponding to one standard deviation increase in noninvasive respiratory support exposure days.

RESULTS

Patient Population

14,830 infants were born during the study period of which 12,618 were alive seven days after birth. After exclusion of infants on mechanical ventilation (n=5,579) or no support (n=703), 6,268 were analyzed for the primary outcome of BPD or death. Most infants were on either nasal ventilation or CPAP at postnatal day seven (80%; 5,033/6,628) (Supplemental Figure 1). Baseline and clinical characteristics that differed between exposure groups included gestational age, birth weight, nonwhite race, chorioamnionitis, PDA treatment, and sepsis (Table 1). These and other baseline characteristics that differed between exposure groups subsequently used in propensity score matching included highest FiO2 on Day 7, postnatal steroid exposure, length of stay, and birth year (Supplemental Table 1).

Instrumental Variable Analysis and Propensity Score Matching

Using instrumental variable analysis, there was no significant association between the percentage of hospital days on noninvasive support and the outcomes of BPD or death, BPD alone, and death alone (Table 2). The instrumental variables method utilized differences in practices across centers to identify the impact of the duration of noninvasive respiratory support exposure on study outcomes. Limited inter-center variation in the duration of noninvasive respiratory support decreases the power of the estimator and may contribute to the insignificant findings. This suggests that variation in center specific practices alone is insufficient in identifying the impact of the duration of noninvasive support exposure on outcomes.

For the generalized propensity score matching analysis, balancing was assessed at 5 different levels (quintiles) of the treatment variable. Across the quintiles, we were able to achieve balance for most of the covariates, but significant differences remained for gestational age, birthweight, postnatal steroids, late onset sepsis, and length of hospital stay within more than one quintile of the treatment variable (Supplemental Table 1). Results from the generalized propensity score analysis were significant for the composite outcome of BPD or death (average marginal effect 0.46; 95% CI 0.33 – 0.60), BPD alone (average marginal effect 0.17; 95% CI 0.02 to 0.36), and death alone (average marginal effect 0.89; 95% CI 0.78 to 0.99). On average the probability of BPD or death for an infant on noninvasive respiratory support is 0.46% higher with every increased percentage of the hospitalization an infant is exposed to noninvasive respiratory support (as a positive average marginal effect indicates an increase in the probability of an outcome).

In assessing the marginal effect at the mean, there was a small but significantly increased risk of BPD or death at the mean treatment duration of 24% of the hospitalization or 18 days of exposure (marginal effect at the mean treatment 0.32; 95% CI 0.19 to 0.44). This increased risk means that at this time point in the hospitalization for two otherwise similar infants (having adjusted for other variables in the model), an infant exposed to noninvasive respiratory support has an increased risk for BPD or death compared to an infant not exposed to noninvasive respiratory support. For death alone, there was a decrease

in risk associated with more exposure to noninvasive respiratory support (marginal effect at the mean treatment −0.03; 95% CI −0.04 to −0.02). The association between noninvasive respiratory support exposure and adverse outcomes remained similar when the covariates of PDA, length of stay, and late onset sepsis were excluded (Supplemental Table 2).

Exposure Subgroups

Outcomes were further analyzed by discrete subgroups (e.g. 1–7 days, 0–10% of the hospitalization) of noninvasive respiratory support exposure (Tables 3 and 4). For analyses by exposure days, the rate of BPD or death differed by the number of weeks of noninvasive respiratory support exposure ($p<0.0001$) with an overall increase in risk for the study outcomes with additional weeks of support ranging from 28% (41/149) risk at >0–1 days of exposure to 58% (733/1262) risk at ≥ 35 days of exposure. Similar trends were observed when analyzed by percentage of hospital days, with lower percentages of hospital days of exposure associated with lower rates of BPD or death ($p<0.0001$) (Table 4). A lower postmenstrual age at discharge was associated with shorter durations of support exposure ranging from 37.6 weeks' postmenstrual age with >0–1 days of exposure to 40.6 weeks' postmenstrual age with exposure >35 days ($p<0.0001$). The rate of growth failure did not differ when analyzed by exposure days, but differed when analyzed by percentage of hospital days of exposure, with shorter exposures being associated with higher rates of growth failure (Table 3 and 4).

In assessing whether the risk of these outcomes differed based on specific durations of noninvasive respiratory support exposure (e.g. whether there was a dose response), for BPD alone, there was a linear increase in the risk for BPD at treatment levels of <50% of infants' hospitalization with less association at higher exposure levels (Figure 1, Panel B). For death alone, there was no association between low levels of noninvasive respiratory support (<50% of infants' hospitalization) and death, while exposure to longer durations of noninvasive respiratory support (>50% of infants' hospitalization) was associated with a higher probability of death though with wider confidence bounds (Figure 1, Panel A).

DISCUSSION

This observational study of extremely preterm infants with RDS on noninvasive respiratory support exposure on postnatal day seven, examined the association between noninvasive respiratory support exposure and the risk for BPD or death. Infants exposed to a longer duration of noninvasive respiratory support were born at lower gestational ages and birth weights and had higher rates of other co-morbid conditions including sepsis and PDA treatment. Results from instrumental variable analysis and propensity score matching used to adjust for disease severity by exposure duration were inconclusive when relating BPD or death to the duration of noninvasive respiratory support exposure. Noninvasive respiratory support exposure duration may be inextricably linked to disease severity and subsequent BPD development.

Meta-analyses of randomized controlled trials comparing CPAP to mechanical ventilation with or without surfactant delivery report a reduction in the outcome of BPD at 36 weeks' gestation and the composite of BPD or death in infants randomized to CPAP.[2] Upon

improvement of RDS signs and symptoms, noninvasive respiratory support is reduced or removed. However, the optimal duration and timing of CPAP discontinuation is unclear.[13] Meta-analyses of randomized controlled trials comparing strategies of CPAP discontinuation suggest that immediate removal of CPAP compared with gradual weaning or cycling results in a shorter duration of CPAP exposure and hospital stay but did not report risk for BPD.[10] In a multicenter randomized controlled trial of infants born at <30 weeks' gestation (N=177), infants were weaned off CPAP by either immediate wean to room air or cycling between CPAP and room air or nasal cannula. Infants weaned from CPAP to room air were exposed to fewer days on CPAP compared to other groups and had a lower rate of BPD (12.5%) when compared to infants cycled from CPAP to room air (42%) and cycled from CPAP to nasal cannula (19%; p=0.011). Infants cycled off of CPAP also had a longer length of stay compared to infants weaned to room air.[9] In another multicenter randomized controlled trial of infant <32 weeks' gestation (N=372) comparing sudden weaning from CPAP to room air to gradual pressure weaning prior to CPAP discontinuation, outcomes did not differ between groups including the days of CPAP exposure following randomization, risk for BPD development, weight gain, and the postmenstrual age at discharge.[15] A trial in infants 26 to 32 weeks' gestation (N=70) on CPAP with an FiO2 of 0.21 and a PEEP of 5 cm H_20 weaned infants either suddenly (immediately to room air) or gradually (by further weaning the PEEP by 1 cm H_20 every 8 hours) and did not find a difference in risk for BPD between groups.[16] Therefore, randomized controlled trials regarding weaning preterm infants from CPAP have either shown no benefit from prolonging CPAP through gradual compared to sudden weaning or have shown an increased risk for BPD.

In the present study, the association between duration of noninvasive respiratory support and risk for adverse outcomes varied between and within prediction models. Within propensity score matching analyses, the direction of the association between the duration of noninvasive respiratory support exposure and death was not consistent. Higher percentages of hospital days on noninvasive respiratory support were associated with higher rates of death when analyzed by average marginal effect but lower rates of death when analyzed by the marginal effect at the mean. Given that low exposure rates (<50% of infants' hospital days) were not associated with death, it is likely that this results from early death precluding further noninvasive respiratory support exposure. Regarding the dose response of percentage of hospital days on noninvasive respiratory support and BPD, a higher percentage of days on noninvasive respiratory support was associated with lower rates of BPD due to a higher probability of death in these infants as well as wide lower and upper bounds from fewer patients available for analysis.

The time at which infants in this cohort exposed to longer durations of noninvasive respiratory support met prespecified weaning criteria detailed by these randomized controlled trials remains unclear. However, in looking at subgroup analyses, the median highest FiO_2 at day seven after birth was 0.21 across five of the seven groups (>0–1, 1–7, 7–14, 14–21, and 21–28 day groups) suggesting that up to half of these infants may have met weaning criteria prior to being weaned from noninvasive respiratory support. As outcomes were analyzed by cumulative duration and not courses of noninvasive respiratory support, it is also unclear whether attempts were made to wean infants from noninvasive respiratory support and, in such infants, what criteria were used to restart noninvasive

respiratory support. Furthermore, longer exposure of noninvasive respiratory support may have been secondary to clinical indication given differences in baseline characteristics and co-morbidities across exposure groups as propensity score matching and instrumental variable analysis results were inconclusive.

Several studies have analyzed the relationship between respiratory support and outcomes in preterm infants. Mechanical ventilation has been associated with a higher risk of pulmonary morbidity in preterm infants. In a retrospective cohort study of infants born at <1000 g (N=3343), more courses of invasive ventilation were associated with an increased risk for BPD. Additionally, the number of days on mechanical ventilation also was associated with a higher risk for BPD.[17] A retrospective study in preterm infants <1000 g (N=3026) including infants prior to the SUPPORT trial compared rates of BPD or death based on exposure to HFNC, CPAP, or both modes of respiratory support. Infants exposed to HFNC had a higher rate of BPD or death compared to infants receiving CPAP.[18] A cohort study from the NRN from 2006 to 2010 in infants born at <27 weeks' gestation (N=3651) analyzed the rate of death or neurodevelopmental impairment based on respiratory support exposure. Exposure to any respiratory support for more than 60 days was associated with a higher risk for death or neurodevelopmental impairment.[19]

In contrast to trials of methods of weaning off noninvasive respiratory support, the results of a recent trial suggest that prolonging CPAP exposure may result in pulmonary benefits.[8] In this randomized controlled trial of infants <32 weeks' gestation requiring >24 hours of CPAP for respiratory distress (N=44), infants meeting stability criteria were randomized to 2 weeks of CPAP versus room air. At the end of the 2-week period and at discharge, infants randomized to prolonged CPAP had a higher functional residual capacity than those infants randomized to room air. While this trial was not powered to compare differences in rates of BPD between groups, these data suggest that prolonged CPAP may provide respiratory benefits to preterm infants. Such randomization of preterm infants meeting similar stability criteria precludes noninvasive respiratory support duration from being confounded by disease severity, which is a limitation of the present study.

The strengths of this study include a large patient population across multiple centers and a prospectively collected database. Given the differences in baseline characteristics, statistical efforts were made to adjust for disease severity as a confounder for prolonged noninvasive respiratory support duration including propensity score matching and instrumental variable analysis. In these analyses differences in the outcome of BPD or death were not significant. The primary limitation of this study is its observational approach and despite matching efforts to control for disease severity, there may have been an insufficient number of comparison infants at different durations of noninvasive respiratory support exposure. Although most control variables were well-balanced in the matching analysis, some statistically significant differences remained, and we were not able to perfectly adjust for all potential confounders. In addition, exclusion of 5,579 infants on mechanical ventilation on postnatal day seven limits generalizability to a population at higher risk for BPD.[20]

In summary, across the models analyzed in this observational study, duration of noninvasive respiratory support had no conclusive association with BPD or death and

BPD alone among preterm infants on noninvasive respiratory support on postnatal day seven. Large, multi-center randomized controlled trials that address different durations of noninvasive respiratory support exposure could be conducted to determine whether extending noninvasive respiratory support exposure reduces adverse outcomes among preterm infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Participating NRN sites collected data and transmitted it to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, RTI International had full access to all of the data in the study, and with the NRN Center Principal Investigators, takes responsibility for the integrity of the data and accuracy of the data analysis.

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NRN Steering Committee Chair: Richard A. Polin, MD, Division of Neonatology, College of Physicians and Surgeons, Columbia University, (2011-present).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) - Abbot R. Laptook, MD; Martin Keszler, MD; Angelita M. Hensman, PhD RNC-NIC; Elisa Vieira, RN BSN; Emilee Little, RN BSN; Lucille St. Pierre, BS.

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364) - Michele C. Walsh, MD MS; Anna Maria Hibbs, MD MSCE; Nancy S. Newman, BA RN.

Children's Mercy Hospital, University of Missouri Kansas City School of Medicine, and Kansas University Medical Center (U10 HD68284) - William E. Truog, MD; Eugenia K. Pallotto, MD MSCE; Howard W. Kilbride, MD; Cheri Gauldin, RN BS CCRC; Anne Holmes, RN MSN MBA-HCM CCRC; Kathy Johnson, RN CCRC; Prabhu S. Parimi, MD; Lisa Gaetano, RN MSN.

Cincinnati Children's Hospital Medical Center, University Hospital, and Good Samaritan Hospital (U10 HD27853, UL1 TR1425) - Brenda B. Poindexter, MD MS; Kurt Schibler, MD; Stephanie L. Merhar, MD MS; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Kristin Kirker, CRC.

Duke University School of Medicine, University Hospital, University of North Carolina, Duke Regional Hospital, and WakeMed Health & Hospitals (UG1 HD40492, UL1 TR1117, UL1 TR1111) - C. Michael Cotten, MD MHS; Ronald N. Goldberg, MD; Joanne Finkle, RN JD; Kimberley A. Fisher, PhD FNP-BC IBCLC; Carl L. Bose, MD; Janice Bernhardt, MS RN; Gennie Bose, RN; Cindy Clark, RN; Stephen D. Kicklighter, MD; Ginger Rhodes-Ryan, ARNP MSN NNP-BC; Donna White, BSN RN-BC.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, UL1 TR454) - David P. Carlton, MD; Barbara J. Stoll, MD; Ravi M. Patel, MD; Yvonne Loggins, RN; Ellen C. Hale, RN BS CCRC; Diane I. Bottcher, RN MSN; Colleen Mackie, BS RT.

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Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, UL1 TR1108) - Gregory M. Sokol, MD; Dianne E. Herron, RN CCRC; Jeff Joyce, CCRC.

McGovern Medical School at The University of Texas Health Science Center at Houston, Children's Memorial Hermann Hospital, Memorial Hermann Southwest Hospital - Jon E. Tyson, MD MPH; Amir M. Khan, MD; Kathleen A. Kennedy, MD MPH; Elizabeth Eason, MD; Emily K. Stephens, BSN RNC-NIC; Georgia E. McDavid, RN; Julie Arldt-McAlister, RN BSN; Katrina Burson, RN BSN; Carmen Garcia, RN CCRP; Donna Hall, RN; Karen Martin, RN; Sara C. Martin, RN BSN; Shawna Rodgers, RN BSN; Patti L. Pierce Tate, RCP; Sharon L. Wright, MT (ASCP)

Nationwide Children's Hospital, Abigail Wexner Research Institute at Nationwide Children's Hospital, Center for Perinatal Research, The Ohio State University College of Medicine, The Ohio State University Wexner Medical Center, Riverside Methodist Hospital (U10 HD68278) - Pablo J. Sánchez, MD; Leif D. Nelin, MD; Sudarshan R. Jadcherla, MD; Patricia Luzader, RN; Erna Clark, BA; Christine A. Fortney, PhD RN; Julie Gutentag, RN; Courtney Park, RN; Julie C. Shadd, BSN RD; Melanie Stein, RRT BBA; Jennifer L. Grothause, RN BSN; Hallie Baugher, BS MSN; Lina Yosseff-Salameh, MD; Jacqueline McCool.

RTI International (U10 HD36790) - Abhik Das, PhD; Marie G. Gantz, PhD; Carla M. Bann, PhD; Dennis Wallace, PhD; Margaret Crawford, BS; Jenna Gabrio, MPH CCRP; David Leblond, BS; Jeanette O'Donnell Auman, BS; Carolyn M. Petrie Huitema, MS; Kristin M. Zaterka-Baxter, RN BSN CCRP.

Stanford University and Lucile Packard Children's Hospital (U10 HD27880, UL1 TR1085) - Krisa P. Van Meurs, MD; Valerie Y. Chock, MD MS Epi; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Melinda S. Proud, RCP; Elizabeth N. Reichert, MA CCRC, R. Jordan Williams, BA.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216) - Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN; Tara McNair, RN BSN; Meredith Estes, RN BSN; Kelli Hagood, RN BSN.

University of California - Los Angeles, Mattel Children's Hospital, Santa Monica Hospital, Los Robles Hospital and Medical Center, and Olive View Medical Center (U10 HD68270) - Uday Devaskar, MD; Meena Garg, MD; Teresa Chanlaw, MPH; Rachel Geller, RN BSN.

University of Iowa, Mercy Medical Center, and Sanford Health (UG1 HD53109, M01 RR59, UL1 TR442) - Edward F. Bell, MD; Tarah T. Colaizy, MD MPH; Michelle L. Baack, MD; Dan L. Ellsbury, MD; Jane E. Brumbaugh, MD; Karen J. Johnson, RN BSN; Megan M. Henning, RN; Chelsey Elenkiwich, RN BSN; Claire A. Goeke, RN; Megan Broadbent, RN BSN; Laurie A. Hogden, MD; Jonathan M. Klein, MD; John M. Dagle, MD PhD; Mendi L. Schmelzel, RN MSN; Jacky R. Walker, RN; Donia B. Bass, RNC-NIC; Tracy L. Tud, RN.

University of New Mexico Health Sciences Center (U10 HD53089, UL1 TR1449) - Kristi L. Watterberg, MD; Janell Fuller, MD; Robin K. Ohls, MD; Conra Backstrom Lacy, RN; Sandra Sundquist Beauman, MSN RNC-NIC; Carol Hartenberger, RN MPH; Mary Hanson, RN BSN; Elizabeth Kuan, RN BSN.

University of Pennsylvania, Hospital of the University of Pennsylvania, Pennsylvania Hospital, and Children's Hospital of Philadelphia (U10 HD68244) - Eric C. Eichenwald, MD; Barbara Schmidt, MD MSc; Haresh Kirpalani, MB MSc; Sara B. DeMauro, MD MSCE; Soraya Abbasi, MD; Christine Catts, CRNP; Aasma S. Chaudhary, BS RRT; Sarvin Ghavam, MD; Toni Mancini, RN BSN CCRC; Jonathan Snyder, RN BSN.

University of Rochester Medical Center, Golisano Children's Hospital, and the University of Buffalo Women's and Children's Hospital of Buffalo (U10 HD68263, UL1 TR42) - Carl T. D'Angio, MD; Ronnie Guillet, MD PhD; Anne Marie Reynolds, MD MPH; Satyan Lakshminrusimha, MD; Alison Kent, MD; Kyle Binion, BS; Melissa Bowman, RN NP; Jennifer Donato, BS; Stephanie Guilford, BS; Julianne Hunn, BS; Rosemary L. Jensen; Emily Li, BA; Deanna Maffett, RN; Constance Orme; Diane Prinzing, AAS; Linda Reubens, RN CCRC; Daisy Rochez, BS MHA; Mary Rowan, RN; Premini Sabaratnam, MPH; Michael Sacilowski, MAT CCRC; Ann Marie Scorsone, MS CCRC; Holly I.M. Wadkins, MA; Ashley Williams, MSEd; Karen Wynn, RN; Rachel Jones.

University of Texas Southwestern Medical Center, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689) - Myra Wyckoff, MD; Pablo J. Sánchez, MD; Luc P. Brion, MD; Diana M. Vasil, MSN BSN RNC-NIC; Lijun Chen, PhD RN; Maria M. DeLeon, RN BSN; Frances Eubanks, RN BSN; Lara Pavageau, MD; Pollieanna Sepulveda, RN.

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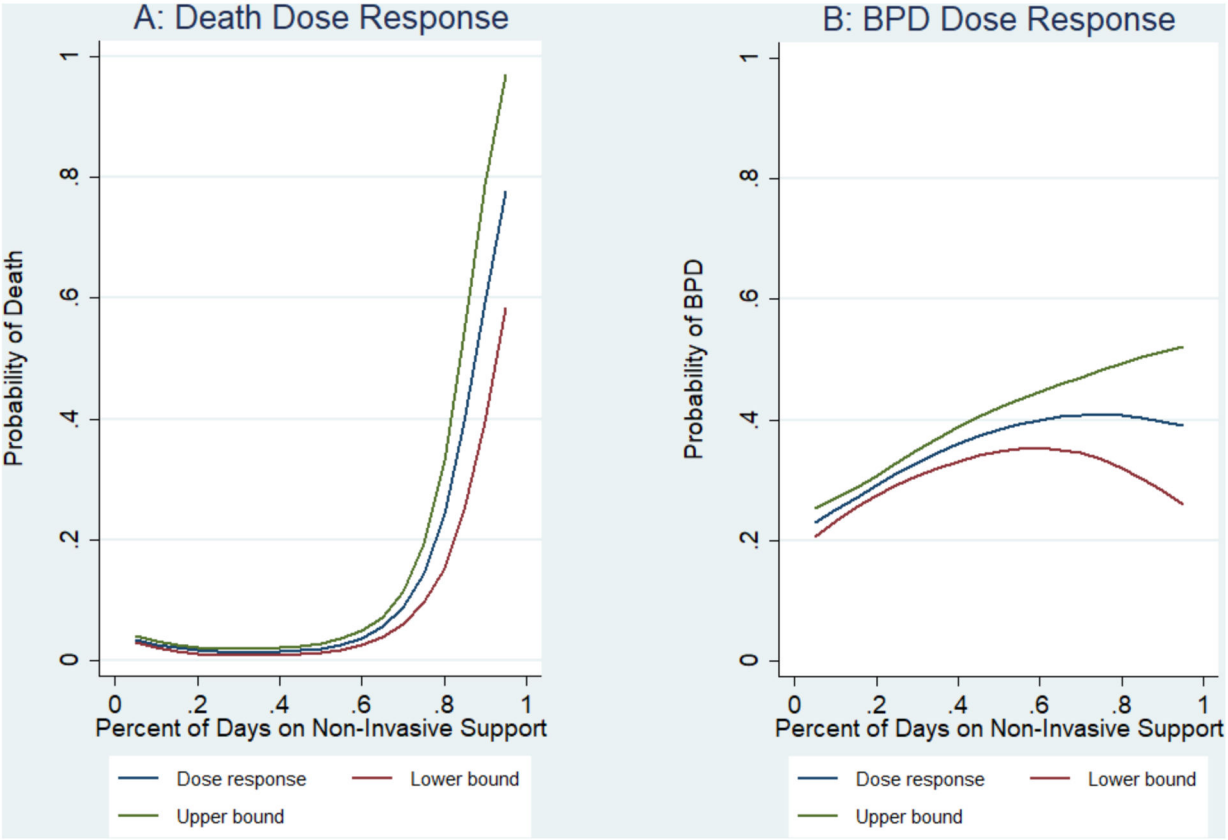

Figure 1.

A, Dose response function linking the percentage of hospital days of noninvasive support exposure and risk of death. B, Dose response function linking support exposure and risk of BPD. Confidence bounds at 0.95% level. Dose response function is the probability of a positive outcome.

Table 1:

Characteristics of Noninvasive Support Exposure Groups *

Noninvasive Support Days *a*	**All infants n=6268**	**>0–1 day n=149**	**>1–7 days n=841**	**>7–14 days n=767**	**>14–21 days n=813**	**>21–28 days n=763**	**>28–35 days n=664**	**>35 days n=1267**
Gestational age (wks): median (Q1, Q3)	27.4 (26.3, 28.1)	27.9 (27.1, 28.4)	27.9 (27.0, 28.4)	27.6 (26.6, 28.3)	27.3 (26.3, 28.3)	27.1 (26.3, 28.0)	27.0 (26.1, 27.9)	26.4 (25.4, 27.3)
Birth weight (g): median (Q1, Q3)	960 (810, 1110)	1050 (910, 1180)	1030 (875, 1165)	980 (850, 1135)	950 (828, 1090)	930 (795, 1075)	910 (790, 1065)	835 (730, 970)
Male: n/N (%)	3089/6266 (49.3)	81/149 (54.4)	398/841 (47.3)	353/767 (46.0)	396/813 (48.7)	383/763 (50.2)	328/662 (49.5)	666/1266 (52.6)
Nonwhite race: n/N (%)	2863/6046 (47.4)	65/144 (45.1)	410/807 (50.8)	353/746 (47.3)	401/796 (50.4)	332/735 (45.2)	287/638 (45.0)	524/1214 (43.2)
Chorioamnionitis: n/N (%)	874/6253 (14.0)	13/149 (8.7)	92/840 (11.0)	93/763 (12.2)	107/808 (13.2)	94/762 (12.3)	98/661 (14.8)	218/1265 (17.2)
Days of mechanical ventilation *b*: median (Q1, Q3)	0 (0, 3)	0 (0, 1)	0 (0, 1)	0 (0, 4)	0 (0, 5)	0 (0, 7)	0 (0, 5)	0 (0, 8)
Highest FiO_2 on Day 7: median (Q1, Q3)	0.21 (0.21, 0.28)	0.21 (0.21, 0.25)	0.21 (0.21, 0.26)	0.21 (0.21, 0.27)	0.21 (0.21, 0.28)	0.21 (0.21, 0.28)	0.23 (0.21, 0.29)	0.25 (0.21, 0.30)
Surgical PDA treatment: n/N (%)	202/5043 (4.0)	3/121 (2.5)	22/698 (3.2)	25/609 (4.1)	18/654 (2.8)	31/633 (4.9)	25/514 (4.9)	69/971 (7.1)
Pharmacological PDA treatment: n/N (%)	762/4866 (15.7)	16/129 (12.4)	73/685 (10.7)	70/588 (11.9)	110/647 (17.0)	108/604 (17.9)	96/498 (19.3)	210/864 (24.3)
Postnatal steroids: n/N (%)	371/6193 (6.0)	3/148 (2.0)	27/827 (3.3)	53/760 (7.0)	47/803 (5.9)	70/753 (9.3)	44/653 (6.7)	116/1245 (9.3)
Early onset sepsis: n/N (%)	89/6267 (1.4)	6/149 (4.0)	9/841 (1.1)	13/767 (1.7)	7/813 (0.9)	13/763 (1.7)	13/663 (2.0)	13/1266 (1.0)
Late onset sepsis: n/N (%)	818/6266 (13.1)	19/148 (12.8)	101/841 (12.0)	94/767 (12.3)	108/813 (13.3)	121/763 (15.9)	94/663 (14.2)	213/1266 (16.8)

FiO_2: fraction of inspired oxygen, PDA: patent ductus arteriosus

*All characteristics with $p<0.05$ other than male sex excluding “All infants” as a comparison group

*a*Cumulative number of support days after the 7th postnatal day

*b*Days of mechanical ventilation exposure after the 7th postnatal day

Table 2:

Outcomes by Instrumental Variable and Propensity Score

	BPD or Death	BPD	Death
Instrumental variables (average marginal effect)[ab]	−0.37 (−1.23, 0.50)	−0.34 (−1.15, 0.46)	0.16 (−0.20, 0.52)
Propensity score matching (average marginal effect)[ab]	0.46 (0.33, 0.60)	0.17 (0.02, 0.36)	0.89 (0.78, 0.99)
Propensity score matching (marginal effect at the mean treatment)[ab]	0.32 (0.19, 0.44)	0.37 (0.25, 0.48)	−0.03 (−0.04, −0.02)

BPD: bronchopulmonary dysplasia (defined as moderate or severe BPD at 36 weeks' postmenstrual age[11])

[a]A one-unit change was one percentage point increase in the percent of hospital days on non-invasive support

[b]Marginal effects reflect the change in the probability of the outcome (out of 100 percent) from a one-unit change in support days. Positive values indicate increases in the outcome and negative values indicate decreases. If confidence intervals include zero, the effect is not statistically significant.

Table 3.

Outcomes by Noninvasive Support Exposure Days

Noninvasive support days[a]	**>0–1 day N=149**	**>1–7 days n=841**	**>7–14 days n=767**	**>14–21 days n=813**	**>21–28 days n=763**	**>28–35 days n=664**	**>35 days n=1267**	**P-value**
BPD or death, %	41/149 (28%)	221/839 (26%)	246/764 (32%)	262/812 (32%)	274/761 (36%)	261/658 (40%)	733/1262 (58%)	<0.0001
BPD, %	24/133 (18%)	171/790 (22%)	210/730 (29%)	241/792 (30%)	260/749 (35%)	257/654 (39%)	726/1256 (58%)	<0.0001
Death, %	17/149 (11%)	58/841 (7%)	41/767 (5%)	22/813 (3%)	20/763 (3%)	7/663 (1%)	21/1267 (2%)	<0.0001
Post menstrual age at discharge (weeks) Median (Q1, Q3)	37.6 (36.5, 39.5)	37.9 (36.4, 39.4)	38.4 (36.9, 40.3)	38.6 (37.0, 40.7)	39.0 (37.4, 41.4)	39.3 (37.7, 41.7)	40.6 (38.9, 43.1)	<0.0001
Growth failure (%)	28/103 (27%)	172/606 (28%)	166/606 (27%)	191/679 (28%)	191/668 (29%)	166/597 (28%)	339/1206 (28%)	0.9994

BPD: bronchopulmonary dysplasia (defined as moderate or severe BPD at 36 weeks' postmenstrual age[11])

[a]Cumulative number of support days after the 7th postnatal day

Table 4:

Outcomes by Percentage of Hospital Days on Noninvasive Support

Noninvasive support Days[a]	**>0%−10% N=864**	**>10%−25% N=1293**	**>25%−50% N=1987**	**>50%−75% N=677**	**>75%−90% N=78**	**>90% N=30**	**P-value**
BPD[b] or death, %	267/862 (31%)	447/1290 (35%)	789/1979 (40%)	323/673 (48%)	55/78 (71%)	26/30 (87%)	<0.0001
BPD[b], %	248/846 (29%)	422/1270 (33%)	765/1955 (39%)	291/641 (45%)	26/49 (53%)	6/10 (60%)	<0.0001
Death, %	34/864 (4%)	33/1293 (3%)	34/1987 (2%)	35/677 (5%)	30/78 (38%)	20/30 (67%)	<0.0001
Growth failure[c] (%)	237/741 (32%)	369/1159 (32%)	495/1838 (27%)	112/592 (19%)	8/44 (18%)	0/8 (0%)	<0.0001

BPD: bronchopulmonary dysplasia (defined as moderate or severe BPD at 36 weeks' postmenstrual age[11])

[a]Cumulative percentage of support days after the 7th postnatal day

[b]Treatment with oxygen or respiratory support at 36 weeks postmenstrual age

[c]Weight less than 10th percentile, for survivors to 36 weeks PMA