Room air challenge predicts duration of supplemental respiratory support for infants with bronchopulmonary dysplasia

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Abstract

Objective: To determine whether a room air challenge (RAC) correlates with duration of respiratory support for infants with bronchopulmonary dysplasia (BPD).

Study design: Prospective study of preterm infants with BPD from 2015–2018. Infants receiving ≤2 liters flow at 36 weeks post-menstrual age (PMA) underwent RAC. Cox regression was used to adjust the duration of respiratory support after 36 weeks PMA for significant covariates.

Results: Of 161 infants with BPD, 91 were eligible for RAC; 51 passed and 40 failed. Infants who failed RAC had longer respiratory support after 36 weeks PMA than infants who passed (median 19 weeks (IQR 15–33) versus 2 weeks (IQR 1–8, p<0.001)), which persisted after multivariable adjustment (hazard ratio −1.42, 95% CI −1.94 to −0.91, p<0.001). Infants failing RAC also had more frequent and longer duration of home oxygen use.

Conclusion: RAC may help provide anticipatory guidance regarding duration of respiratory support for infants with BPD.

Background

Bronchopulmonary dysplasia (BPD) is a common complication of extremely preterm birth; it occurs in up to 15,000 infants annually in the United States.(1) The proportion of infants with BPD varies widely across NICUs, in part because definitions based on receipt of oxygen at 36 weeks post-menstrual age (PMA) do not account for individual differences in
timing of attempts to wean respiratory support. Michele Walsh and colleagues reported the use of a room air challenge at 36 weeks PMA to establish the need for supplemental oxygen. Use of a room air challenge decreased variation in diagnosis of BPD across the National Institute for Child Health and Human Development Neonatal Research Network. However, a comparison of BPD definitions within the Prematurity and Respiratory Outcomes Program (PROP) study found that the definition using a room air challenge resulted in the most frequently missing data. More recent proposed definitions of BPD now differ on whether to include supplemental oxygen requirement.

Despite the logistic difficulties in obtaining a room air challenge, it may still be important to prospectively assess the need for subsequent respiratory support. The PROP study, which enrolled patients from 2011–2013, noted that a room air challenge resulted in fewer changes to patient categorizations than previous reports from the Neonatal Research Network. However, as some NICUs have adopted higher oxygen saturation targets after the publication of multiple oxygen saturation targeting trials, there may be increasing use of supplemental oxygen closer to the time of discharge. Since higher oxygen saturation targets have been associated with more frequent use of home oxygen therapy after NICU discharge, more infants may be discharged with home oxygen therapy. We wondered whether a room air challenge, despite its missing data from a large-scale study perspective, could still provide helpful clinical information for infants receiving respiratory support near NICU discharge.

The objective of this study was to compare the duration of supplemental respiratory support after 36 weeks PMA for infants stratified by a room air challenge. We hypothesized that infants who passed a room air challenge would have a shorter duration of respiratory support, both in the NICU and among the subset of infants discharged with home oxygen. This information would be useful for parents anticipating discharge of an infant with the potential for home oxygen, and for clinics trying to schedule appropriate follow up.

**Methods**

We conducted a prospective cohort study at our single-center level IV NICU, which admits infants of all gestational ages either referred for specialty management or born at a co-located birth hospital. We included all infants born <32 weeks gestational age who were alive in our NICU at 36 weeks’ post-menstrual age (PMA) between August 2015 and June 2018. We excluded infants with major congenital anomalies and those who were transferred to another hospital before 36 weeks PMA, admitted after 36 weeks PMA, were still receiving mechanical ventilation at 36 weeks PMA, or those who died or received a tracheostomy before NICU discharge.

We defined BPD as receipt of any respiratory support at 36 weeks PMA; we did not exclude infants receiving room air low flow cannula because that is uncommon practice at our institution. At 36 weeks PMA, infants who were receiving respiratory support ≤2 liters per minute nasal cannula received a room air challenge. Infants receiving high-flow nasal cannula >2 liters per minute or nasal continuous positive airway pressure at any effective FiO2 were not considered eligible for weaning attempts by consensus of our provider and
nursing teams, in order to limit stress to infants and staff. Our center generally reserves high flow nasal cannula for flows above 2 liters; the few infants on 2 liters per minute high flow nasal cannula around 36 weeks PMA had RAC performed a few days later, once they transitioned to regular nasal cannula. All room air challenges were performed by study team members (PA or AD) in communication with the bedside nurse, at least 1 hour after the infant was fed. Infants were gradually weaned to room air over 30 minutes. If the infant’s oxygen saturations remained >90% in room air, they were counted as passing. If the infant’s oxygen saturations were between 80–90% for over 5 continuous minutes or <80% for 15 seconds, infants were counted as failing the test and were immediately put back on oxygen. (3) Following the test, all infants were placed back on their baseline respiratory support.

The primary outcome of interest was the duration of supplemental respiratory support after 36 weeks PMA, including the remainder of the NICU stay plus the total duration of any home oxygen use. Secondary outcomes included discharge with home oxygen, duration of home oxygen for those receiving this therapy, and prescribed liter flow of home oxygen (0.25 or 0.5 liters per minute, which are the usual practices at our institution). Our BPD clinic is staffed by a pediatric pulmonary team who manages all infants discharged from the NICU with home oxygen therapy following a structured protocol of monthly visits, clinic room air challenges, and recorded home oximetry reviewed by the pulmonary team. (14) Duration of home oxygen therapy was recorded up to 1 year corrected age; any infants still on home oxygen by therapy 1 year corrected age were retained in the data and were recorded as a failure to wean from oxygen. To understand additional factors which may explain differences in duration of oxygen therapy between groups, we also recorded the length of stay from 36 weeks to NICU discharge; in the outpatient setting we recorded the number of visits to pulmonary clinic, any missed visits at pulmonary clinic, failed clinic room air trials and failed recorded home oximetry challenges. For infants receiving a room air challenge, we recorded the liter flow of respiratory support at the time of the room air challenge. The infant’s NICU chart was reviewed for additional clinical covariates, which included gestational age, birth weight, sex, maternal age, outborn status, cesarean section, use of surfactant, postnatal systemic steroids, ductus arteriosus ligation, necrotizing enterocolitis Bell’s stage 2 or greater, and blood culture positive bacteremia.

**Statistical analysis**

First, we described NICU illness covariates for the study cohort, divided into groups: 1) No BPD, room air at 36 weeks PMA; 2) passed a room air challenge; 3) failed a room air challenge; 4) did not receive room air challenge due to being on positive pressure respiratory support at 36 weeks PMA. We compared rates of NICU illness covariates for the entire cohort, as well as for the subgroups of infants who passed versus failed a room air challenge. For infants with BPD, we compared the duration of supplemental respiratory support from 36 weeks PMA to final discontinuation of any supplemental support, the need for home oxygen therapy, and the duration of home oxygen therapy between groups. Differences in duration of respiratory support were compared by performing a log-rank test of differences in hazard functions. Differences between proportions were compared by chi-squared or Fisher’s exact tests; differences between medians were compared by Kruskal-Wallis non-parametric tests. A Cox proportional hazards regression was used to test the association.
between room air challenge response (passed, failed, or ineligible due to positive pressure support) and the primary outcome of duration of respiratory support, adjusted for other illness covariates which significantly differed between groups in bivariate analysis. Because we were specifically trying to test whether passing versus failing a room air challenge was associated with differences in subsequent respiratory support, we performed a priori comparison of these two subgroups after the omnibus test; we did not perform all possible two-way comparisons. A p value <0.05 was accepted for statistical significance. The outcomes study was approved by the IRB of the Children’s Hospital of Wisconsin; the room air challenge protocol was considered not human subjects research since it was conducted for quality improvement purposes to improve transition of care between the NICU and pulmonary teams and was within the team’s scope of clinical practice.

Results

Out of 334 infants who were screened, 79 infants were excluded due to death, tracheostomy, or transfer to another NICU after 36 weeks PMA. Of 255 eligible infants, 7 were lost to follow-up such that we were unable to determine the duration of respiratory support, leaving a cohort of 248 infants available for analysis. At 36 weeks’ PMA, 87 (35%) were in room air, so not considered to have BPD. Another 70 (28%) were receiving positive pressure ventilation >2 liters per minute flow at 36 weeks PMA, and thus did not receive a room air challenge. The remaining 91 infants received a room air challenge. Of these, 40 failed (16%) and 51 passed (21%). Figure 1 illustrates the cohort.

Clinical characteristics of the cohort are shown in Table 1. Infants receiving positive pressure support at 36 weeks PMA were more likely born at earlier gestational age, lower birth weight, outborn, given postnatal steroids, received ductus arteriosus ligation, and had a positive blood culture. Of the subgroup of infants who received a room air challenge, infants who failed the room air challenge were more likely born at earlier gestational age and lower birth weight, and more likely to receive postnatal steroids.

Table 2 shows respiratory outcomes for the 161 infants with BPD. The median duration of respiratory support starting from 36 weeks PMA through final discontinuation was 2 weeks for infants who passed a room air challenge (4 of those infants weaned in one week or less), 19 weeks for infants who failed a room air challenge, and 34 weeks for infants who were on positive pressure support so ineligible for room air challenge. This difference was significant both overall and for the subset of infants receiving a room air challenge (p<0.001 for each). For infants who received a room air challenge, infants who passed versus failed a room air challenge did not have significant differences in baseline liter flow at the time of the room air challenge or subsequent NICU length of stay. Among infants who passed a room air challenge, 32% were discharged with home oxygen, compared to 88% of those who failed a room air challenge and 90% of those who were on positive pressure support at 36 weeks PMA. Among infants discharged with home oxygen, the median duration of home oxygen also varied significantly by groups; the median duration was 13 weeks for infants passing a room air challenge, 17 weeks for infants failing a room air challenge, and 28 weeks for infants on positive pressure support at 36 weeks. There were no differences between rates of
missed clinic appointments. Figure 2 depicts the significant differences in duration of respiratory support after 36 weeks PMA by response to a room air challenge.

Table 3 shows results of a Cox proportional hazards regression adjusting for potential confounders of the association between room air challenge response and duration of respiratory support. Compared to infants who passed a room air challenge, and adjusted for other potential confounders, infants who failed a room air challenge had 39% the rate of successfully weaning respiratory support, meaning they had a 61% longer duration of respiratory support after 36 weeks PMA. Infants who did not receive a room air challenge due to positive pressure support at 36 weeks had a 71% longer duration of respiratory support.

In general, the room air challenge protocol was well accepted anecdotally by nursing, respiratory therapy staff, and parents. In most cases when the infant failed the room air trial, the bedside nurse expressed afterward that the infant had already failed an informal trial or desaturated following a dislodged nasal cannula within the previous 2–3 days.

Discussion

The goal of this study was to determine whether a room air challenge for infants with BPD was associated with duration of subsequent respiratory support. We found significant differences in outcomes between infants who passed a room air challenge, failed a room air challenge, or did not receive a room air challenge due to receipt of positive pressure support; this finding was consistent across outcomes of total duration of respiratory support after 36 weeks PMA, discharge with home oxygen, and duration of home oxygen therapy. For the infants who did receive a room air challenge, we found that infants who passed a room air challenge had significantly less need for respiratory support than infants who failed a room air challenge.

When Walsh and colleagues tested a room air challenge to classify infants with BPD across the Neonatal Research Network, 227 infants underwent a room air challenge; 101 (44%) infants passed the test and were assigned an outcome of no BPD. Of those infants who passed a room air challenge and were classified as having no BPD, 26% were still ultimately discharged with home oxygen therapy, as compared to 58% of the infants who failed a room air challenge. Since that time, results from oxygen saturation targeting trials have resulted in higher oxygen saturation targets for some NICUs. The potential role of a room air challenge in the setting of higher oxygen saturation targets is not clear. The Prematurity and Respiratory Outcomes Program study found that fewer infants passed a room air challenge than in the original studies of this test, and speculated that more tightly controlled oxygen saturation targets may contribute the reduced contribution of room air challenge to patient categorization. On the other hand, Foglia and colleagues noted an increase in proportion of infants with BPD among Neonatal Research Network centers who increased their oxygen saturation targets over time. The impact of a room air challenge on BPD categorization may still depend on individual center practice regarding weaning of respiratory support near 36 weeks PMA.
Our study extends the potential impact of a room air challenge by assessing the total duration of respiratory support including the outpatient setting. This was possible in our cohort because it was conducted in a single center with a standardized protocol for home oxygen weaning. Until recently there has been little reported about duration of home oxygen in the outpatient setting, with wide variation between centers both in decisions to prescribe home oxygen therapy and in strategies for its use after NICU discharge. Rhein and colleagues recently reported results of a multicenter randomized controlled trial comparing different strategies for weaning home oxygen in the outpatient setting. The duration of home oxygen therapy in our study is similar to the Rhein trial, which is a shorter duration of home oxygen therapy than has been previously reported. This suggests that a standardized home oxygen weaning protocol can shorten duration of home oxygen therapy. Further, our findings suggest that in the setting of a standardized protocol for home oxygen therapy, it is possible to use duration of home oxygen therapy as a meaningful outcome to test whether potential NICU illness measures might help counsel families and plan appropriate follow-up.

A physiologic test documenting need for respiratory support has demonstrated limitations in defining BPD. The studies by Walsh and colleagues classified infants as having BPD or no BPD, but did not specify severity of BPD for infants receiving positive pressure support. The 2001 National Heart, Lung and Blood Institute workshop definition classified illness severity by need for respiratory support and effective fraction of inhaled oxygen at 36 weeks PMA, but did not explicitly require a physiologic test confirming the need for that degree of support. One of the main limitations of using physiologic tests like a room air challenge in defining BPD is the high proportion of missing data. Upcoming studies of physiologic parameters involved with control of breathing in preterm infants may shed additional light on whether already-collected electronic vital signs parameters could be turned into an algorithm predicting subsequent respiratory support requirements. In the meantime, if centers like ours find that a room air challenge provides clinical value in addition to research stratification, it might incentivize providers to complete the testing. Based on our study findings, RAC is now performed by respiratory therapists at our center. Our next steps are to determine whether we can use RAC results prospectively as part of risk stratification for infants with BPD. Our goal moving forward is to identify appropriate infants to attempt to shorten the duration of home oxygen therapy without compromising important safety outcomes such as growth and retinopathy of prematurity. If we can identify infants who are expected to wean quickly, we can better counsel parents prior to NICU discharge regarding expectations for home oxygen weaning, and we can optimize timing of outpatient pulmonary appointments.

We intentionally did not use a severity-based definition of BPD in this study, partially because the definitions of BPD changed during the study period. Recently proposed definitions of BPD differ in whether to include fraction of inhaled oxygen in the severity classification. We were unable to retrospectively apply the proposed 2018 NHLBI workshop definition to our study population to determine whether a room air challenge could help distinguish outcomes within those groups, since we did not try to wean infants on high flow nasal cannula or nasal continuous positive airway pressure. Further, most infants in our center receiving <1 liter per minute nasal cannula flow receive 100% fraction
of inhaled oxygen and wean flow instead, in preparation for potential home oxygen therapy; these infants would be classified as having more severe disease than an infant on high-flow nasal cannula for whom we would not have attempted a room air challenge. The proposed definition by Jensen and colleagues is the easiest to apply retrospectively to our study, since all infants receiving a room air challenge were receiving ≤2 liters per minute flow and would be classified as Grade I BPD. Using the Jensen definition, our study findings would suggest that a room air challenge could provide additional information to distinguish respiratory outcomes. One potential reason may be that many components of the outcomes used to discriminate between definitions in the Jensen study are relatively uncommon in infants with Grade I BPD, including death after 36 weeks PMA, tracheostomy, and respiratory support at 18–26 month follow-up. BPD definitions to support risk stratification of the highest risk infants with severe BPD are crucial for designing clinical and research programs to prevent adverse outcomes. At the same time, understanding anticipated clinical outcomes for infants with Grade I BPD has the potential to help many infants and families optimize the transition from NICU to home.

Strengths of this study include the prospective design, standardized clinical protocol to wean home oxygen support, and high degree of follow-up. The biggest limitations are related to logistics in weaning infants from respiratory support in a research context. Infants were trialed off oxygen for a maximum of 30 minutes in what was thought to be the “ideal time” to perform the test. More infants could have failed the test if trialed off oxygen for longer than 30 minutes, or if the test were performed around feeding or random times. The oxygen saturation cutoffs were chosen following previous studies; other cutoffs may have different results. Variability in use of non-invasive respiratory support, even within a single center with generally similar practice, affected the number of infants receiving a room air challenge. Examples noted during our study included use of heated humidified nasal cannula for humidification rather than to provide non-invasive positive pressure. Similarly, at times an infant’s respiratory support had been escalated around 36 weeks CGA because of brief issues like retinopathy of prematurity treatment or inguinal hernia repair. Infants who received tracheostomies for long-term ventilation were excluded from this analysis; had they been included, the median duration of supplemental support for infants receiving positive pressure at 36 weeks PMA would be even longer as these infants were still receiving home ventilator support at 1 year of age. Some infants who died of respiratory failure prior to 36 weeks’ PMA were not included in this analysis, both in our center and likely at the several level III NICUs in our referral area who care for extremely preterm infants. Had some of these infants survived, most of them presumably would have had Grade 2–3 BPD, and therefore would have been at high risk for longer duration of respiratory support. Finally, this is a single center study and may not represent the preterm population broadly. Our NICU has a high proportion of preterm patients transferred for specialist intervention for issues such as ductus arteriosus and intraventricular hemorrhage. As a result, our BPD rate is higher than many centers caring for mostly inborn preterm infants, and many outborn infants have more severe lung disease. Our center also has a relatively high rate of home oxygen use and short length of stay for infants with BPD compared to other children’s hospital NICUs; this may be because of our close relationship with pulmonology and standardized outpatient management that facilitates easy discharge with home oxygen.
In conclusion, for preterm infants with BPD receiving low flow nasal cannula at 36 weeks PMA, response to a room air challenge distinguished duration of subsequent respiratory support including need for home oxygen and duration of home oxygen therapy. Despite the limitations of including a room air challenge in a broad definition of BPD, these findings could be applied by NICUs or follow-up teams in counseling families and planning outpatient follow-up.

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**References:**

1. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. American journal of respiratory and critical care medicine. 2001 6;163(7):1723–9. Epub 2001/06/13. eng. [PubMed: 11401896]
2. Ambalavanan N, Walsh M, Bobashev G, Das A, Levine B, Carlo WA, et al. Intercenter differences in bronchopulmonary dysplasia or death among very low birth weight infants. Pediatrics. 2011 1;127(1):e106–16. Epub 2010/12/15. eng. [PubMed: 21149431]
3. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaro A. Safety, Reliability, and Validity of a Physiologic Definition of Bronchopulmonary Dysplasia. Journal of Perinatology. 2003 9/01;23(6):451–6. [PubMed: 13679930]
4. Walsh MC, Yao Q, Guttner P, Hale E, Collins M, Hensman A, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics. 2004 11;114(5):1305–11. [PubMed: 15520112]
5. Poindexter BB, Feng R, Schmidt B, Aschner JL, Ballard RA, Hamvas A, et al. Comparisons and Limitations of Current Definitions of Bronchopulmonary Dysplasia for the Prematurity and Respiratory Outcomes Program. Annals of the American Thoracic Society. 2015 12;12(12):1822–30. [PubMed: 26397992]
6. 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 9;197:300–8. [PubMed: 29551318]
7. 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. American journal of respiratory and critical care medicine. 2019 9 15;200(6):751–9. Epub 2019/04/18. eng. [PubMed: 30995069]
8. Jensen EA, Wright CJ. Bronchopulmonary Dysplasia: The Ongoing Search for One Definition to Rule Them All. The Journal of Pediatrics. 2018;197:8–10. [PubMed: 29605396]
9. Network SS GotEKSNR Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, et al. Target ranges of oxygen saturation in extremely preterm infants. The New England journal of medicine. 2010 5 27;362(21):1959–69. [PubMed: 20472937]
10. Darlow BA, Vento M, Beltempo M, Lehtonen L, Hakansson S, Reichman B, et al. Variations in Oxygen Saturation Targeting, and Retinopathy of Prematurity Screening and Treatment Criteria in Neonatal Intensive Care Units: An International Survey. Neonatology. 2018;114(4):323–31. Epub 2018/08/09. eng. [PubMed: 30089298]
11. Foglia EE, Carper B, Gantz M, DeMauro SB, Lakshminrusimha S, Walsh M, et al. Association between Policy Changes for Oxygen Saturation Alarm Settings and Neonatal Morbidity and Mortality in Infants Born Very Preterm. The Journal of Pediatrics. 2019;209:17–22.e2. [PubMed: 30961990]
12. Ejiawoko A, Lee HC, Lu T, Lagatta J. Home Oxygen Use for Preterm Infants with Bronchopulmonary Dysplasia in California. The Journal of pediatrics. 2019 7;210:55–62 e1. Epub 2019/04/17. eng. [PubMed: 30987778]
13. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. The New England journal of medicine. 2003 9 4;349(10):959–67. [PubMed: 12954744]

14. Dawson SLynn DA; Lau Ryan; Lagatta Joanne. High pCO2 Levels at 36 Weeks Is Associated with Longer Duration of Home Oxygen in Infants with Bronchopulmonary Dysplasia (BPD). American journal of respiratory and critical care medicine. 2019;199:A4266.

15. Ellsbury DL, Acarregui MJ, McGuinness GA, Klein JM. Variability in the use of supplemental oxygen for bronchopulmonary dysplasia. The Journal of pediatrics. 2002;140(2):247–9. [PubMed: 11865280]

16. Rhein LM, Konnikova L, McGeachey A, Pruchniewski M, Smith VC. The Role of Pulmonary Follow-up in Reducing Health Care Utilization in Infants With Bronchopulmonary Dysplasia. Clinical Pediatrics. 2012 7 1, 2012;51(7):645–50. [PubMed: 22492835]

17. Lagatta J, Clark R, Spitzer A. Clinical predictors and institutional variation in home oxygen use in preterm infants. The Journal of pediatrics. 2012 2;160(2):232–8. [PubMed: 21962601]

18. Lagatta JM, Clark RH, Brousseau DC, Hoffmann RG, Spitzer AR. Varying patterns of home oxygen use in infants at 23–43 weeks’ gestation discharged from United States neonatal intensive care units. The Journal of pediatrics. 2013 10;163(4):976–82 e2. [PubMed: 23769504]

19. Rhein, L; Monitoring Oxygen Levels of Premature Babies at Home and in the Clinic -- The RHO Trial. 2019. [3/20/2020]. Available from: https://www.pcori.org/research-results/2014/monitoring-oxygen-levels-premature-babies-home-and-clinic-rho-trial.

20. Don Hayes J, Wilson KC, Krivchenia K, Hawkins SMM, Balfour-Lynn IM, Gozal D, et al. Home Oxygen Therapy for Children. An Official American Thoracic Society Clinical Practice Guideline. American journal of respiratory and critical care medicine. 2019;199(3):e5–e23. [PubMed: 30707039]

21. Prematurity-Related Ventilatory Control: Role in Respiratory Outcomes (Pre-Vent). 2020.
Figure 1. Study cohort.
7 of 255 infants were lost to follow-up such that we were unable to determine the duration of respiratory support: 0 infants in room air at 36 weeks PMA; 1 infant who passed a room air challenge; 2 infants who failed a room air challenge; 4 infants who were receiving positive pressure support at 36 weeks. PMA = post-menstrual age.
Figure 2. Time to weaning from respiratory support after 36 weeks postmenstrual age. Survival analysis comparison of weaning from respiratory support from 36 weeks postmenstrual age until final discontinuation of respiratory support, of three groups: Passed RAC = passed room air challenge; Failed RAC = failed room air challenge; Positive Pressure Support (No RAC) = did not receive room air challenge due to receipt of positive pressure support. P values indicate log rank tests of hazard functions.
# Table 1.

Clinical characteristics of study cohort.

| Variable                                      | No BPD     | Passed RAC | Failed RAC | Positive Pressure Support | P value overall | P value pass vs fail RAC |
|-----------------------------------------------|------------|------------|------------|---------------------------|----------------|--------------------------|
| N                                             | 87         | 51         | 40         | 70                        |                |                          |
| Gestational age, completed weeks, median (IQR)| 30 (28–31) | 28 (27–29) | 26 (25–28) | 26 (24–27)                | <0.001         | <0.001                   |
| Birth weight, kg, median (IQR)                | 1.4 (1.1–1.6) | 1.0 (0.9–1.3) | 0.9 (0.7–1.0) | 0.7 (0.6–1.0)            | <0.001         | 0.01                      |
| Maternal age, median (IQR)                    | 29 (25–32) | 29 (27–35) | 29 (24–33) | 30 (24–33)                | 0.439          | 0.13                      |
| Outborn, %                                    | 21%        | 27%        | 25%        | 64%                       | <0.001         | 0.79                      |
| Cesarean section, %                           | 38%        | 22%        | 28%        | 31%                       | 0.15           | 0.4                       |
| Postnatal steroids, %                         | 6%         | 14%        | 38%        | 70%                       | <0.001         | 0.01                      |
| Ductus arteriosus ligation, %                 | 1%         | 6%         | 10%        | 30%                       | <0.001         | 0.46                      |
| Necrotizing enterocolitis >= stage 2, %       | 3%         | 12%        | 3%         | 9%                        | 0.155          | 0.1                       |
| Blood culture positive, %                     | 2%         | 8%         | 20%        | 16%                       | 0.005          | 0.09                      |

P value overall indicates differences between all 4 groups, by chi-squared test or Kruskal-Wallis, as appropriate. P value pass vs fail RAC indicates differences for those subgroups alone. RAC = room air challenge; IQR = interquartile range.
### Table 2.

Respiratory outcomes for infants with bronchopulmonary dysplasia.

| Variable                                                                 | Passed RAC | Failed RAC | Positive Pressure Support | P value overall | P value pass vs fail RAC |
|--------------------------------------------------------------------------|------------|------------|--------------------------|-----------------|--------------------------|
| n                                                                        | 51         | 40         | 70                       |                 |                          |
| Time from 36 weeks - stopping respiratory support, weeks, median (IQR)   | 2 (1–8)    | 19 (15–33) | 34 (23–43)               | <0.001          | <0.001                   |
| Length of stay from 36 weeks - discharge, weeks, median (IQR)            | 3 (2–5)    | 3 (1–5)    | 7 (5–11)                 | <0.001          | 0.961                    |
| Respiratory support at time of room air challenge, liters, median (IQR)  | 1 (0.25–2) | 1 (0.25–2) | -                        |                 | 0.972                    |
| Home oxygen, n (%)                                                       | 17 (32%)   | 36 (88%)   | 66 (90%)                 | <0.001          | <0.001                   |

For infants discharged with home oxygen:

| Home oxygen flow >0.25 liters per minute, n (%)                          | 0          | 34%        | 54%                      | <0.001          | 0.007                    |
| Time from 36 weeks - stopping home oxygen, weeks, median (IQR)           | 13 (12–21) | 22 (16–37)| 35 (29–45)              | <0.001          | 0.028                    |
| Time from NICU discharge - stopping home oxygen, weeks, median (IQR)     | 13 (10–20) | 17 (13–31)| 28 (19–38)              | <0.001          | 0.079                    |
| Number of visits to pulmonary clinic, median (IQR)                       | 2 (1–2)    | 2 (2–3)    | 3 (2–4)                 | 0.004           | 0.042                    |
| Any missed visits to pulmonary clinic, n (%)                            | 19%        | 11%        | 16%                      | 0.761           | 0.664                    |
| Any failed clinic room air trials, n (%)                                 | 0%         | 9%         | 32%                      | 0.002           | 0.314                    |
| Any failed recorded home oximetry challenges, n (%)                     | 12%        | 17%        | 21%                      | 0.840           | 0.512                    |

P value overall indicates differences between all 3 groups, as calculated by chi-squared or Fisher’s exact, Kruskal-Wallis, or log-rank tests of hazard functions, as appropriate. P value pass vs fail RAC indicates differences between those two subgroups. IQR = interquartile range; RAC = room air challenge.
Table 3.
Multivariable association between response to room air challenge and duration of respiratory support.

| Variable                  | Category                        | Hazard ratio | 95% CI      | p     |
|--------------------------|---------------------------------|--------------|-------------|-------|
| BPD group                | Passed RAC                      | REF          |             |       |
|                          | Failed RAC                      | 0.39         | 0.24 to 0.62| <0.001|
|                          | Ineligible (positive pressure support) | 0.22         | 0.14 to 0.35| <0.001|
| Gestational age, weeks   |                                 | 1.06         | 0.96 to 1.17| 0.252 |
| Ductus arteriosus ligation| Yes                            | 0.93         | 0.56 to 1.53| 0.778 |
| Outborn                  | Yes                             | 1.10         | 0.75 to 1.62| 0.611 |
| Blood culture positive   | Yes                             | 0.85         | 0.50 to 1.43| 0.532 |

Cox proportional hazards regression evaluating the association between response to a room air challenge with the primary outcome of duration of respiratory support after 36 weeks PMA, adjusted for other covariates that were significantly associated with response to a room air challenge in Table 1. The hazard ratio indicates the rate of final weaning from oxygen; a lower hazard ratio indicates lower rates of successful weaning from oxygen. BPD = bronchopulmonary dysplasia; RAC = room air challenge.