# Bronchopulmonary Dysplasia and Perinatal Characteristics Predict 1-Year Respiratory Outcomes in Newborns Born at Extremely Low Gestational Age: A Prospective Cohort Study

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**Objective** To assess the utility of clinical predictors of persistent respiratory morbidity in extremely low gestational age newborns (ELGANs).

**Study design** We enrolled ELGANs (<29 weeks' gestation) at ≤7 postnatal days and collected antenatal and neonatal clinical data through 36 weeks' postmenstrual age. We surveyed caregivers at 3, 6, 9, and 12 months' corrected age to identify postdischarge respiratory morbidity, defined as hospitalization, home support (oxygen, tracheostomy, ventilation), medications, or symptoms (cough/wheeze). Infants were classified as having postprematurity respiratory disease (PRD, the primary study outcome) if respiratory morbidity persisted over ≥2 questionnaires. Infants were classified with severe respiratory morbidity if there were multiple hospitalizations, exposure to systemic steroids or pulmonary vasodilators, home oxygen after 3 months or mechanical ventilation, or symptoms despite inhaled corticosteroids. Mixed-effects models generated with data available at 1 day (perinatal) and 36 weeks' postmenstrual age were assessed for predictive accuracy.

**Results** Of 724 infants (918 ± 234 g, 26.7 ± 1.4 weeks' gestational age) classified for the primary outcome, 68.6% had PRD; 245 of 704 (34.8%) were classified as severe. Male sex, intrauterine growth restriction, maternal smoking, race/ethnicity, intubation at birth, and public insurance were retained in perinatal and 36-week models for both PRD and respiratory morbidity severity. The perinatal model accurately predicted PRD (c-statistic 0.858). Neither the 36-week model nor the addition of bronchopulmonary dysplasia to the perinatal model improved accuracy (0.856, 0.860); c-statistic for BPD alone was 0.907.

**Conclusion** Both bronchopulmonary dysplasia and perinatal clinical data accurately identify ELGANs at risk for persistent and severe respiratory morbidity at 1 year. *(J Pediatr 2017;187:89-97).*

**Trial registration** ClinicalTrials.gov: NCT01435187.

Premature birth has a profound impact on postnatal pulmonary development. Fetal lung development is disrupted by early delivery, leading to lifelong morbidity and diminished pulmonary function.[1] In particular, extremely low gestational age newborns (ELGANs) have substantial rates of persistent respiratory morbidity following hospital discharge. Bronchopulmonary dysplasia (BPD), defined at 36 weeks' postmenstrual age (PMA), has been used as both predictor and surrogate for this later morbidity.[2-4] Various studies have identified male sex, degree of immaturity, and greater levels of respiratory support as important early predictors of BPD or death in ELGANs.[5-7] Similarly, male sex, decreased intrauterine growth, singleton birth, exposure to young children, sociodemographic factors, and a diagnosis of BPD have been associated with increased respiratory morbidity in early childhood.[8,9]

The primary aim of the Prematurity and Respiratory Outcomes Program (PROP) is to identify early predictors of later respiratory morbidity, allowing for the prediction of ELGANs at risk for persistent respiratory morbidity, defined at 1-year

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| BPD | Bronchopulmonary dysplasia |
| ELGAN | Extremely low gestational age newborn |
| PMA | Postmenstrual age |
| PRD | Postprematurity respiratory disease |
| PROP | Prematurity and Respiratory Outcomes Program |
| RMS | Respiratory morbidity severity |

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Supported by National Heart, Lung, and Blood Institute (U01 HL101456) (PI: Aschner, Vanderbilt), (U01 HL101798) (PI: Keller, University of California, San Francisco), (U01 HL101813) (PI: Pryhuber, University of Rochester), (U01 HL101465) (PI: Hamvas, University of Washington), (U01 HL 101800) (PI: Jobe, Cincinnati Children's Hospital Medical Center), (R01 HL105702) (PI: Voynow, Duke), and (U01 HL101794) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Best Pharmaceuticals for Children Act (PI: B Schmidt). The authors declare no conflicts of interest.

Portions of this study were presented as an abstract during the Pediatric Academic Societies, Baltimore, Maryland, April 30-May 3, 2016.



http://dx.doi.org10.1016/j.jpeds.2017.04.026

corrected age. Epidemiologic studies from populations born at term demonstrate that lower respiratory tract infection in early childhood increases the risk of later wheezing illness and impaired lung function.[10-13] However, these types of studies are not available in more heterogeneous populations born preterm. Because infants born preterm manifest respiratory illness both with and apart from infection, the PROP Steering Committee considered broader descriptors of infant respiratory morbidity, drawing from previously published markers of persistent respiratory morbidity in infants born preterm.[8,14] Thus, the PROP Steering Committee chose primary and secondary outcomes that were felt to represent persistence (infants that were affected at least one-half of the first year, with unaffected infants likely to have limited manifestations of respiratory disease) and severity (graded intensity of care) of respiratory morbidity.

We hypothesized that perinatal (identified in the first day of life) and 36-week (describing infant status through 36 weeks' PMA) clinical factors would predict accurately the persistence and severity of respiratory morbidity in ELGANs. We used step-wise selection to develop perinatal and 36-week multivariate models from these clinical factors, assessed the accuracy of the models for the prediction of respiratory morbidity, and compared the models with the accuracy of BPD alone.

## Methods

The detailed design of the PROP Study (ClinicalTrials.gov: NCT01435187), including data-collection forms and a CONSORT diagram, has been described.[15,16] To summarize, ELGANs $23^{0/7}$-$28^{6/7}$ weeks' gestational age were enrolled by 7 postnatal days at 6 academic centers (13 hospitals) in the US if they were without cardiopulmonary anomalies and deemed viable and available for follow-up. Written parental consent was obtained following each institutional review board approval, with central oversight by a National Institutes of Health-appointed Observational Safety Monitoring Board. Demographics, perinatal clinical information, and daily respiratory, nutrition, and growth data were collected to discharge or 40 weeks' PMA (term). Intrauterine growth was normalized to gestational age via contemporary, multinational fetal reference curves.[17] At discharge, caregivers were interviewed regarding potential exposures that might affect respiratory status, including anticipated daycare arrangements, young children and pets in the home, and smoking rules.

BPD status was determined at $36^{0/7}$ weeks' PMA or earlier discharge from a modification of the proposed National Institutes of Health workshop definition.[3,16] Infants receiving positive pressure respiratory support or prescribed fraction of inspired oxygen ≥0.30 were classified as severe, those receiving nasal cannula support and prescribed fraction of inspired oxygen 0.22-0.29 were classified as moderate, and those without respiratory support or nasal cannula flow with no supplemental oxygen were classified as no/mild.

Questionnaires were administered by research staff to parents/caregivers at 3, 6, 9, and 12 months' corrected (for prematurity) age. All follow-up was completed by August 2015. From initial hospital discharge (for first questionnaire) or previous interview (for subsequent questionnaires), we documented hospitalization for respiratory indication, home respiratory support (including tracheostomy and mechanical ventilation), respiratory medication administration (**Table I**; available at www.jpeds.com), and respiratory symptoms (cough without cold or wheeze at least once per week). Decisions regarding prescription of home respiratory support and medications were made by local clinicians.

The predetermined primary outcome for the PROP Study was termed postprematurity respiratory disease (PRD).[15] An infant was classified with PRD if there were positive responses indicating respiratory morbidity on at least 2 caregiver questionnaires. Respiratory morbidity was defined as mentioned previously: hospitalization for respiratory indication, home respiratory support, respiratory medication administration, and respiratory symptoms. PRD was chosen as a clinically relevant description of persistent respiratory morbidity. Similarly, the predetermined secondary outcome was a severity scale for respiratory morbidity for which specific markers of morbidity were placed, by consensus of the PROP Steering Committee, into categories of respiratory morbidity severity (RMS) accounting for both the level of illness indicated by a particular marker and potential adverse effects associated with that marker. Infants were classified into 1 of 3 mutually exclusive, ordered categories of RMS as (1) severe, if there were ≥2 respiratory hospitalizations, home supplemental oxygen after 3 months or any home mechanical ventilation, systemic steroid exposure or pulmonary vasodilators at any time, or symptoms despite concurrent inhaled corticosteroids in ≥2 questionnaires; (2) moderate/mild, if 1 hospitalization, home oxygen <3 months' corrected age or tracheostomy without ventilation, any inhaled corticosteroid exposure, or bronchodilator or symptoms in ≥2 questionnaires; and (3) minimal/none for all other cases. Infants who died secondary to a cardiopulmonary cause were classified with PRD and severe RMS.

### Statistical Analyses

The PROP Request for Applications specified a sample size of 750 infants available for follow-up at 36 weeks' PMA. All analyses used SAS 9.4 (SAS Institute Inc, Cary, North Carolina). In univariate analyses, the relationship of clinical variables to PRD and RMS was evaluated in generalized linear mixed effects models to account for correlation between siblings, via the cumulative logit link and proportional odds model for RMS. The proportional odds assumption wasn't violated. Trends from ordered predictors were evaluated by treating these variables as continuous covariates. Multivariate predictive perinatal (considering only perinatal variables) and 36-week (considering perinatal variables and variables from the neonatal hospitalization describing infant status through 36 weeks) models were developed independently. Variables with $P < .05$ in univariate analyses (**Tables II** and **III**) were considered for inclusion in multivariate models. Gestational age was retained in all models. Other variables were retained if determined to have an important contribution ($P \leq .2$) by backward selection using