Prediction of Bronchopulmonary Dysplasia by Postnatal Age in Extremely Premature Infants

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***Rationale*: Benefits of identifying risk factors for bronchopulmonary dysplasia in extremely premature infants include providing prognostic information, identifying infants likely to benefit from preventive strategies, and stratifying infants for clinical trial enrollment.**
***Objectives*: To identify risk factors for bronchopulmonary dysplasia, and the competing outcome of death, by postnatal day; to identify which risk factors improve prediction; and to develop a Web-based estimator using readily available clinical information to predict risk of bronchopulmonary dysplasia or death.**
***Methods*: We assessed infants of 23–30 weeks' gestation born in 17 centers of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network and enrolled in the Neonatal Research Network Benchmarking Trial from 2000–2004.**

***Measurements and Main Results*: Bronchopulmonary dysplasia was defined as a categorical variable (none, mild, moderate, or severe). We developed and validated models for bronchopulmonary dysplasia risk at six postnatal ages using gestational age, birth weight, race and ethnicity, sex, respiratory support, and $F_{I_{O_2}}$, and examined the models using a C statistic (area under the curve). A total of 3,636 infants were eligible for this study. Prediction improved with advancing postnatal age, increasing from a C statistic of 0.793 on Day 1 to a maximum of 0.854 on Day 28. On Postnatal Days 1 and 3, gestational age best improved outcome prediction; on Postnatal Days 7, 14, 21, and 28, type of respiratory support did so. A Web-based model providing predicted estimates for bronchopulmonary dysplasia by postnatal day is available at https://neonatal.rti.org.**
***Conclusions*: The probability of bronchopulmonary dysplasia in extremely premature infants can be determined accurately using a limited amount of readily available clinical information.**

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Bronchopulmonary dysplasia is the most common serious pulmonary morbidity in premature infants. Although accurate predictive models of bronchopulmonary dysplasia risk are sometimes used in research, none are currently used in common clinical practice for a variety of reasons.

What This Study Adds to the Field

In this study, we identified the change in the relative contributions of a variety of risk factors to the prediction of bronchopulmonary dysplasia with advancing postnatal age. This tool may help identify patients most likely to benefit from postnatal treatment and assist in the design of clinical trials to assess the efficacy of preventive therapies in high-risk populations.

(*Received in original form January 11, 2011; accepted in final form March 4, 2011*)

Supported by The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, which provided grant support for the Neonatal Research Network's Benchmarking Study (clinical trial registered with www.clinicaltrials.gov [NCT67613] and Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) (clinical trial registered with www.clinicaltrials.gov [NCT233324]). The funding agency provided overall oversight for study conduct. All analyses and interpretation of the data and the preparation, review, and approval of this manuscript were independent of the funding agency. Dr. Smith received support from the National Institute of Child Health and Human Development (1K23HD060040–01 and DHHS-1R18AE000028–01). Data collected at participating sites of the National Institute of Child Health and Human Development Neonatal Research Network were transmitted 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 Neonatal Research Network, Dr. Abhik Das (DCC principal investigator), Mr. John Langer, and Dr. Marie Gantz (DCC statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 183. pp 1715–1722, 2011
Originally Published in Press as DOI: 10.1164/rccm.201101-0055OC on March 4, 2011
Internet address: www.atsjournals.org

Keywords: bronchopulmonary dysplasia; prematurity; low-birth-weight infant

Bronchopulmonary dysplasia (BPD) is the most common serious pulmonary morbidity in premature infants (1, 2). The costs of the disorder are both social and economic and are measured in impaired childhood health and quality of life (3), family stress and economic hardship, and increased healthcare costs (4). Clinicians, parents, and researchers would benefit from an accurate predictive model of BPD risk based on readily available clinical information. Previous predictive models of BPD risk have been reported (5–14). Although sometimes used in research (15), none are currently used in common clinical practice for a variety of reasons (e.g., the populations were from the presurfactant era or before widespread use of antenatal steroids, BPD was defined as a dichotomous variable at a postnatal age of limited relevance [28 d], or death was not included in all models as a competing outcome for BPD).

An additional problem with previously reported analyses is a lack of detail regarding the change in BPD risk with advancing postnatal age (5–14). Traditionally, researchers identified risk factors for BPD by categorizing premature infants as having or not having BPD at 28 postnatal days or 36 weeks postmenstrual age, and then examining all factors that influenced risk up to the time of diagnosis. Subsequent multivariable models included risk factors identifiable at birth, and exposures up to the time of diagnosis of BPD. Using this approach, risk factors for BPD include lower birth weight, lower gestational age, male sex, patent ductus arteriosus (PDA), sepsis, and mechanical ventilation, among many others (16–19). These models typically do not include postnatal age and therefore cannot quantify the variable contribution of neonatal exposures over time. Including postnatal age facilitates the development and evaluation of potentially time-sensitive preventive or therapeutic strategies to modify BPD risk.

Our objectives were to identify risk factors for BPD (defined according to the National Institute of Child Health and Human Development consensus definition of no, mild, moderate, and severe BPD [20, 21]) and the competing outcome of death, by postnatal day; to identify which risk factors improve prediction; and to develop a Web-based "BPD estimator" using readily available clinical information that accurately predicts the risk of BPD or death. Some of the results of these studies have been previously reported in the form of abstracts at the Pediatric Academic Societies Meetings (22–24).

METHODS

Eligibility Criteria

We performed a secondary analysis of data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network Benchmarking Trial. This study enrolled infants from 17 centers admitted from 2000–2004 in a cluster-randomized, controlled trial to test whether neonatal intensive care units trained in benchmarking and multimodal quality improvement techniques could improve survival without BPD compared with centers with usual practice (25). All sites' institutional review boards approved the study. To be eligible for the Benchmarking Trial, infants needed to survive more than 12 hours and have a birth weight of 401–1,250 g. For this secondary analysis, infants less than 23 weeks of age were not included because they all developed BPD, and infants greater than 30 weeks of age were not included because less than 1% of these infants developed BPD.

Risk Factors

In the Benchmarking Trial, trained research coordinators using standardized definitions collected data before discharge, including gestational age, birth weight, race and ethnicity, and sex at birth; respiratory support and $F_{I_{O_2}}$ were recorded on specified postnatal days (26). Gestational age (completed weeks of age) was determined by the best obstetric estimate using the last menstrual period or early ultrasonographic examination, except in unusual circumstances when only an estimate by the pediatrician (27) was available.

Race and ethnic group were assigned by maternal report. The $F_{I_{O_2}}$ and respiratory support were recorded every 6 hours starting at 0600 hour on each of the Postnatal Days 1, 3, and 7, and then once on Days 14, 21, and 28. Mean $F_{I_{O_2}}$ was used on Days 1, 3, and 7 when more than one $F_{I_{O_2}}$ was recorded. We assigned the respiratory support as none, nasal cannula, nasal continuous positive airway pressure (NCPAP), conventional mechanical ventilation (either synchronized or nonsynchronized intermittent mandatory ventilation), or high-frequency ventilation every 6 hours on Days 1, 3, 7, 14, 21, and 28. Infants who never received mechanical ventilation (i.e., NCPAP only) were included in the data. If an infant had more than one respiratory support recorded, we used the "highest" form of ventilation for that day (e.g., if an infant received both conventional mechanical ventilation and NCPAP, the infant was coded as having received conventional mechanical ventilation on that day). Five infants who received oxygen via hood were included in the nasal cannula group. We did not assess the type (e.g., continuous flow vs. variable flow) or manufacturer of any positive–pressure device, including mechanical or high-frequency ventilation. The nasal cannula flow rate was not recorded.

We examined the use of postnatal corticosteroids (15) and the diagnoses of necrotizing enterocolitis (NEC) (28, 29) and sepsis (30), and therapy for PDA (31) by postnatal day using standardized Neonatal Research Network definitions. The date of surgical ligation of the PDA was unavailable.

Definition of BPD

BPD was defined as a categorical variable (none, mild, moderate, or severe) among survivors by modifying the National Institutes of Health consensus definition of BPD (20, 21) to include infants transferred before 36 weeks and by defining the need for oxygen at 36 weeks using a physiologic challenge (32). BPD was defined as follows: no BPD as not receiving supplemental oxygen (O_2) for 28 days or at 36 weeks; mild BPD as receiving O_2 for greater than or equal to 28 days but not at 36 weeks; moderate BPD as receiving O_2 for greater than or equal to 28 days plus treatment with less than 30% O_2 at 36 weeks; and severe BPD as receiving O_2 for greater than or equal to 28 days plus greater than or equal to 30% O_2 or positive pressure at 36 weeks. For infants transferred between 28 days and 36 weeks, we defined BPD using the O_2 therapy at the time of transfer. For infants who were discharged or transferred less than 28 postnatal days for whom 28-day data were unavailable, we defined no BPD as not receiving O_2, mild BPD as receiving $F_{I_{O_2}}$ 0.21–0.30, moderate BPD as receiving $F_{I_{O_2}}$ 0.31–0.5, and severe BPD as $F_{I_{O_2}}$ greater than 0.5 at the time of transfer.

Statistical Methods

A set of *a priori* risk factors was considered for inclusion in each postnatal day model based on their known association with the outcomes of BPD or death and availability in clinical records. Those selected for potential inclusion in the models included gestational age, birth weight, race and ethnicity, sex, respiratory support, $F_{I_{O_2}}$, treatment for PDA, sepsis, NEC, postnatal corticosteroids, and center (16–19). We examined each risk factor in each category of BPD or death, first using unadjusted analysis and then in multivariable analysis.

A series of multinomial logistic regressions were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC), simultaneously modeling level of BPD or death as a function of the previously mentioned risk factors to develop predictive models for severity of BPD or death. Models were developed separately for each of six time periods: Postnatal Days 1 (day of birth), 3, 7, 14, 21, and 28. Infants were included in the model if they survived through the day of prediction (e.g., infants in the Postnatal Day 7 model had to survive to that day).

Final model selection was based less on statistical significance and more on how a predictor enhanced the predictive ability of the model. Each covariate was entered into the model using stepwise forward selection. Six risk factors were included in the final model: (*1*) gestational age, (*2*) birth weight, (*3*) race and ethnicity, (*4*) sex, (*5*) respiratory support, and (*6*) $F_{I_{O_2}}$. Other variables, such as sepsis, NEC (either medical or surgical), treatment for PDA (a substitute for

diagnosis of PDA because this variable was not in the dataset), and postnatal corticosteroids, did not enhance the predictive ability of the models beyond that achieved by the previously mentioned six factors and thus were not further evaluated. Because of the need to develop a predictive model that can be widely used, we could not include clinical center as a factor in the models. We tested for the effect of adding center to the models and found that the predictive ability of the models increased only marginally: the C statistic increased by 0.9%–1.3% for models that included center.

Predictive performance of our models was assessed using a C statistic, which corresponds to the area under the receiver–operating characteristic curve, which is suitable for multinomial outcomes, such as our five-level outcome. Internal validation was accomplished by dividing the cohort into two parts: two-thirds of the infants were randomly selected from each site as the model development cohort, and the remaining third were used as an internal model validation cohort. External validation was accomplished by applying the development models on two different cohorts of infants and comparing the results. One cohort included infants in the recently reported Neonatal Research Network Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low-birth-weight Infants (SUPPORT) trial who were at the same centers as the Benchmarking Trial, and the other cohort included infants in the Benchmarking Trial who were at the same gestational age and center as those in SUPPORT (33, 34).

RESULTS

We identified 4,095 infants with Benchmarking Trial data: 3,636 (88.8%) infants were eligible for this study; 68 infants were excluded because of death at less than or equal to 12 hours. Ten infants at less than 23 weeks (100% developed BPD) and 381 infants at more than 30 weeks gestation (<1% developed BPD) were also excluded. There were seven infants for whom an outcome was not determined.

The mean birth weight for the cohort was 897 ± 203 g, the mean gestational age was 26.7 ± 1.9 weeks, the mean maternal age was 27.2 ± 6.5 years, 51% were male, and 13% received postnatal corticosteroids (Table 1). In addition, 85% received antenatal steroids, and 81% received surfactant.

When examining categories of BPD, increasing severity of BPD was inversely proportional to gestational age and birth weight (Table 1). As the severity of BPD increased, the percentage of male infants increased. Infants with increasing severity of BPD were also more likely to have other morbidities of prematurity, such as PDA, sepsis, and surgical NEC (Table 1). A higher proportion of infants receiving mechanical ventilation, either conventional or high-frequency, compared with NCPAP, nasal cannula, or no support at each postnatal day developed severe BPD (Table 2). At each time point studied, F_{IO_2} was higher with increasing severity of BPD and death. We present the adjusted odds ratios for each of the risk factors by postnatal day for all outcomes in Appendix 1.

The six covariates in the final models were (*1*) gestational age; (*2*) birth weight; (*3*) race and ethnicity; (*4*) sex; (*5*) respiratory support (none, nasal cannula, NCPAP, conventional mechanical ventilation, or high-frequency ventilation); and (*6*) F_{IO_2}. These six covariates were independently strongly associated with outcome and collectively predicted outcome well. Using the six risk-factor model, the C statistic for the Postnatal Day 1 model was 0.793. Models for subsequent days had a steadily increasing C statistic, reaching a maximum of 0.854 on Postnatal Day 28 (Table 3). The factor that contributed most to model prediction changed depending on the postnatal day (Table 3). Gestational age best improved prediction of the outcome on Postnatal Days 1 (C statistic = 0.750) and 3 (C statistic = 0.745). On Postnatal Days 7, 14, 21, and 28, type of respiratory support increasingly improved outcome prediction (from a C statistic of 0.771–0.823) more than any of the other factors.

C statistics derived by fitting these models to the internal validation cohort were similar (Table 4). In addition, we identified 1,055 infants in the Benchmarking Trial and 722 infants in SUPPORT between 23 and 27 weeks' gestation and at the same centers. We applied the Postnatal Day 1, 3, 7, and 14 development models to both cohorts of infants and found that the C statistic was always within 2% (Table 4). F_{IO_2} data after Day 14 were unavailable in SUPPORT.

Estimator

A prediction tool was developed that provides individual predicted estimates of BPD risk or death at each of six postnatal days. The model requires birth weight, gestational age, sex, race and ethnicity, respiratory support, and F_{IO_2} as inputs. Table 5 presents two examples of BPD risk or death for two hypothetical infants. A Web-based version of this tool is available at https://neonatal.rti.org/.

DISCUSSION

Our large, multicenter study identified the change in the relative contributions of a variety of risk factors to the prediction of BPD with advancing postnatal age. This knowledge is important because the benefits of postnatal treatment strategies might depend on baseline BPD risk. For example,

TABLE 1. RISK FACTORS OF STUDY POPULATION, INCLUDING OVERALL AND BY OUTCOME

	No BPD	Mild BPD	Moderate BPD	Severe BPD	Death	All
Number of subjects with outcome	1,218	757	714	472	468	3,629
Birth weight, g, mean ± SD	1,042 ± 149	891 ± 174	839 ± 180	788 ± 177	727 ± 173	897 ± 203
Gestational age, wks, mean ± SD	28.2 ± 1.4	26.4 ± 1.4	26.2 ± 1.6	25.8 ± 1.7	25.1 ± 1.7	26.7 ± 1.9
Male, %	44.2	49.4	55.9	58.9	56.4	51.1
Race: black not Hispanic, %	42.5	38.3	34.5	38.6	45.1	39.9
Ethnicity: Hispanic, %	18.1	18.8	15.4	15.7	18	17.4
Patent ductus arteriosus, n (%)	301 (25)	346 (46)	388 (54)	278 (59)	230 (49)	1,543 (43)
Indomethacin, n (%)	228 (19)	296 (39)	330 (46)	228 (48)	172 (37)	1,254 (35)
Ligation, n (%)	22 (2)	73 (10)	146 (20)	141 (30)	37 (8)	419 (12)
Early onset sepsis ⩽ 72 h, n (%)	13 (1)	14 (2)	13 (2)	10 (2)	25 (5)	75 (2)
Late-onset sepsis >72 h, n (%)	211 (17)	243 (32)	276 (39)	270 (57)	164 (35)	1,164 (32)
Necrotizing enterocolitis						
Medical, n (%)	46 (4)	49 (6)	29 (4)	33 (7)	18 (4)	175 (5)
Surgical, n (%)	19 (2)	25 (3)	20 (3)	35 (7)	73 (16)	172 (5)
Postnatal corticosteroids, n (%)	9 (1)	62 (8)	154 (22)	222 (47)	32 (7)	479 (13)

Definitions of abbreviations: BPD = bronchopulmonary dysplasia; SD = standard deviation.

TABLE 2. RESPIRATORY SUPPORT AND MEAN F_{IO_2} FOR EACH OUTCOME BY POSTNATAL DAY (ROW PERCENTS)

Day	Respiratory Support	No BPD	Mild BPD	Moderate BPD	Severe BPD	Death
		Maximum N = 1,218	Maximum N = 757	Maximum N = 714	Maximum N = 472	Maximum N = 468
1	HFV, %	6	16	22	17	39
	CMV, %	27	23	22	15	13
	NCPAP, %	63	15	11	7	4
	Nasal cannula, %	74	18	5	3	0
	No ventilation, %	85	8	3	0	5
	Mean F_{IO_2}, %	38	39	42	46	53
3	HFV, %	7	19	24	19	31
	CMV, %	16	25	28	18	14
	NCPAP, %	53	20	14	9	4
	Nasal cannula, %	63	22	8	4	3
	No ventilation, %	87	6	3	2	3
	Mean F_{IO_2}, %	35	37	37	38	47
7	HFV, %	1	14	31	24	31
	CMV, %	7	25	31	24	13
	NCPAP, %	37	28	21	10	5
	Nasal cannula, %	56	24	12	6	2
	No ventilation, %	86	7	4	1	2
	Mean F_{IO_2}, %	41	37	36	37	44
14	HFV, %	1	11	30	33	26
	CMV, %	5	25	34	27	10
	NCPAP, %	27	33	24	13	3
	Nasal cannula, %	47	32	17	3	2
	No ventilation, %	93	3	2	2	2
	Mean F_{IO_2}, %	44	42	43	46	54
21	HFV, %	1	12	33	34	20
	CMV, %	5	23	36	29	9
	NCPAP, %	22	37	26	13	2
	Nasal cannula, %	43	34	17	5	2
	No ventilation, %	97	1	1	1	1
	Mean F_{IO_2}, %	41	42	44	47	55
28	HFV, %	1	11	31	39	19
	CMV, %	4	20	37	32	7
	NCPAP, %	16	37	30	16	1
	Nasal cannula, %	32	41	21	5	1
	No ventilation, %	97	1	1	1	1
	Mean F_{IO_2}, %	36	41	44	47	54

Definitions of abbreviations: BPD = bronchopulmonary dysplasia; CMV = conventional mechanical ventilation; HFV = high-frequency ventilation; NCPAP = nasal continuous positive airway pressure.

the benefits of postnatal steroids for the prevention of BPD seem to outweigh the risks only in populations of premature infants at high risk of BPD. A meta-regression analysis of randomized, controlled trials of BPD demonstrated that, as the BPD risk increased above 65% in the control groups, postnatal steroid use was associated with a decrease in the risk of mortality or cerebral palsy; at lower baseline risk, treatment was associated with increased risk of mortality or cerebral

TABLE 3. MODEL PREDICTION C STATISTIC (AKIN TO AREA UNDER THE RECEIVER–OPERATING CHARACTERISTIC CURVE) AND INDIVIDUAL VARIABLES FOR DAYS 1–28 MODELS FOR THE DEVELOPMENT COHORT*

Day 1		Day 3		Day 7	
Variable	C Statistic	Variable	C Statistic	Variable	C Statistic
Gestational age	0.750	Gestational age	0.745	Respiratory support	0.771
Birth weight	0.772	Respiratory support	0.787	Gestational age	0.806
F_{IO_2}	0.784	Birth weight	0.798	Birth weight	0.814
Respiratory support	0.790	F_{IO_2}	0.805	F_{IO_2}	0.817
Race and ethnicity	0.791	Male sex	0.807	Race and ethnicity	0.817
Male sex	0.793	Race and ethnicity	0.807	Male sex	0.818
Day 14		**Day 21**		**Day 28**	
Variable	C Statistic	Variable	C Statistic	Variable	C Statistic
Respiratory support	0.795	Respiratory support	0.802	Respiratory support	0.823
Birth weight	0.819	F_{IO_2}	0.831	F_{IO_2}	0.852
Gestational age	0.825	Gestational age	0.833	Birth weight	0.851
F_{IO_2}	0.826	Birth weight	0.835	Race and ethnicity	0.853
Race and ethnicity	0.826	Race and ethnicity	0.835	Gestational age	0.853
Male sex	0.827	Male sex	0.836	Male sex	0.854

* For example, on Day 7, respiratory support provides 77.1% of the predictive ability of the C statistic, with a small incremental increase in the C statistic with additional variables to a final model C statistic of 81.8%.

TABLE 4. INTERNAL AND EXTERNAL VALIDATION OF THE PREDICTIVE MODELS

	Internal Validation		External Validation	
	Benchmarking: Development (*n = 2,415*)	Benchmarking: Validation (*n = 1,214*)	Benchmarking* (*n = 1,055*)	SUPPORT (*n = 722*)
Demographics				
Gestational age, wk ± SD	26.7 ± 1.9	26.8 ± 1.9	25.7 ± 1.1	25.7 ± 1.1
Birth weight, g ± SD	894 ± 203	903 ± 202	830 ± 175	842 ± 168
Male, %	49	54	50	56
Black, %	40	40	43	46
Hispanic, %	17	18	18	6
White, %	43	42	39	48
Antenatal steroids, %	85	85	87	96
Outcome at 36 wks PMA, %				
No BPD	33	34	19	21
Mild BPD	21	21	25	30
Moderate BPD	20	19	26	23
Severe BPD	13	14	19	13
Death	13	12	11	13
Models: C statistic				
Day 1	0.793	0.795	0.721	0.720
Day 3	0.807	0.810	0.738	0.732
Day 7	0.818	0.823	0.744	0.736
Day 14	0.827	0.834	0.757	0.761
Day 21	0.836	0.848	N/A	N/A
Day 28	0.854	0.854	N/A	N/A

Definitions of abbreviations: BPD = bronchopulmonary dysplasia; PMA = postmenstrual age; SD = standard deviation.
* Subset of Benchmarking Trial development model subjects who have comparable birth weight, gestational age, and clinical center to the SUPPORT study subjects.

palsy (35). In infants with more severe lung disease, corticosteroids seemed to reduce risk of adverse neurodevelopmental outcome (15). In addition, steroids seem to be of greatest benefit if used after the first postnatal week (36, 37). Our models provide a precise and objective estimate of BPD risk at various postnatal ages, which is essential information for conducting trials to determine if preventive therapies, such as postnatal corticosteroids or inhaled nitric oxide, are beneficial in high-risk populations. These models might serve as a foundation for researchers to assess long-term respiratory risk including the development of asthma, long-term pulmonary function test status, and potential development of emphysema in adult life.

Previously identified risk factors for BPD include birth weight, gestational age, male sex, oxygen therapy at 24 hours, mechanical ventilation at 48 hours, and duration of assisted ventilation (16–19). These factors, measured in greater detail and at different time points, were included in our model. We added the contribution of these factors relative to each other and their relative importance at different postnatal ages. For example, although oxygen exposure is a risk factor, its independent contribution to prediction of BPD risk is

TABLE 5. TABLE OF ESTIMATED PROBABILITIES OF BRONCHOPULMONARY DYSPLASIA OR DEATH BY POSTNATAL DAY FOR TWO HYPOTHETICAL INFANTS

25-wk gestational age, 700-g birth weight, white, male

		Probability of Outcome				
Day	Respiratory support and F_{IO_2}	Death	Severe BPD	Moderate BPD	Mild BPD	No BPD
1	HFV and F_{IO_2} = 50%	0.31	0.17	0.31	0.20	0.01
3	HFV and F_{IO_2} = 100%	0.52	0.17	0.19	0.12	0.00
7	HFV and F_{IO_2} = 100%	0.42	0.20	0.28	0.10	0.00
14	CMV and F_{IO_2} = 50%	0.07	0.28	0.36	0.27	0.02
21	NCPAP and F_{IO_2} = 50%	0.02	0.19	0.36	0.39	0.04
28	Nasal cannula and F_{IO_2} = 50%	0.01	0.06	0.28	0.57	0.07

28-wk gestational age, 1,000-g birth weight, black, female

		Probability of Outcome				
Day	Respiratory support and F_{IO_2}	Death	Severe BPD	Moderate BPD	Mild BPD	No BPD
1	CMV and F_{IO_2} = 70%	0.06	0.09	0.15	0.23	0.47
3	CMV and F_{IO_2} = 35%	0.05	0.09	0.22	0.30	0.34
7	Nasal cannula and F_{IO_2} = 50%	0.01	0.04	0.09	0.21	0.65
14	No ventilation and room air	0.02	0.01	0.01	0.03	0.93
21	No ventilation and room air	0.01	0.01	0.01	0.01	0.96
28	No ventilation and room air	0.01	0.00	0.00	0.01	0.97

Definitions of abbreviations: BPD = bronchopulmonary dysplasia; CMV = conventional mechanical ventilation; HFV = high-frequency ventilation; NCPAP = nasal continuous positive airway pressure.

small relative to gestational age on Postnatal Day 1 and to respiratory support thereafter. Risk factors that were found to be significant in previous studies but that we did not include in our final models include PDA, NEC, sepsis, and postnatal corticosteroids (16–19). None of these factors improved prediction of the risk of BPD after adjustment for the six critical risk factors.

Previous BPD prediction scoring systems have been described, but none has been widely adopted. Some have satisfactory sensitivity and specificity but use oxygen therapy at 28 postnatal days as a definition of BPD, which is now outdated (5–7). Some include radiographs as part of the scoring system, which introduces subjectivity and reduces generalizability (8–11). Other problems limiting the use of these models are the inclusion of ventilated infants only, the lack of categorization of BPD by severity, the exclusion of infants who die, and underuse of antenatal corticosteroids and surfactant therapy (8–13, 38, 39). Most importantly, none examined models by postnatal day through the first 28 postnatal days. In addition, we internally and externally validated our models; our models were able successfully to classify infants in the internal validation sample into the correct level of BPD or death in more than 8 out of 10 cases. The models performed similarly in subjects in the SUPPORT trial who were born between 2004 and 2009. The C statistic is lower for both the subset of subjects in the reduced Benchmarking group and SUPPORT group because the excluded subjects had higher and lower gestational ages, and outcome is more accurately predicted at the extreme values (i.e., subjects with higher gestational age have better outcomes, with more accuracy; subjects with lower gestational age have worse outcomes, again with more accuracy).

We developed an on-line application of the prediction models. Caution should be exercised when using the on-line estimator to identify BPD risk in populations in which the demography or care practices differ markedly from our cohort. Our models and the on-line application were based on data from Level III neonatal intensive care units at large, mostly urban academic medical centers. Because our BPD definitions depended in part on various respiratory therapies, center-specific use of these therapies might influence the prediction models. For example, we speculate that high-frequency ventilation was most likely used in our study centers as a "rescue" therapy for infants with profound respiratory failure or pulmonary interstitial emphysema (40), and therefore BPD risks were higher among infants exposed to high-frequency ventilation. In centers where high-frequency ventilation is used as a primary therapy, BPD risk might be overestimated using our model (41).

In conclusion, we found that gestational age conveyed the most predictive information for BPD risk on Postnatal Days 1 and 3, and respiratory support on Days 7, 14, 21, and 28. The BPD estimator will provide prognostic information for families and clinicians, and will assist in identifying the optimal candidates for enrollment in clinical trials to prevent BPD.

Author Disclosure: M.M.L. was on a Data Safety and Monitoring Board for Pfizer and was a consultant for Nycomed Inc. and Astellas Pharma Inc. He received grant support from Biosynexus and received lecture fees from Duke University. J.C.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.L.B. is a Board Member of the Vermont Oxford Network. P.B.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. N.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.A.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.J.S. is an employee of Emory University. S.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.R.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.A.E. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.M.C. received institutional grant support from Duke University. He gave expert testimony for medical malpractice case reviews and received lecture fees from Casolini Medical Center. D.E.W.-C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.P.V.M. received travel accommodations from Ikaria. A.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.G.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. N.N.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.A.Y. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.G.F. was a consultant for Biosynexus and gave expert testimony for various firms on neonatal and prenatal issues. W.A.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.R.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. N.S.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.D.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.C.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Acknowledgment: The authors are indebted to their medical and nursing colleagues and the infants and their parents who agreed to take part in this study. Study concept and design: Matthew Laughon, Carl Bose, Brian Smith, Michael Cotten, Namasivayam Ambalavanan, Bradley Yoder, Waldemar Carlo, Kathleen Kennedy, Krisa Van Meurs, Richard Ehrenkranz, Marie Gantz, and Deanne Wilson-Costello. Acquisition of data: Barbara Stoll, Richard Ehrenkranz, Waldemar Carlo, Rosemary Higgins, Seetha Shankaran, Deanne Wilson-Costello, Roger Faix, Bradley Yoder, Krisa Van Meurs, Kurt Schibler, Susan Buchter, Neil Finer, Richard Ehrenkranz, Abhik Das, Marie Gantz, Nancy Newman, and Michael Cotten. Analysis and interpretation of data: Matthew Laughon, Carl Bose, P. Brian Smith, Alexis Davis, Namasivayam Ambalavanan, Barbara Stoll, Abbot Laptook, Bradley Yoder, Roger Faix, Waldemar Carlo, Rosemary Higgins, Abhik Das, Krisa Van Meurs, Kathleen Kennedy, Michael Cotten, and Deanne Wilson-Costello. Drafting of the manuscript: Matthew Laughon, Carl Bose, Waldemar Carlo, Alexis Davis, and Michael Cotten. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Matthew Laughon, John Langer, Michele Walsh, P. Brian Smith, Waldemar Carlo, Marie Gantz, and Abhik Das. Obtained funding: Barbara Stoll, Waldemar Carlo, Seetha Shankaran, Michele Walsh, Krisa Van Meurs, Waldemar Carlo, Neil Finer, Rosemary Higgins, Abhik Das, Roger Faix, and Michael Cotten. Administrative, technical, or material support: Matthew Laughon, Barbara Stoll, Richard Ehrenkranz, Waldemar Carlo, Rosemary Higgins, Abhik Das, Kurt Schibler, and Neil Finer. Study supervision: Matthew Laughon, Carl Bose, Abbot Laptook, Bradley Yoder, Waldemar Carlo, Rosemary Higgins, Abhik Das, Roger Faix, Deanne Wilson-Costello, Susan Buchter, and Michael Cotton.

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