Validation of the National Institutes of Health Consensus Definition of Bronchopulmonary Dysplasia

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ABSTRACT. *Objective.* **A number of definitions of bronchopulmonary dysplasia (BPD), or chronic lung disease, have been used. A June 2000 National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute Workshop proposed a severity-based definition of BPD for infants <32 weeks' gestational age (GA). Mild BPD was defined as a need for supplemental oxygen (O_2) for ≥28 days but not at 36 weeks' postmenstrual age (PMA) or discharge, moderate BPD as O_2 for ≥28 days plus treatment with <30% O_2 at 36 weeks' PMA, and severe BPD as O_2 for ≥28 days plus ≥30% O_2 and/or positive pressure at 36 weeks' PMA. The objective of this study was to determine the predictive validity of the severity-based, consensus definition of BPD.**

Methods. **Data from 4866 infants (birth weight ≤1000 g, GA <32 weeks, alive at 36 weeks' PMA) who were entered into the National Institute of Child Health and Human Development Neonatal Research Network Very Low Birth weight (VLBW) Infant Registry between January 1, 1995 and December 31, 1999, were linked to data from the Network Extremely Low Birth Weight (ELBW) Follow-up Program, in which surviving ELBW infants have a neurodevelopmental and health assessment at 18 to 22 months' corrected age. Linked VLBW Registry and Follow-up data were available for 3848 (79%) infants. Selected follow-up outcomes (use of pulmonary medications, rehospitalization for pulmonary causes, receipt of respiratory syncytial virus prophylaxis, and neurodevelopmental abnormalities) were compared among infants who were identified with BPD defined as O_2 for 28 days (28 days definition), as O_2 at 36 weeks' PMA (36 weeks' definition), and with the consensus definition of BPD.**

Results. **A total of 77% of the neonates met the 28-days definition, and 44% met the 36-weeks definition. Using the consensus BPD definition, 77% of the infants had BPD, similar to the cohort identified by the 28-days definition. A total of 46% of the infants met the moderate (30%) or severe (16%) consensus definition criteria, identifying a similar cohort of infants as the 36-weeks definition. Of infants who met the 28-days definition and 36-weeks definition and were seen at follow-up at 18 to 22 months' corrected age, 40% had been treated with pulmonary medications and 35% had been rehospitalized for pulmonary causes. In contrast, as the severity of BPD identified by the consensus definition worsened, the incidence of those outcomes and of selected adverse neurodevelopmental outcomes increased in the infants who were seen at follow-up.**

Conclusion. **The consensus BPD definition identifies a spectrum of risk for adverse pulmonary and neurodevelopmental outcomes in early infancy more accurately than other definitions.** *Pediatrics* **2005;116:1353–1360;** ***bronchopulmonary dysplasia, chronic lung disease, extremely preterm infants, neurodevelopmental.***

ABBREVIATIONS. BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; PMA, postmenstrual age; VLBW, very low birth weight; GA, gestational age; ELBW, extremely low birth weight; NICHD, National Institute of Child Health and Human Development; CPAP, continuous positive airway pressure; RSV, respiratory syncytial virus; CP, cerebral palsy.

Several definitions of bronchopulmonary dysplasia (BPD), or chronic lung disease (CLD), have been used since 1967, when Northway et al[1] first described the clinical, radiologic, and pathologic changes seen in infants who had severe respiratory distress syndrome and had been treated with prolonged mechanical ventilation and high inspiratory oxygen levels. The term BPD had been applied to that condition so as to emphasize that all of the tissues of the lung, airways, and parenchyma were involved in the pathologic process.

During the late 1970s and early 1980s, the radiologic stages of worsening BPD that were described in the initial description were rarely seen, and a number of investigators defined BPD by clinical characteristics that were present at 1 month of age in association with an abnormal or "characteristic" chest radiograph.[2–4] In 1988, Shennan et al[5] suggested that the need for or treatment with oxygen at 36 weeks' postmenstrual age (PMA) was a better predictor of abnormal pulmonary outcome in infancy for very low birth weight (VLBW; birth weight ≤1500 g) infants <32 weeks' gestational age (GA) than the need for or treatment with oxygen at 1 month of age. The

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Accepted for publication Apr 21, 2005.
doi:10.1542/peds.2005-0249
Presented in part at the annual meeting of the Pediatric Academic Societies; April 28–May 1, 2001; Baltimore, MD.
No conflict of interest declared.

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term "chronic lung disease" was used to describe those infants.

BPD/CLD continues to be a major cause of mortality and long-term morbidity in VLBW, especially extremely low birth weight (ELBW; birth weight ≤1000 g) infants. The definitions of BPD/CLD have become less precise as survival of ELBW infants has increased, and the terms are now often used interchangeably. Most current diagnostic criteria are based solely on treatment with supplemental oxygen therapy at 36 weeks' PMA and do not require or specify chest radiographic abnormalities.

The definition of BPD/CLD in preterm infants was reviewed at a June 2000 National Institute of Child Health and Human Development (NICHD)/National Heart, Lung, and Blood Institute Workshop, "From BPD to CLD: Emergence of a New Disease."[6] A consensus of workshop participants chose to refer to the condition as BPD because "it is clearly distinct from the multiple chronic lung diseases of later life." In addition, a consensus, severity-based definition of BPD was proposed (Table 1). One of the aims of the consensus BPD definition was to acknowledge that infants who had been treated with oxygen for >28 days but no longer required oxygen at 36 weeks' PMA might have residual lung disease. Although not specified in the consensus BPD definition, it was recommended that a physiologic test confirming the need for supplemental oxygen be performed.[7] Furthermore, specific radiographic findings were not required as part of the workshop definition because these findings had not been found to increase diagnostic sensitivity or specificity.[8,9] The primary objective of this project was to determine the predictive validity of the proposed severity-based diagnostic criteria for BPD on pulmonary, neurodevelopmental, and growth outcomes at 18 to 22 months' corrected age.

TABLE 1. Severity-Based Diagnostic Criteria for BPD

Gestational Age	<32 wk
Time point of Assessment	36 wk PMA or discharge home, whichever comes first
	Therapy with oxygen >21% for at least 28 d plus:
Mild BPD	Breathing room air
Moderate BPD	Need* for <30% oxygen
Severe BPD	Need* for ≥30% oxygen and/or positive pressure (PPV or nasal CPAP)

BPD usually develops in neonates who are being treated with oxygen and positive-pressure ventilation for respiratory failure, most commonly respiratory distress syndrome. Persistence of clinical features of respiratory disease (tachypnea, retractions, rales) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing severity. Infants who are treated with oxygen >21% and/or positive pressure for nonrespiratory disease indications (eg, central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress. A day of treatment with oxygen >21% means that the infant received oxygen >21% for >12 hours on that day. Treatment with oxygen >21% and/or positive pressure at 36 weeks' PMA or discharge should not reflect an "acute" event but rather reflect the infant's usual daily therapy for several days before and after 36 weeks' PMA or discharge. Adapted from reference 6.

* A physiologic test confirming an oxygen requirement at the assessment time point remains to be defined. The test may include a pulse oximetry saturation range.

METHODS

A total of 7439 infants who had a birth of ≤1000 g, were <32 weeks' GA, and were born at 1 of the 14 NICHD Neonatal Research Network centers between January 1, 1995, and December 31, 1999, were listed in the Network's VLBW Registry. Of those infants, 1075 (14.5%) died within the first 12 hours after birth and 1456 (19.6%) died after 12 hours but before discharge (1314 before 36 weeks' PMA). An additional 42 infants had missing oxygen use or outcome variables and were excluded from data analysis. Data from the remaining 4866 (65.4%) infants who were alive at 36 weeks' PMA and/or survived to discharge or transfer to another hospital were linked to data in the Network's ELBW Follow-up Registry. Linked follow-up data were available on 3848 (79.1%) of the surviving ELBW infants.

NICU data were abstracted from the infants' charts by trained research nurses using previously described definitions.[10–12] After discharge, families were invited to participate in the NICHD Neonatal Research Network ELBW Follow-up Program for a comprehensive assessment at 18 to 22 months' corrected age. The follow-up assessment has been described in detail; it is performed by certified examiners and included a standardized neurologic examination, Bayley Scales of Infant Development II-R (Mental Scale, Motor Scale, and Behavioral Rating Scale), structured parent interviews about medical and social history and functional performance, and anthropometric measurements.[13] Anthropometric measures were compared with the 2000 Centers for Disease Control and Prevention growth curves[14] after adjustment for gender and age at the time of the follow-up assessment.

For the purpose of this report, the incidence of selected follow-up outcomes was compared among infants who were identified with BPD defined variously as (1) supplemental oxygen therapy for all 28 days of the first 28 days of life (28-days definition), (2) supplemental oxygen for all 28 days of the first 28 days of life and an abnormal chest radiograph consistent with parenchymal lung disease (28 days–CXR definition), (3) receipt of supplemental oxygen at 36 weeks' PMA (36-weeks definition), (4) receipt of supplemental oxygen at 36 weeks' PMA and an abnormal chest radiograph consistent with parenchymal lung disease (36 weeks–CXR definition), and (5) by the consensus BPD definition (Table 1). Although the diagnostic criteria outlined in the consensus BPD definition specified that a day of treatment with supplemental oxygen meant that the infant received >21% oxygen for >12 hours on that day and that a physiologic assessment be used to confirm oxygen dependence at 36 weeks' PMA,[7] that information was not available in the Network VLBW Registry. Respiratory support and supplemental inspired oxygen therapy were administered at the discretion of the infant's clinical team. Data describing the mode of respiratory support (ventilator, nasal continuous positive airway pressure [CPAP], oxyhood, or nasal cannula) and the highest measured concentration of oxygen received on day 28 of life and at 36 weeks' PMA or discharge were recorded by trained neonatal research nurses. In addition, the total duration of different modes of respiratory support and of supplemental oxygen therapy were recorded. Therefore, the analyses described in this report were based on therapies received. Furthermore, because data to permit calculation of the effective inspiratory oxygen concentration had not been collected, an infant who was receiving nasal cannula oxygen at 36 weeks' PMA was considered to have moderate BPD, whereas an infant who was receiving ≥30% oxygen via an oxyhood and/or positive pressure from a mechanical ventilator or nasal CPAP at 36 weeks' PMA was considered to have severe BPD. The decision about whether respiratory syncytial virus (RSV) prophylaxis was prescribed was made by each infant's primary care provider. Abnormal pulmonary outcomes at 18 to 22 months' corrected age included the incidence of treatment with diuretics or bronchodilators (referred to as pulmonary medications) and rehospitalization for pulmonary causes between discharge and the 18- to 22-months' corrected age follow-up visit. Neurodevelopmental impairment was defined as the presence of any of the following: cerebral palsy (CP), Bayley Mental Developmental Index <70, Bayley Psychomotor Developmental Index <70, deaf/hearing loss requiring amplification in both ears, or bilaterally blind.

Infants (n = 672) who were transferred to another hospital

before discharge home were categorized similarly to infants who were discharged directly home. Of the 473 infants who were transferred before 36 weeks' PMA, 271 were still being treated with oxygen and/or respiratory support at the time of transfer; for this analysis, they were classified according to their therapies at transfer. Because transfer to another hospital occurred after 36 weeks' PMA for the remaining 199 infants, sufficient data were available to determine whether BPD developed and, if so, which definitions were met. Length of stay was defined as the number of days to discharge or transfer from a network participating center. However, the accuracy of that analysis is limited because the number of days spent by transferred infants in the other hospital or chronic care facility was not included in the data set.

Statistical Analyses

χ^2 tests, odds ratios, Mantel-Haenszel χ^2 tests and analysis of variance were used to examine the relationship among BPD diagnostic category, maternal and neonatal characteristics, and outcomes in the NICU and at 18 to 22 months' corrected age. $P < .05$ was considered significant. Analyses were completed at RTI International (Research Triangle Park, NC) using SAS Software.

RESULTS

The proportion of the study population ($n = 4866$) that was classified as having BPD according to the 5 BPD definitions and among the 3848 infants who were seen at follow-up is displayed in Table 2. The addition of information about the presence of an abnormal chest radiograph to the 28-days definition and 36-weeks definition of BPD did not improve significantly the ability of those definitions to predict abnormal pulmonary outcomes. As expected, fewer infants met the 36-weeks definition than the 28-days definition, because many infants who needed oxygen during the first 28 days of life no longer needed it at 36 weeks' PMA. Furthermore, the 28-days definition identified a similar proportion of infants with BPD as the combined mild, moderate, and severe categories of the consensus BPD definition, whereas the 36-weeks definition identified a similar proportion of infants as the combined moderate and severe categories of consensus definition.

Of the cohort of infants ($n = 3848$) who were seen at follow-up, use of pulmonary medications, rehospitalization for pulmonary causes, and receipt of RSV prophylaxis were compared for infants with BPD versus those without BPD using the 28-days, 28 days–CXR, 36-weeks, and 36 weeks–CXR definitions of BPD and across the diagnostic categories of the consensus definition of BPD (Table 2). A significant association between BPD defined by the 28-days and 36-weeks definitions (vs no BPD) and each outcome, as well as a significant linear association between the level of BPD (by the consensus definition) and all outcomes, was found. Of infants who met the 28-days definition and 36-weeks definition and were seen at follow-up at 18 to 22 months' corrected age, 40% had been treated with pulmonary medications, 35% had been rehospitalized for pulmonary causes, and 20% received RSV prophylaxis. In contrast, as the severity of BPD identified by the consensus definition worsened, the incidence of those outcomes and of selected adverse neurodevelopmental outcomes increased in the infants who were seen at follow-up ($P < .0001$ for all outcomes). Pairwise comparisons across the diagnostic categories of the consensus definition of BPD were also performed for these selected pulmonary outcomes (Table 3). Although the percentage of infants with these pulmonary outcomes increased significantly as the severity of BPD increased, for some pairwise comparisons, the differences were not always statistically significant.

Given this relationship between the consensus BPD definition and the incidence of abnormal pulmonary outcomes, the relationship between the consensus definition and neurodevelopmental and growth outcomes then was examined. Selected neonatal characteristics, by diagnostic category of the consensus definition, of the 4866 infants included in the study population are displayed in Table 4. Compared with infants without BPD, infants with BPD

TABLE 2. BPD Definitions and Selected Pulmonary Outcomes at 18 to 22 Months' Corrected Age*

BPD Definition	NICU Infants, *n* (%; *N* = 4866)	Follow-up Infants, *n* (%; *N* = 3848)	Pulmonary Medications (% of Follow-up†)	Rehospitalized Pulmonary Cause (% of Follow-up†)	RSV Prophylaxis (% of Follow-up†)
28 days					
Yes	3742 (76.9)	2972 (77.2)	37.6‡	32.1‡	20.2‡
No	1124 (23.1)	876 (22.8)	27.2	23.9	12.5
28 days–CXR					
Yes	2882 (59.4)	2301 (60.0)	39.8‡	33.9‡	20.2§
No	1967 (40.6)	1534 (40.0)	28.5	24.6	15.7
36 weeks					
Yes	2152 (44.2)	1683 (43.7)	43.8‡	36.1‡	23.2‡
No	2714 (55.8)	2165 (56.3)	28.6	25.6	14.8
36 weeks–CXR					
Yes	1876 (38.7)	1485 (38.7)	44.7‡	36.6‡	22.9‡
No	2978 (61.3)	2355 (61.3)	29.3	26.1	15.6
Consensus					
None	1124 (23.1)	876 (22.8)	27.2	23.9	12.5
Mild	1473 (30.3)	1186 (30.8)	29.7	26.7	16.6
Moderate	1471 (30.2)	1143 (29.7)	40.8	33.5	19.2
Severe	798 (16.4)	643 (16.7)	46.6‡	39.4‡	28.4‡

* Missing data: 28 days–CXR, 17 infants (13 for follow-up cohort); 36 weeks–CXR, 12 (8 for follow-up cohort); pulmonary medications, 17; rehospitalizations for pulmonary causes, 35; RSV prophylaxis, 17.
† Cohort of infants who were seen at 18 to 22 months' corrected age.
‡ $P < .0001$, §$P < .001$ versus no BPD for the 28 days, 28 days–CXR, 36 weeks, and 36 weeks–CXR definitions, Mantel-Haenszel χ^2; for linear association across the categories of the consensus definition (none to severe), Mantel-Haenszel χ^2.

TABLE 3. Results of Pairwise Comparisons for Diagnostic Categories of the Consensus BPD Definition and Selected Pulmonary Outcomes at 18 to 22 Months' Corrected Age

Diagnostic Category Comparison	Pulmonary Medications	Rehospitalized Pulmonary Causes	RSV Prophylaxis
Mild versus None	1.13* (0.93–1.38)	1.16 (0.95–1.42)	1.39† (1.08–1.79)
Moderate versus None	1.84‡ (1.53–2.23)	1.61‡ (1.32–1.96)	1.67‡ (1.30–2.14)
Severe versus None	2.33‡ (1.88–2.90)	2.08‡ (1.66–2.59)	2.78‡ (2.14–3.62)
Moderate versus Mild	1.63‡ (1.37–1.93)	1.38§ (1.16–1.65)	1.20 (0.97–1.48)
Severe versus Mild	2.06‡ (1.69–2.51)	1.79‡ (1.46–2.19)	2.00‡ (1.59–2.51)
Severe versus Moderate	1.27† (1.04–1.54)	1.29† (1.06–1.58)	1.67‡ (1.33–2.09)

* Odds ratio (95% confidence interval).
† $P < .05$.
‡ $P < .0001$.
§ $P < .001$.

TABLE 4. Characteristics of the NICU Population by Diagnostic Category of the Consensus BPD Definition

Characteristic*	No BPD ($N = 1124$)	Mild BPD ($N = 1473$)	Moderate BPD ($N = 1471$)	Severe BPD ($N = 798$)
Birth weight†, g	867 (108)	791 (132)	766 (132)	737 (135)‡
Gestational age†, wk	27.8 (1.8)	25.7 (1.5)	25.7 (1.6)	25.6 (1.8)‡
% Male	38.7	42.5	50.9	56.0‡
Race, %‡				
Black	49.1	46.0	39.9	44.0
White	36.2	38.1	44.6	41.7
Hispanic	12.5	13.8	11.7	12.1
Other	2.2	2.2	3.8	2.3
% IVH ≥3 or 4	8.8	16.9	18.7	24.6‡
% PVL	3.2	4.9	5.8	9.5‡
% NEC	4.5	7.8	7.6	13.9‡
% Late-onset sepsis (culture positive)	21.2	35.4	40.8	54.0‡
% Late-onset sepsis (culture negative)	25.8	48.3	55.5	67.2‡
% Postnatal steroids	9.3	45.5	67.6	78.2‡
% Discharge on oxygen	2.5	3.1	62.8	67.4‡
Length of stay†, d	64 (27)	90 (29)	99 (35)	127 (65)‡
Postdischarge deaths, n	20	22	30	38‡

IVH indicates intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis.
* Missing data: race, 15 infants; IVH, 29; PVL, 53; NEC, 2; culture-positive sepsis, 1; culture-negative sepsis, 2; postnatal steroids, 2; D/C on oxygen, 20; length of stay, 9.
† Mean ± SD.
‡ $P < .0001$, χ^2 test for race; Mantel-Haenszel χ^2 for linear association across the consensus definition categories for all other categorical variables; analysis of variance for continuous variables.

had significantly lower birth weights and gestational ages and significantly longer hospital stays. Although the overall gender and the racial distribution of the study population are similar to that previously described in ELBW infants who were cared for in the NICHD Neonatal Research Network centers during this period,[10–12] significantly more boys developed moderate to severe BPD, and a significant association was noted between race and BPD severity. In addition, as severity of BPD worsened, the proportion of infants with grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, late-onset infection (both culture-proven and culture-negative), prescription for postnatal steroid therapy and for oxygen for home use, and postdischarge deaths increased significantly.

Selected neurodevelopmental and growth outcomes at 18 to 22 months' corrected age, by diagnostic category of the consensus BPD definition, of the 3848 infants included in the linked study population are displayed in Table 5. The incidence of any neurodevelopmental impairment, CP, Mental Developmental Index <70, Psychomotor Developmental Index <70, blindness, and hearing impairment requiring amplification significantly increased as the severity of BPD increased. Growth outcomes were also significantly affected as the severity of BPD increased, with an increased number of infants having anthropometric measurements below the 2000 Centers for Disease Control and Prevention 10th percentile values. Although the proportion of infants with oxygen prescribed for home use increased significantly as the severity of BPD worsened, the age when home oxygen was discontinued was similar for infants with no, mild, and moderate BPD and higher for infants with severe BPD.

DISCUSSION

The characteristics and treatment of infants who develop BPD today are markedly different from those described by Northway et al[1] in 1967. Compared with infants with an average birth weight of ~1900 g and an average gestational age of ~32 weeks, the typical infant who develops BPD today is ≤1000 g birth weight and <30 weeks' gestation.[10–12] However, although widespread use of antenatal steroids and surfactant replacement therapy after delivery have reduced the risk for severe acute lung disease in larger, more mature preterm infants, BPD continues to be a major cause of mortality and mor-

TABLE 5. Selected Neurodevelopmental and Growth Outcomes at 18 to 22 Months' Corrected Age by Diagnostic Category of the Consensus BPD Definition

Outcome*	No BPD (N = 876)	Mild BPD (N = 1186)	Moderate BPD (N = 1143)	Severe BPD (N = 643)
% CP	8.1	11.3	17.0	26.8†
% MDI <70	21.0	25.6	35.1	49.8†
% PDI <70	12.2	16.4	26.1	41.7†
Blind†				
% Unilateral	0.23	0.17	1.1	1.6
% Bilateral	0.11	0.68	1.2	2.2
% Hearing impairment	0.82	2.7	3.7	6.0†
% Hearing aids	0.35	1.7	2.0	3.9†
% Neurodevelopmental impairment	28.1	34.4	44.6	61.9†
Weight‡, kg	10.3 (1.5)	10.4 (1.5)	10.2 (1.5)	10.0 (1.5)†
Length‡, cm	80.4 (4.5)	80.6 (4.3)	80.1 (4.4)	79.1 (4.4)†
Head circumference‡, cm	46.8 (1.7)	46.9 (1.8)	46.7 (1.9)	46.3 (2.1)†
% Weight <10th percentile	48.8	49.8	55.2	62.6†
% Length <10th percentile	30.6	28.9	37.9	46.2†
% Head circumference <10th percentile	21.8	21.7	27.3	39.4†
Home oxygen prescribed, n (%)	23 (2.7)	88 (7.5)	656 (57.8)	395† (62.1)
Age home oxygen stopped, mo (SD; n)	7.3 (3.8; 19)	7.2 (4.4; 81)	7.6 (4.1; 601)	9.7† (4.8; 311)

MDI indicates Mental Developmental Index; PDI, Psychomotor Developmental Index.
* Missing data: CP, 24; MDI, 271; PDI, 320; blind, 30; hearing impairment, 53; hearing aids, 54; weight, 41; length, 50; head circumference, 36; weight <10th percentile, 60; length < 10th percentile, 69; head circumference <10th percentile 58; oxygen for home use, 41.
† $P < .0001$, χ^2 test for Blind; Mantel-Haenszel χ^2 for linear association across the consensus definition categories for categorical variables; analysis of variance for continuous variables.
‡ Mean ± SD.

bidity in VLBW, and especially ELBW, infants. Recent NICHD Neonatal Research Network data have demonstrated that the incidence of BPD (defined by treatment with O_2 at 36 weeks' PMA) decreased with increasing birth weight, from 52% in infants of 501 to 750 g birth weight, to 34% in infants of 751 to 1000 g birth weight, to 15% in infants of 1001 to 1250 g birth weight, to 7% in infants of 1251 to 1500 g birth weight.[12]

During the past 35 years, the diagnostic criteria used to define BPD have also changed. In addition, a number of investigators have attempted to describe scoring systems for predicting the risk or severity of BPD,[15–17] to identify risk factors that are associated with the development of BPD,[18,19] or to identify diagnostic criteria that predicted abnormal pulmonary and functional outcomes.[20–23] Older studies have tended to define BPD as treatment with supplemental oxygen for longer than 28 to 30 days,[15–18] whereas more recent studies have defined BPD as treatment with supplemental oxygen at 36 weeks' PMA.[19–23] However, studies[20–23] that have described the relationship between the duration of oxygen therapy, especially supplemental oxygen therapy at 36 weeks' PMA, and pulmonary outcomes such as treatment with pulmonary medications (bronchodilators and/or steroids) and rehospitalization for respiratory causes have reported variable findings. Palta et al[20] reported that the presence of radiographic evidence of moderate to severe BPD (as defined by a radiographic scoring system) was more predictive of the need for pulmonary medications up to 2 years of age and for rehospitalization for respiratory causes up to 5 years of age than treatment with oxygen at 36 weeks' PMA. Davis et al[22] reported that the duration of oxygen therapy, including need for or treatment with supplemental oxygen at 36 weeks' PMA, was found to be a poor surrogate for long-term pulmonary abnormalities, whereas Gregoire et al[21] observed an association with longer hospital stays during readmissions for respiratory problems but not with the number of rehospitalizations, and Smith et al[23] noted an increased rate of rehospitalization. We observed an increasing incidence of adverse pulmonary outcomes as the severity of BPD, defined by the consensus definition, worsened from mild to severe but did not find that the presence of an abnormal chest radiograph improved the ability of the 28-days or 36-weeks definitions of BPD in predicting adverse pulmonary outcomes (Table 2). In addition, consistent with reports that healthy preterm infants have abnormal lung function at term PMA[24] and altered airway development during infancy,[25] making them prone to airway problems during early childhood, we observed a substantial rate of adverse pulmonary outcomes in the infants who did not meet any of the definitions of BPD (Table 2).

Although some investigators have suggested that BPD is not independently associated with poor neurodevelopmental outcome,[26,27] most[13,28–32] have reported that BPD was a significant risk factor for the development of CP and poor functional outcomes. Vohr et al,[13] reporting for the NICHD Neonatal Research Network, previously described logistic regression analyses in which both BPD and postnatal steroids for pulmonary disease were significant risk factors associated with the likelihood of neurodevelopmental impairment in ELBW survivors at 18 to 22 months' corrected age. Evaluating children at 8 years of age, Short et al[31] demonstrated that compared with VLBW infants without BPD and with term infants, VLBW infants with BPD were more likely to receive special education services and to have difficulties with motor and cognitive skills. After controlling for birth weight and neurologic complications, these outcomes were found to be significantly related to the severity of BPD and the duration of supplemental oxygen.[30] Although Davis et al[22] reported

that BPD defined by duration of oxygen therapy had limited accuracy in predicting long-term neurosensory outcomes, the study by Gregoire et al[21] found that oxygen dependence at 36 weeks' PMA by infants of 24 to 28 weeks' GA predicted developmental delay at 18 months of age; of note, infants who needed oxygen at 28 days and not at 36 weeks' PMA had similar developmental outcomes to infants who needed oxygen for <28 days. One report[32] indicated that >75% of ELBW infants who remain ventilator dependent beyond 60 days of life have abnormal long-term neurodevelopment and that ~25% will die before hospital discharge. Furthermore, postnatal corticosteroid therapy for prevention or treatment of BPD has been increasingly incriminated as a factor that contributes to the development of CP.[33–38] Our study found that the incidence of postnatal corticosteroid use (Table 4) and of neurodevelopmental impairment and head circumference growth (Table 5) corresponded to the severity of BPD defined by the consensus definition.

With increasing survival of ELBW infants, a definition of BPD based on the duration of oxygen therapy or treatment with supplemental oxygen at 36 weeks' PMA may no longer accurately identify all infants with BPD.[6,22,39] Methods for assessing the need for supplemental oxygen are not standardized between NICUs and among physicians; thus, the incidence of BPD varies with clinical practice, rather than being determined by an objective physiologic test.[6,7,20,39] Because the development of BPD as defined by the treatment with supplemental oxygen at 36 weeks' PMA has been the primary outcome for many multicenter, intervention, randomized, controlled trials (eg, [40–44]), practice variation might reduce the likelihood that a therapeutic intervention would be found efficacious[38] and account for some of the variability in the relationship between the need for oxygen at 36 weeks' PMA and pulmonary and neurodevelopmental outcomes.[21,22,26–31]

In addition, infants who are <32 weeks' GA, treated with supplemental oxygen for >28 days but not at 36 weeks' PMA, or are receiving room air via nasal CPAP at 36 weeks' PMA may not be counted as having BPD by some clinicians, although they may have an abnormal chest radiograph, are being treated with diuretics or bronchodilators for pulmonary disease, and will receive RSV prophylaxis. Because neonatal ventilation and oxygen exposure have been shown to be risk factors for bronchial hyperresponsiveness and asthma,[45] children with a history of mild BPD may have a greater risk than children with a history of oxygen therapy for <28 days and thus warrant closer follow-up. This limitation of a definition of BPD based on the duration or treatment with supplemental oxygen has been acknowledged by others.[6,7,20,22,39]

This study restricted its analysis to infants who were ≤1000 g birth weight and <32 weeks' GA, although the consensus definition was developed for all infants who are <32 weeks' gestation. In addition, as noted above, accurate classification of study infants by the consensus BPD definition was limited by the lack of an objective physiologic test confirming oxygen dependence. Walsh et al[7] recently reported that a physiologic assessment that was based on an oxygen reduction challenge at 36 weeks' PMA led to a 10% reduction in the number of infants who received a diagnosis of BPD defined as oxygen treatment at 36 weeks' PMA. Reports by the NICHD Neonatal Research Network[10–12] listing the incidence of treatment with supplemental oxygen at 36 weeks' PMA and of the use of postnatal corticosteroids display wide center-to-center differences, reflecting known practice variations related to criteria for oxygen treatment and the target range for pulse oximetry. Nonetheless, although such a physiologic assessment might alter the percentages of mild and moderate BPD within this study cohort, the overall incidence would not be expected to change greatly.

By identifying infants with mild to severe BPD, the severity-based diagnostic criteria correspond with the spectrum of pulmonary and neurodevelopmental outcomes observed in surviving ELBW infants with BPD. As severity increased, length of hospital stay increased and the use of postnatal steroids for pulmonary disease increased. In contrast to the 28-days and 36-weeks definitions that identified similar percentages of infants with abnormal pulmonary outcomes (Table 2), the incidence of adverse pulmonary (Table 2) and neurodevelopmental outcomes (Table 5) corresponded to the severity of BPD defined by the consensus BPD definition. However, similar to the administration of oxygen therapy, the decision to treat infants with pulmonary medications during the first 1 to 2 years of life and to rehospitalize for respiratory causes was determined by the clinical team, and wide practice variations exist.

The consensus definition, as modified for the current study, refines current practice-based definitions by grading severity. Because the definition can be applied easily to widely available clinical information, it is well suited to investigations that use a retrospective design, such as epidemiologic studies focused on pulmonary function outcomes during infancy or childhood. By including the recommended physiologic assessment of oxygen dependence at 36 weeks' PMA with the severity-based diagnostic criteria, an objective outcome that is suitable for prospective cohort studies and randomized controlled trials can be defined.

Two recent reports support our contention about the usefulness of the severity-based diagnostic criteria for BPD. In a retrospective study, Sahni et al[46] reported that our system for grading the severity of BPD offered a better description of an infant's underlying pulmonary disease and correlated with growth, length of hospital stay, and overall severity of illness. Hjalmarson and Sandberg[47] performed pulmonary function tests at term PMA on preterm infants who had BPD classified with these severity-based criteria and found that the magnitude of functional impairments was related to the clinical severity of BPD.

We conclude, therefore, that these severity-based diagnostic criteria for BPD reflect the continuum of lung injury and repair present in BPD and identify a spectrum of risk for adverse pulmonary and neuro-

developmental outcomes in early infancy more accurately than other definitions. We believe that these criteria will be useful to clinicians in their NICU practice and to clinical investigators who evaluate therapeutic intervention strategies in randomized, controlled trials. We also believe that they should permit comparisons between different NICUs and facilitate benchmarking and epidemiologic studies.

ACKNOWLEDGMENTS

Participants in the NICHD Neonatal Research Network (1995–1999): Chairman, Alan H. Jobe, MD, PhD; University of Alabama (U10 HD34216): Waldemar A. Carlo, MD, Kathy Nelson, MD, Monica V. Collins, RN; Case Western Reserve University (U10 HD21364): Avroy A. Fanaroff, MB, BCh, Maureen Hack, MD, Nancy Newman, RN, Harriet Friedman, MA; University of Cincinnati (U10 HD27853, M01 RR 08084): Edward F. Donovan, MD, Jean J. Steichen, MD, Cathy Grisby, RN, Tari Gratton, RN; Emory University (U10 HD27851): Barbara J. Stoll, MD, Neal Simon, MD, Ellen Hale, RN; RTI International (U01 HD36790): W. Kenneth Poole, PhD, Betty Hastings; Indiana University (U10 HD27856, M01 RR 00750): James A. Lemons, MD, Anna Dusick, MD, Diane Appel, RN (NC), Julie Ahlrichs, RN; University of Miami (U10 HD21397): Charles R. Bauer, MD, Amy Mur Worth, RN, Wendy Griffin, RN; NICHD: Linda L. Wright, MD, Elizabeth McClure, Med; University of New Mexico (U10 HD27881, M01 RR 00997): Lu-Ann Papile, MD, Conra Backstom, RN, Jeanne Lowe, PhD, Barbara Woodward, MPH, OTR/L; Stanford University (U10 HD27880, M01 RR 00070): David K. Stevenson, MD, Barry E. Fleisher, MD, Bethany Ball, CCRC; University of Tennessee, Memphis (U10 HD21415): Sheldon B. Korones, MD, Henrietta Bada, MD, Tina Hudson, RN; University of Texas Southwestern Medical Center (U10 HD21373): Jon E. Tyson, MD, MPH, Sue Broyles, MD, Susan Madison, RN, Jackie Hickman, RN; Wayne State University (U10 HD21385): Seetha Shankaran, MD, Geraldine Muran, RN, Rebecca Bara, RN; Yale University (U10 HD27871, M01 RR 06022): Richard A. Ehrenkranz, MD, Linda Mayes, MD, Patricia Gettner, RN, Elaine Romano, MSN; Brigham and Women's Hospital (U10 HD34167, M01 RR 02635, M01 RR 02172, M01 RR 01032): Ann R. Stark, MD, Kerri Fournier, RN, Stacy Dow, RN; Brown University (U10 HD27904): William Oh, MD, Betty Vohr, MD, Angelita Hensman, RNC, Terri Leach, MEd.

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Conflict of Interest?

"Some doctors helping to evaluate the effectiveness of an increasingly popular device for clearing clogged arteries own stock and options in the company that makes it, regulatory filings show. . . . As of the end of last year, 12 doctors were supplying information about the catheter's effectiveness to a registry the company uses to evaluate the SilverHawk—its only product—and to promote it to other doctors. . . . The registry is controversial because the company isn't using the more standard method of proving that a health-care product is effective—a clinical trial. . . . Based on limited testing on patients in Europe and on animals, the Food and Drug Administration has approved SilverHawk as safe, though the agency hasn't weighed in on whether it is effective. FoxHollow Technologies [the manufacturer of SilverHawk] says it doesn't want to conduct trials to test SilverHawk's effectiveness against other procedures because that would be expensive and unnecessary, given the positive registry data. It also notes that some rivals marketing alternative treatments, including some stent makers, also haven't undertaken clinical trials. . . . Sales soared to almost $29 million in the second quarter, up from $7.5 million a year ago. They are expected to top $120 million in 2005. . . . [A] Morgan Stanley analyst said in a report the SilverHawk will remain a niche product, due to the lack of rigorous data."

Zuckerman G. *Wall Street Journal*. August 15, 2005

Noted by JFL, MD