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Comparisons and Limitations of Current Definitions of Bronchopulmonary Dysplasia for the Prematurity and Respiratory Outcomes Program

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Abstract

Rationale: Bronchopulmonary dysplasia is the most common morbidity of prematurity, but the validity and utility of commonly used definitions have been questioned.

Objectives: To compare three commonly used definitions of bronchopulmonary dysplasia in a contemporary prospective, multicenter observational cohort of extremely preterm infants.

Methods: At 36 weeks postmenstrual age, the following definitions of bronchopulmonary dysplasia were applied to surviving infants with and without imputation: need for supplemental oxygen (Shennan definition), National Institutes of Health Workshop definition, and "physiologic" definition after a room-air challenge.

Measurements and Main Results: Of 765 survivors assessed at 36 weeks, bronchopulmonary dysplasia was diagnosed in 40.8, 58.6, and 32.0% of infants, respectively, with the Shennan, workshop and physiologic definitions. The number of unclassified infants was lowest with the workshop definition (2.1%) and highest with the physiologic definition (16.1%). After assigning infants discharged home in room air before 36 weeks as no bronchopulmonary dysplasia, the modified Shennan definition compared favorably to the workshop definition, with 2.9% unclassified infants. Newer management strategies with nasal cannula flows up to 4 L/min or more and 0.21 $F_{I_{O_2}}$ at 36 weeks obscured classification of bronchopulmonary dysplasia status in 12.4% of infants.

Conclusions: Existing definitions of bronchopulmonary dysplasia differ with respect to ease of data collection and number of unclassifiable cases. Contemporary changes in management of infants, such as use of high-flow nasal cannula, limit application of existing definitions and may result in misclassification. A contemporary definition of bronchopulmonary dysplasia that correlates with respiratory morbidity in childhood is needed.

Clinical trial registered with www.clinicaltrials.gov (NCT01435187).

Keywords: bronchopulmonary dysplasia; infant; premature; oxygen inhalation therapy; neonatal lung disease

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*A complete list of study participants is included in the Appendix in the online supplement.

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Bronchopulmonary dysplasia (BPD) is the most frequent lung morbidity diagnosed among survivors of very preterm birth (1–3), and most prediction models for BPD have limited utility for clinical use (4). The pathophysiology of BPD is complex and may differ substantially between infants with different antenatal and early postnatal exposures (5). Almost all very low birth weight infants, even those with normal saturations in room air, have abnormal pulmonary function at 36 weeks (6). Conversely, pulmonary-related deaths before 36 weeks are not captured by current definitions of BPD (7, 8) and remain a frequent cause of mortality in extremely premature infants (9).

A substantial problem for the field is the validity and utility of the various definitions of BPD (10). Northway and colleagues described BPD in 1967 (11) as a ventilation- and oxygen-mediated injury in relatively mature preterm infants. Tooley (12) suggested in 1979 that oxygen use at 28 days of age might better identify preterm infants with BPD. With increasing survival of more immature infants, Shennan and colleagues proposed in 1988 that the best predictor of abnormal pulmonary outcomes at 2 years of age among very low birth weight premature infants was the clinical use of oxygen at 36 weeks postmenstrual age (PMA) (13). Given clinical variations in oxygen administration, a workshop convened by the National Institutes of Health (NIH) National Institute of Child Health and Human Development and the NHLBI proposed severity-based diagnostic criteria for BPD (14) that included the use of oxygen for at least 28 days (not necessarily consecutive) and an assessment of respiratory support at 36 weeks PMA, recognizing that some infants breathing room air at 36 weeks PMA may have residual lung disease. The workshop definition was refined with a test for the need for supplemental oxygen at 36 weeks to control for the variable clinical use of oxygen as an outcome for clinical trials and epidemiology studies (15, 16). In practice, most trials and epidemiology reports have used modifications of the Shennan definition of BPD as oxygen use at 36 weeks without testing need for supplemental oxygen (17). Recent changes in the variable use of noninvasive respiratory support with nasal catheters with high flow rates across a range of $F_{I_{O_2}}$ levels including 0.21 or very low flows with high oxygen concentrations may confound the categorization of BPD.

Our goal is to characterize the respiratory support at 36 weeks PMA of the cohort of extremely premature infants who were enrolled in the NHLBI Prematurity and Respiratory Outcomes Program (PROP). We strictly applied three commonly used definitions of BPD without imputation and in a second step with practical modifications to evaluate their relevance to a contemporary cohort of extremely low gestational age (GA) newborns. We compared the incidence of BPD using these three definitions and also identified specific areas where misclassifications of respiratory disease of prematurity may occur.

Methods

PROP is an observational prospective cohort study performed by a consortium of six clinical centers incorporating 13 tertiary neonatal intensive care units and a data-coordinating center. A key scientific aim of PROP is to identify early clinical, physiologic, and biochemical biomarkers during the initial neonatal intensive care unit hospitalization that can predict respiratory morbidity through 1 year of age. A detailed description of the PROP study protocol and the target sample size of 750 infants have been published (10, 18).

Study Infants

Infants born between $23^{0/7}$ and $28^{6/7}$ weeks' gestation were eligible for enrollment within the first 7 days after birth, with specific eligibility criteria and a target sample size of 750 (18). The study was approved by the institutional review board at each participating clinical site and by the data-coordinating center at the University of Pennsylvania with written informed consent from a parent or guardian.

Measurements and Procedures

Trained research personnel collected maternal and infant data. Detailed growth, nutrition, and medication data as well as

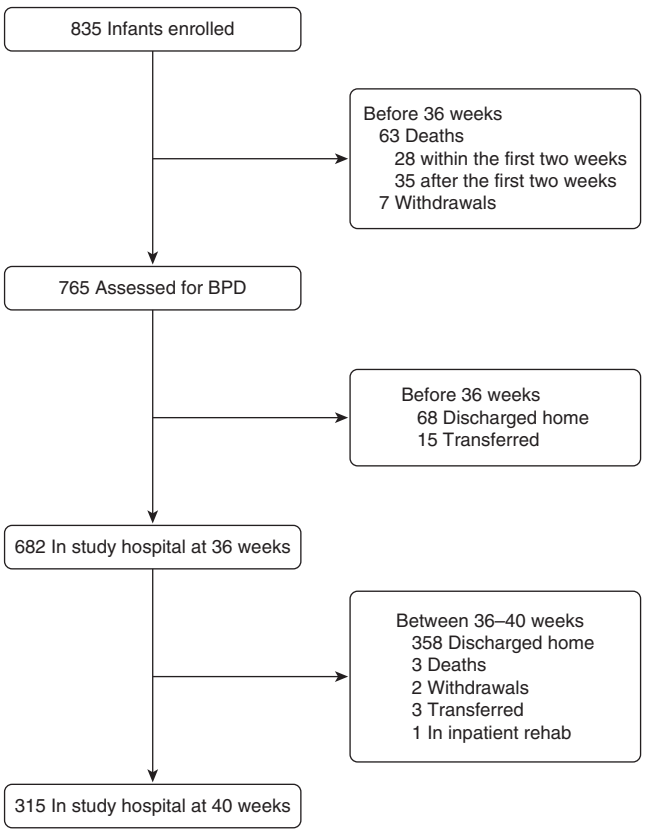

Figure 1. PROP (Prematurity and Respiratory Outcomes Program) participant flow. BPD = bronchopulmonary dysplasia.

respiratory data, including supplemental oxygen and type of respiratory support, were recorded on a daily basis until discharge home, transfer, or 40 weeks PMA.

Room Air Challenge

A trial of oxygen and flow reduction was performed at 36 ± 1 weeks PMA as previously described (18). Because some infants are supported with flow via nasal cannula without supplemental oxygen, this test was adapted from the protocol described by Walsh and colleagues (19) by decreasing F_{IO_2} before reducing flow to discriminate between effects of F_{IO_2} and flow on oxygen saturations.

Outcomes

The frequency of BPD was initially determined using three previously published definitions: the Shennan definition (13), the NIH workshop summary (14), and a physiologic definition with a room-air challenge (RAC). Potential reasons for unclassified babies with each definition are listed (*see* online supplement text box).

To reduce the number of unclassified infants, we applied practical modifications to two of the definitions. First, the Shennan definition was modified by assigning the outcome of "no BPD" to infants who were discharged home in room air before 36 weeks (the original publication was from an era when few premature infants were discharged home before 36 wk). Second, we modified the workshop definition by omitting the requirement for at least 28 days of supplemental oxygen, as this information is seldom readily available to clinicians. This modification of the workshop definition also yields a binary outcome, as infants previously classified as mild BPD become "no BPD" when the requirement of at least 28 days of supplemental oxygen is omitted.

The last postnatal day on invasive support, noninvasive respiratory support, and supplemental oxygen were recorded for each baby. If a baby remained on respiratory support on the day of transfer or discharge, the postnatal age at that day was considered as the last day of observation.

Comorbidities of prematurity were ascertained using medical record review by research staff at the earliest of 36 weeks PMA or discharge. Data collection forms for the PROP study have been previously published (18).

Statistical Analysis

Maternal demographic variables and risk factors, labor and delivery outcomes, and infant characteristics at both birth and enrollment were summarized with descriptive statistics. Kaplan-Meier survival curves were calculated for postnatal age at last use of any respiratory support and separately by type of support (invasive vs. noninvasive). We also examined the age at last use of respiratory support (including nasal cannula with 0.21 F_{IO_2}) separately by GA group. Associations of BPD with neonatal morbidities were assessed using χ^2 tests. All statistical tests were two sided and at the 0.05 level for significance. Statistical analyses were performed with SAS 9.3 software (SAS Institute, Cary, NC).

Results

Of 1,883 infants screened for eligibility, 835 infants were enrolled between August 2011 and November 2013 (Figure 1). There were 63 deaths before 36 weeks PMA, and seven infants were withdrawn from study participation, leaving 765 infants potentially available for assessment at 36 weeks. At 36 weeks PMA, 89% of the cohort assessed for BPD remained in the study hospital; the majority of those not in a study hospital at 36 weeks had been discharged home, and 15 had been transferred to another facility. Of note, 315 (41%) infants remained in the study hospital at 40 weeks PMA.

Maternal characteristics and infant characteristics at birth are provided in Tables 1 and 2, respectively. The majority of infants received oxygen, and 78% of infants were intubated in the delivery room. Infant characteristics at time of study enrollment (Day 3) are shown in Table 3. At enrollment, nearly three-fourths of the cohort were receiving supplemental oxygen, with a median F_{IO_2} of 0.26.

Kaplan-Meier curves for the postnatal age at last use of supplemental oxygen on invasive (with endotracheal tube) and noninvasive respiratory support for the entire cohort are shown in Figure 2A and for GA groups in Figures 2B–2D. The majority of infants in the PROP cohort did not require invasive support beyond the first few days, whereas the use of noninvasive ventilation continued for many infants. Supplemental oxygen and

Table 1. Characteristics of the Prematurity and Respiratory Outcomes Program cohort of 765 infants

Maternal Characteristics	
Age, mean (SD), yr	28.1 (6.3)
Race	
White	454/765 (59.3)
Black/African American	273/765 (35.7)
Asian	23/765 (3.0)
Other/unknown*	15/765 (2.0)
Hispanic or Latino	85/765 (11.1)
Diabetes	77/764 (10.1)
Insulin dependent	34/764 (4.5)
Hypertension	183/764 (24.0)
Asthma	66/764 (8.6)
Smoker	146/764 (19.1)
Labor and delivery data	
Placental abruption	111/765 (14.5)
Clinical chorioamnionitis	127/765 (16.6)
Ruptured membrane	
>18 h	171/765 (22.4)
>7 d	77/765 (10.1)
Any antibiotics	528/763 (69.2)
Any antenatal corticosteroids	655/765 (85.6)
At least 1 complete course	494/765 (64.6)
Any magnesium sulfate	311/761 (40.9)
Spontaneous labor	537/765 (70.2)
Delivery mode, Cesarean section	522/765 (68.2)

Data presented as n/total (%) unless otherwise noted.
*American Indian, Pacific Islander, multiracial, and others.

Table 2. Characteristics of the Prematurity and Respiratory Outcomes Program cohort of 765 infants

Infant Characteristics at Birth	
Gestational age, mean (SD), wk	26.7 (1.4)
Gestational age, completed wk	
23	25/765 (3.3)
24	82/765 (10.7)
25	117/765 (15.3)
26	160/765 (20.9)
27	193/765 (25.2)
28	188/765 (24.6)
Birth weight, mean (SD), g	915.8 (232.2)
Birth weight	
⩽500 g	14/765 (1.8)
501–600 g	37/765 (4.8)
601–700 g	100/765 (13.1)
701–800 g	113/765 (14.8)
801–900 g	122/765 (15.9)
901–1,000 g	131/765 (17.1)
1,001–1,100 g	82/765 (10.7)
1,101–1,200 g	78/765 (10.2)
>1,200 g	88/765 (11.5)
Birth weight < 10th percentile for GA	40/765 (5.2)
Female	372/765 (48.6)
Multiple births	194/765 (25.4)
Twins	156/765 (20.4)
Higher orders	38/765 (5.0)
Apgar score, median (IQR)	
1 min	4 (2, 7)
5 min	7 (6, 8)
Resuscitation	759/765 (99.2)
O_2	665/765 (86.9)
CPAP	370/765 (48.4)
PPV	323/765 (42.2)
T-piece resuscitator	198/765 (25.9)
Intubation	597/765 (78.0)
Chest compressions	84/765 (11.0)
Cardiac drugs	33/765 (4.3)
Surfactant	462/765 (60.4)

Definition of abbreviations: CPAP = continuous positive airway pressure; GA = gestational age; IQR = interquartile range; PPV = positive pressure ventilation.
Data presented as n/total (%) unless otherwise noted.

noninvasive ventilation remained high in the 23- and 24-week GA infants at 15 weeks after birth. Many of the 25- to 26-week GA infants received prolonged noninvasive support, although few required invasive support at 36 weeks PMA. These curves capture the approach to respiratory and oxygen support for infants in the current era. At 36 weeks PMA, 359 (46.9%) infants in the cohort were on nasal cannula flow. The distribution of flow and $F_{I_{O_2}}$ varied widely for these infants (Table 4). A total of 104 (13.6%) infants were receiving respiratory support with 0.21 $F_{I_{O_2}}$ at 36 weeks PMA (95 on nasal cannula flow, 4 on continuous positive airway pressure [CPAP], and 5 on mechanical ventilation). In contrast, 34 infants were receiving $F_{I_{O_2}}$ 1.0 with less than 0.1 L/min flow. Between birth and 36 weeks PMA, infants in the PROP cohort were exposed to respiratory medications, including caffeine (97.3%), dexamethasone (10.6%), and diuretics (57.1%).

The frequencies of BPD in the cohort by the Shennan, workshop, and physiologic definitions without imputation are given in Table 5. The percentage of infants with BPD at 36 weeks PMA ranged from 32.0 to 58.6% depending on the definition, but a number of babies were not classifiable. Reasons for unclassified status for each definition of BPD varied (online supplement text box). Application of the Shennan definition, based on the need for supplemental oxygen at exactly $36^{0/7}$ weeks PMA, resulted in 84 (11%) unclassified infants because they were discharged home or transferred from the study hospital before 36 weeks. The workshop definition yielded 16 (2.1%) unclassified babies, as this definition includes provision for infants discharged home (but not for those transferred) before 36 weeks; 15 of 16 unclassified infants with this definition were transferred from the study hospital before 36 weeks PMA. The physiologic definition based on the RAC was most problematic, with 123 (16.1%) infants unclassified. Although the protocol specified a 2-week window for performance of the RAC (36 ± 1 wk PMA), 78 infants had no RAC within the window, and 45 infants had no RAC performed at all due to early discharge, staff oversight, physician and/or parent refusal, and other reasons related to the clinical stability of the baby. For eligible infants with an RAC performed in the study window, the overall failure rate was 70%.

Table 3. Infant characteristics at enrollment

Characteristics	
Postnatal age at enrollment, median (IQR), d	3 (1–4)
Supplemental oxygen	562/765 (73.5)
$F_{I_{O_2}}$, median (IQR)	0.26 (0.21–0.30)
Positive airway pressure with endotracheal tube	377/765 (49.3)
Conventional mechanical ventilation	250/763* (32.8)
High-frequency ventilation	125/763* (16.4)
Noninvasive respiratory support	373/765 (48.8)
Nasal intermittent mandatory ventilation	56/765 (7.3)
CPAP	184/765 (24.1)
Nasal cannula	133/765 (17.4)
Any caffeine	579/765 (75.7)
Any enteral feeds	407/765 (53.2)

Definition of abbreviations: CPAP = continuous positive airway pressure; IQR = interquartile range.
Data presented as n/total (%) unless otherwise noted.
*Missing data; two infants receiving positive airway pressure with endotracheal tube, type not specified.

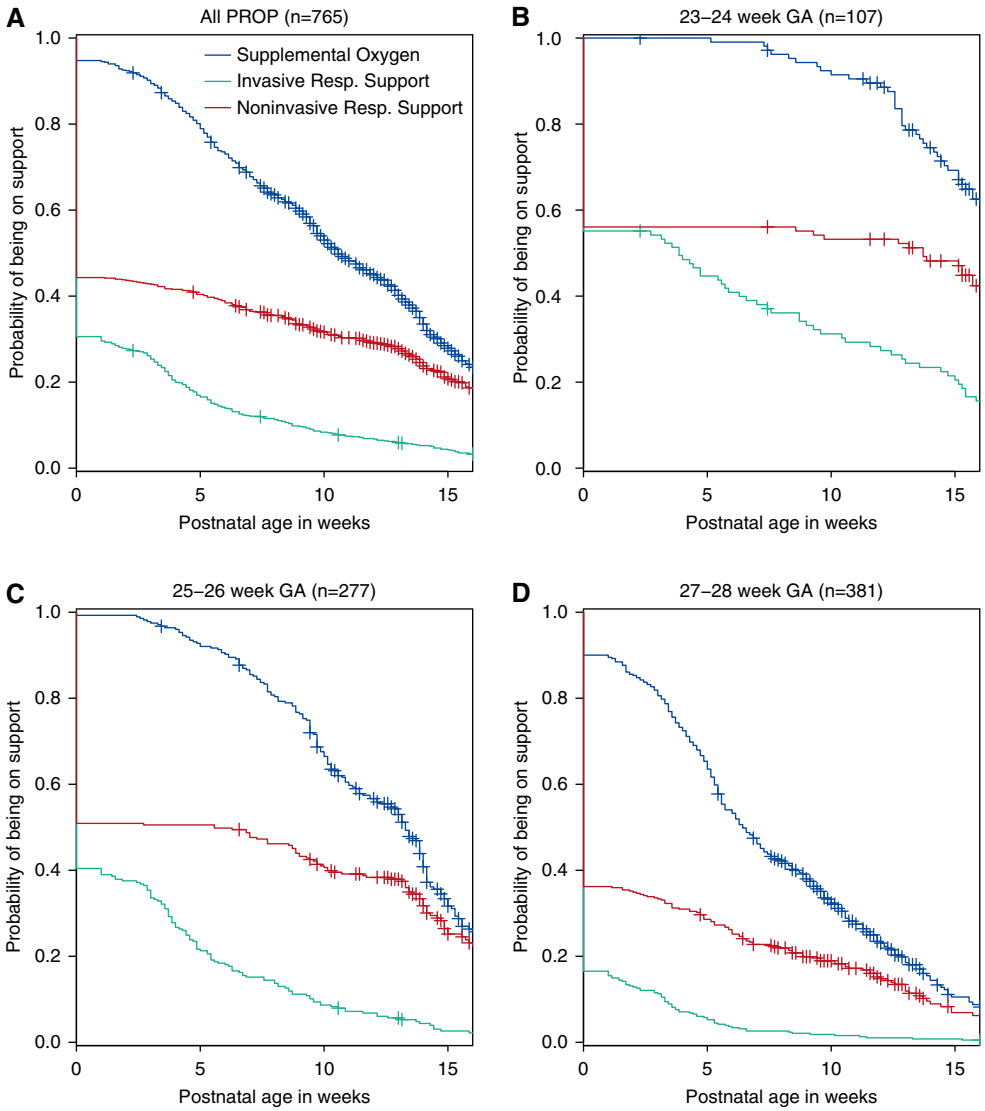

Figure 2. Kaplan-Meier curves for time to last use of invasive and noninvasive respiratory support and supplemental oxygen. Probability of being on invasive respiratory support (*green*), noninvasive respiratory support (*red*), and supplemental oxygen (*blue*) over time for entire cohort (*A*), 23 to 24 week gestational age (GA) (*B*), 25 to 26 week GA (*C*), and 27 to 28 week GA (*D*) subgroups. PROP = Prematurity and Respiratory Outcomes Program.

Modification of the Shennan definition increased the percentage of infants assigned a diagnosis of "no BPD" to 56.3%, as 62 infants in the cohort discharged home before 36 weeks PMA were in room air, and 22 (2.9%) infants remain unclassified. Modification of the workshop definition similarly increased the percentage of infants defined as "no BPD" to 55.7%, as the category of mild BPD was eliminated (Table 5).

Of the 431 infants classified as no BPD by the modified Shennan definition, 101 (23.4%) were receiving respiratory support with 0.21 F_{IO_2} (95 nasal cannula, 4 CPAP, and 5 ventilator). None of the published definitions include nasal cannula flow. Thirty-four of 95 infants being managed with room-air nasal cannula flow were receiving greater than or equal to 2 L/min.

Of the 359 infants receiving nasal cannula flow at 36 weeks (or discharge if before 36 wk), 266 had an RAC completed; 80 (30.1%) infants passed the challenge. In contrast, of the 95 infants receiving nasal cannula flow with 0.21 F_{IO_2}, 81 had an RAC completed, and 55 (67.9%) passed the flow reduction challenge.

Of the 210 infants with severe BPD by the workshop definition, 26% met definition criteria of receiving positive airway pressure via endotracheal tube, nasal intermittent mandatory ventilation, or CPAP, and 87% met definition criteria of F_{IO_2} greater than or equal to 0.30 (mean F_{IO_2}, 0.61; range, 0.3–1.0). However, 30 infants classified as severe BPD by the workshop definition were receiving flow rates of less than 0.1 L/min with 1.0 F_{IO_2}, an effective F_{IO_2} that may be more consistent with moderate BPD.

The major neonatal morbidities were determined for the total cohort and for the dichotomous outcome of BPD using the modified Shennan and the modified workshop definitions (Table 6). At 36 weeks PMA, the incidences of all major neonatal morbidities were higher in infants with

Table 4. Distribution of flow and F_{IO_2} among infants on nasal cannula at 36 weeks postmenstrual age

F_{IO_2}	Nasal Cannula Flow in L/min					
	<0.1	0.1–0.99	1–1.99	2–3.99	>4	Total
0.21	0	28	33	31	3	95
0.22–0.29	0	17	32	36	11	96
0.30–0.99	0	6	21	47	15	89
1.0	34	44	1	0	0	79
Total	34	95	87	114	29	359

Nontransferred survivors on nasal cannula at 36 weeks postmenstrual age or at discharge (if discharged before 36 wk); six infants discharged before 36 weeks were receiving supplementary oxygen via nasal cannula.

BPD than in infants without BPD. There was remarkable congruence between these two definitions and the expected differential rates of morbidities that are known to be associated with a diagnosis of BPD.

Deaths and BPD

For most clinical trials with a BPD outcome, death before 36 weeks is analyzed as a competing outcome. However, many of these are deaths from respiratory failure (early death from BPD) and are an underreported adverse respiratory outcome. We evaluated the 63 deaths before 36 weeks for respiratory failure associated deaths (Figure 1). Of these, 28 deaths occurred within 2 weeks of birth and were not considered as death from chronic lung disease. Of the remaining 35 deaths, 25 could be reasonably assigned as primary pulmonary-related deaths. Furthermore, two of the three deaths that occurred between 36 weeks and 40 weeks were infants with severe BPD.

Discussion

In this large, multicenter, observational cohort study, we applied the three commonly used definitions of BPD to determine their relevance given current clinical management practices. The three definitions differ with respect to the ease of data collection and number of missing/unclassifiable values. The modified Shennan and modified workshop definitions are easy to apply and produce very similar results. However defined, BPD remains a frequently reported morbidity of preterm birth.

Although the modified Shennan definition left very few infants unclassified, infants on respiratory support (nasal cannula, CPAP, or invasive ventilation) without supplemental oxygen may be falsely categorized as not having BPD. Of the 430 infants classified as no BPD by the modified Shennan definition, 9 were receiving positive airway pressure and 95 were receiving room-air nasal cannula flow.

Table 5. Frequency of bronchopulmonary dysplasia in Prematurity and Respiratory Outcomes Program cohort using strict definitions without imputation and modified definitions

Total (*n* = 765)	Shennan	Workshop	Physiologic	Modified Shennan*	Modified Workshop†
No BPD	369 (48.2)	301 (39.3)	397 (51.9)	431 (56.3)	426 (55.7)
BPD	312 (40.8)		245 (32.0)	312 (40.8)	
Mild	—	149 (19.5)	—	—	—
Moderate	—	89 (11.6)	—	—	96 (12.5)
Severe	—	210 (27.5)	—	—	227 (29.7)
Unclassified	84 (11.0)	16 (2.1)	123 (16.1)	22 (2.9)	16 (2.1)

Definition of abbreviation: BPD = bronchopulmonary dysplasia.
Data presented as n (%).
*Modified Shennan by assigning infants discharged before 36 weeks in room air as no BPD.
†Modified Workshop by omitting need for 28 days of supplemental oxygen; without consideration of receipt of supplemental oxygen before 36 weeks, the category of mild BPD is eliminated.

Not all infants receiving room-air flow had the RAC evaluation, but of those who did, approximately one-third failed the attempt to wean off flow with desaturations. Some of these infants were likely to have underlying pulmonary parenchymal disease, but others may have failed due to the instability of respiratory control (21). Further modifications of the Shennan definition may be needed to address the issue of positive airway pressure with room air and reduce the number of potentially misclassified infants.

A similar potential for false-negative assignment could occur with the modified workshop definition for those infants on high-flow nasal cannula with room air. The use of high-flow nasal cannula was not considered in the original NIH workshop definition. Although nasal cannula flow can provide supplemental oxygen and some airway pressure (20), the delivery of both is highly variable and unpredictable and therefore cannot be used to classify the severity of lung disease. In fact, nasal cannula with very low flows may obstruct the airway and worsen respiratory status.

The requirement for 28 days of supplemental oxygen in the original workshop definition is often misinterpreted as being 28 consecutive days of supplemental oxygen or as need for supplemental oxygen at 28 days of age (14). Our modification of the workshop definition to omit the requirement of 28 days of oxygen did not make a significant difference for the classification but may not be appropriate for individual cases, as the chronicity of the condition is not considered and an infant with an acute respiratory event around 36 weeks PMA could be erroneously classified as having severe BPD.

The physiologic definition resulted in the greatest number of unclassified infants, with many infants having the RAC not performed within the window or not done at all, despite research incentives to perform the RAC. Furthermore, the RAC, when performed, did not have large effects on patient categorization in the current era when oxygen use is more tightly regulated than when the RAC was first introduced (21). Although the failure rate was lower for infants who had an RAC performed outside of the study window, we did not include these results into a modified physiologic definition, as the assessment typically took place much closer to 40 weeks PMA.

Table 6. Major neonatal morbidities

	PROP Cohort (*n* = 765)	Modified Shennan*		Modified Workshop†	
		BPD = Yes (*n* = 312)	BPD = No (*n* = 431)	BPD = Yes (*n* = 323)	BPD = No (*n* = 426)
Pulmonary hemorrhage‡	20/765 (2.6)	15/312 (4.8)	5/431 (1.2)	15/323 (4.6)	5/426 (1.2)
Pneumothorax‡	24/765 (3.1)	16/312 (5.1)	7/431 (1.6)	17/323 (5.3)	6/426 (1.4)
PDA§	385/765 (50.3)	206/312 (66.0)	166/431 (38.5)	213/323 (65.9)	163/426 (38.3)
Echo confirmed§	375/765 (49.0)	199/312 (63.8)	163/431 (37.8)	206/323 (63.8)	160/426 (37.6)
Received indomethacin§	189/765 (24.7)	107/312 (34.3)	76/431 (17.6)	110/323 (34.1)	74/426 (17.4)
Received ibuprofen‡	45/765 (5.9)	28/312 (9.0)	15/431 (3.5)	28/323 (8.7)	15/426 (3.5)
Surgical ligation§	63/765 (8.2)	43/312 (13.8)	20/431 (4.6)	43/323 (13.3)	20/426 (4.7)
Pulmonary hypertension§	65/765 (8.5)	46/312 (14.7)	17/431 (3.9)	50/323 (15.5)	15/426 (3.5)
Sepsis§	459/765 (60.1)	215/312 (68.9)	236/431 (54.8)	221/323 (68.4)	233/426 (54.7)
Culture proven‖	151/765 (19.8)	75/312 (24.0)	74/431 (17.2)	76/323 (23.5)	73/426 (17.1)
NEC	63/765 (8.2)	30/312 (9.6)	32/431 (7.4)	32/323 (9.9)	30/426 (7.0)
Surgery	37/765 (4.8)	17/312 (5.4)	19/431 (4.4)	19/323 (5.9)	17/426 (4.0)
ROP§	392/765 (51.2)	210/312 (67.3)	179/431 (41.5)	216/323 (66.9)	175/426 (41.1)
Therapy for‡	64/764¶ (8.4)	39/312 (12.5)	25/430¶ (5.8)	41/323 (12.7)	23/425¶ (5.4)
Brain imaging					
Any IVH‡	202/765 (26.4)	100/312 (32.1)	94/431 (21.8)	103/323 (31.9)	93/426 (21.8)
Grade III/IV IVH‡	72/765 (9.4)	40/312 (12.8)	30/431 (7.0)	41/323 (12.7)	29/426 (6.8)
PVL	20/765 (2.6)	11/312 (3.5)	9/431 (2.1)	11/323 (3.4)	9/426 (2.1)
Weight < 10th percentile at 36 wk§	314/765 (41.0)	154/312 (49.4)	153/431 (35.5)	157/323 (48.6)	150/426 (35.2)

Definition of abbreviations: BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; PROP = Prematurity and Respiratory Outcomes Program; PVL = periventricular leukomalacia; ROP = retinopathy of prematurity.
Data presented as n/total (%) unless otherwise noted.
*Modified Shennan definition; 16 babies were unclassified.
†Modified Workshop definition; 16 babies were unclassified.
‡$0.001 < P$ value < 0.01, χ^2 test for comparing proportions in BPD and no-BPD groups.
§P value < 0.001, χ^2 test for comparing proportions in BPD and no-BPD groups.
‖$0.01 < P$ value < 0.05, χ^2 test for comparing proportions in BPD and no-BPD groups.
¶Missing data irresolvable.

The PROP study protocol already allowed for a 2-week window in which to perform the RAC; therefore, further imputation did not seem appropriate because data for the other two definitions had to be collected at exactly 36 weeks PMA. The RAC test may not improve classifications for future interventional trials of BPD and may be impractical for epidemiologic studies.

The RAC for this cohort differs from that used by the Neonatal Research Network and other investigations in two important ways: (*1*) all infants receiving respiratory support via nasal cannula, regardless of flow or effective F_{IO_2}, were eligible for the RAC in PROP; and (*2*) F_{IO_2} was weaned before any attempt to wean flow in an effort to better detect changes in oxygenation due to alterations in the delivery of positive pressure. Indeed, results of respiratory inductive plethysmography testing from a single center within PROP concluded that the need for supplemental oxygen or airflow does not account for multiple respiratory control abnormalities that are likely contributing to the need for respiratory support (22).

To avoid large numbers of unclassified infants, we applied practical modifications to the definitions, but the resulting categorizations likely are suboptimal, particularly in the context of predicting future respiratory outcomes. Management practices related to respiratory support are quite different than when the definitions were first described. As a result, these definitions may not accurately capture the underlying pulmonary pathology of BPD. For example, at the time of the NIH workshop, high-flow nasal cannulae were not part of routine practice. The three commonly used definitions provide no guidance on how to categorize infants on nasal cannulae. Flows greater than 2 L/min likely provide some but variable positive airway pressure (20). In addition, practice variation related to management of oxygen saturations has decreased after the completion of trials such as SUPPORT (23), the Canadian Oxygen Trial (24), and the Boost II trial (25), potentially minimizing the wide variation in the incidence of BPD based on use of supplemental oxygen observed by Walsh and colleagues (26).

Given that the majority of infants tested in the PROP cohort failed the RAC, this test did not substantially alter BPD assignment. In this cohort, 30 infants were categorized as severe BPD by the workshop definition, yet were on flow rates of less than 0.1 L/min. Thus, these categorizations of an infant to BPD—yes or no—may not accurately reflect lung function or correlate with longer-term outcomes.

Although a variety of definitions have been used in randomized clinical trials to evaluate the primary outcome of BPD (or the combined outcome of death or BPD), the most frequent is the need for oxygen at 36 weeks PMA (17). The current definitions of BPD have poor predictive value for longer-term pulmonary outcomes (4), in part because these outcomes are frequent in this population without BPD (27, 28). The early CPAP versus immediate intubation and surfactant arm of the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) trial illustrates the problem (7). Although there was no difference in the primary outcome of BPD between the intervention groups,

infants randomized to CPAP had fewer episodes of wheezing, physician-diagnosed respiratory illness, and physician or emergency room visits for breathing problems by 18 to 22 months corrected age (29). The UK Oscillation Study recently reported better small airway function at 11 to 14 years in the infants originally randomized to high-frequency ventilation rather than conventional ventilation, although there were no differences in rates of BPD at 36 weeks PMA (30). Although a simplistic view would be to assume that the severity of BPD at 36 weeks PMA is a good predictor of long-term respiratory outcome, other factors such as nutrition, viral infections, and environmental exposures can also have a significant impact on the evolution of lung disease in these infants.

Although deaths attributed to pulmonary causes in extremely premature infants have declined over the past decade, pulmonary-related mortality remains a frequent cause of mortality before 36 weeks PMA (9). In this cohort, 40% of the deaths before 36 weeks were pulmonary related, yet not captured by the three commonly used definitions of BPD. In the future, these severely affected babies could be considered for innovative interventions (such as stem cell therapy) (31) to treat BPD early in its clinical course to decrease pulmonary mortality.

The assignment of the outcome BPD at 36 weeks is a historical convention that is not well justified, given that lung development is far from complete at this postnatal age. Of the 315 infants in this cohort who remained hospitalized at 40 weeks, 184 (58.4%) had a diagnosis of BPD assigned at 36 weeks based on supplemental oxygen. Studies conducted before widespread clinical management with high-flow nasal cannula have shown mixed results related to prediction of pulmonary outcomes if BPD is categorized by oxygen therapy at 40 weeks rather than at 36 weeks PMA (32, 33).

Existing definitions of bronchopulmonary dysplasia fail to adequately classify infants. The NIH Workshop definition cannot be recommended at present, as infants on high-flow nasal cannula cannot be classified, and those on low flow with 1.0 F_{IO_2} should arguably not be classified as severe BPD. The physiologic definition in this cohort of infants did not refine the outcome and was difficult to complete, even in the context of a research protocol. Consequently, pending new frameworks for defining BPD that correlate with later respiratory morbidity in childhood, the Shennan definition of BPD, modified to assign infants discharged home before 36 weeks PMA in room air as no BPD, is the easiest definition to apply, yields a low number of infants as unclassified, and has face validity, as demonstrated by neonatal morbidities associated with BPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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