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Point Prevalence, Clinical Characteristics, and Treatment Variation for Infants with Severe Bronchopulmonary Dysplasia

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Abstract

Objectives—Despite improvements in survival of preterm infants, bronchopulmonary dysplasia (BPD) remains a persistent morbidity. The incidence, clinical course, and current management of severe BPD (sBPD) remain to be defined. To address these knowledge gaps, a multicenter collaborative was formed to improve outcomes in this population.

Study Design—We performed a “snapshot” in eight neonatal intensive care units (NICUs) on December 17, 2013. A standardized clinical data form for each inpatient born at < 32 weeks was completed and collated centrally for analysis. sBPD was defined as receiving 30% supplemental oxygen and/or receiving positive pressure ventilation at 36 weeks postmenstrual age (PMA).

Results—Of a total census of 710 inpatients, 351 infants were born at < 32 weeks and 128 of those (36.5%) met criteria for sBPD. The point prevalence of sBPD varied between centers (11–58%; $p < 0.001$). Among infants with sBPD there was a variation among centers in the use of mechanical ventilation at 28 days of life ($p < 0.001$) and at 36 weeks PMA ($p = 0.001$). We observed differences in the use of diuretics ($p = 0.018$), inhaled corticosteroids ($p < 0.001$), and inhaled β -agonists ($p < 0.001$).

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*All authors are member of Bronchopulmonary Dysplasia Collaborative.

Conflict of Interest

All authors have no conflicts of interest to disclose this includes in: (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the article for publication.

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Conclusion—The high point prevalence of sBPD and variable management among NICUs emphasizes the lack of evidence in guiding optimal care to improve long-term outcomes of this high-risk, understudied population.

Keywords

chronic lung disease of prematurity; multicenter collaborative; snapshot; bronchopulmonary dysplasia

Despite extensive research in the prevention of bronchopulmonary dysplasia (BPD), the condition remains very prevalent. It has major life-long effects, especially in those with severe disease. The reported incidence of BPD among infants born at < 32 weeks gestational age (GA) varies significantly by care center, ranging from 13.7% in the Israeli Neonatal Network¹ to 12.3 and 14.6% in the Canadian and Japanese Neonatal Networks, respectively,² and to 26 to 30% in the Vermont Oxford Network.³ In the 2010 report of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network as high as 68% in infants between 22 and 28 weeks had BPD.⁴ However, these reports combine the incidence of all severities of BPD, making the incidence of severe BPD (sBPD) unclear. In addition, there are few studies describing the clinical course and management of patients with established BPD. Specifically, there is a lack of multicenter studies concerning the optimal timing and indications for respiratory and pharmacological management, as well as surgical procedures indicated in infants with sBPD. Multiple assessments, before and after the development of BPD, and assessments of management practices across referral centers managing BPD could aid in determining optimal practices for sBPD management.

To characterize the course and nature of sBPD in the present era, we performed a multicenter study to determine the point prevalence and variation in care of sBPD infants. We included neonatal intensive care units (NICUs) from eight academic medical centers in the United States that constitute the BPD Collaborative. We performed a “snapshot,” or point prevalence study, in which investigators collected clinical data on the same day at each site for each inpatient in their NICU meeting criteria for high risk of sBPD.

Methods

Data Sources and Study Sample

The BPD Collaborative Group was comprised of eight academic medical centers in the United States, each with an established BPD program. Each institution obtained local institutional review board approval. Centers performed a prospective “snapshot” data survey on December 17, 2013 on their inpatient NICU populations. We used a predetermined standardized data form for each inpatient born at < 32 weeks, extracted from chart review. The forms were collated centrally for analysis.

Definitions

The National Institutes of Health workshop proposed a new BPD definition in 2001, in patients born at < 32 weeks GA using the need for supplemental oxygen at 28 days of life

(DOL), with severity based on further criteria at 36 weeks postmenstrual age (PMA).⁵⁻⁷ Mild BPD was defined as need for supplemental oxygen at 28 DOL but no supplemental oxygen at 36 weeks PMA, moderate BPD as the need for < 30% supplemental oxygen at 36 weeks PMA, and severe BPD as the need for ≥ 30% supplemental oxygen and/or the need for positive pressure ventilation (PPV) at 36 weeks PMA. For our study sBPD was defined as receiving ≥ 30% supplemental oxygen and/or receiving PPV at 36 weeks PMA. We defined PPV as any respiratory support with mechanical ventilation, nasal intermittent positive pressure ventilation, nasal continuous positive airway pressure (NCPAP), sigh positive airway pressure (Si-PAP) or high-flow nasal cannula (HFNC) at ≥ 2 L. Invasive PPV was defined as receiving any type of ventilation via endotracheal tube or tracheostomy. Pulmonary hypertension (PH) was defined as diagnosis of PH supported by echocardiogram (ECHO). At the time of the snapshot, each center was asked two yes/no questions related to pulmonary hypertension after 28 days of life. First, "Has the patient been diagnosed with pulmonary hypertension?" Second, "Is this diagnosis confirmed by ECHO after 28 days of life?" Echocardiographic details were not recorded.

Center Characteristics for 2013

Center data for the calendar year 2013 and for the month of December 2013 were collected and included: Size of the unit, average daily census, yearly admission rate, number of deliveries, percentages and numbers of infants born at < 32 weeks GA delivered at the center (inborn) or transferred from other institutions (outborn), percentage of infants born at < 32 weeks with any BPD, and numbers of tracheostomies, gastrostomies, and funduplications performed in infants with any BPD. Data were also collected regarding the availability of a specific BPD program/area in each center, subspecialty follow-up for BPD patients after NICU discharge, and infant home ventilation programs as well as the number of patients discharged from the NICU with tracheostomies with and without home ventilators.

Clinical Data

GA and growth parameters at birth were ascertained via chart review in all infants. In infants who met the criteria for sBPD, respiratory support data (F_{IO_2} and means of support) were collected at the time of the snapshot and retrospectively at 28 DOL and 36 weeks PMA. Data on the use of medications on the day of the snapshot, such as diuretics, bronchodilators, systemic and inhaled steroids, antireflux medications, and PH medications were collected. Tracheostomies, gastrostomies, and/or funduplications reflected procedures performed on or by the date of the snapshot, and not any future planned procedures. We also collected whether infants were diagnosed with PH.

Data Analyses

The primary outcome assessed was the center point prevalence of sBPD in infants born at < 32 weeks GA on the day of snapshot. Comparisons between infants with sBPD (or PH) and those without were made using Student *t*-test. The variation in demographic frequencies and clinical data between centers was assessed using analysis of variance for continuous variables with Bonferroni correction and Fisher exact tests for categorical variables. STATA

IC 11 (StataCorp LP, College Station, TX) was used for all statistical analyses. *p*-Values < 0.05 were considered statistically significant.

Results

Center Characteristics for 2013

The characteristics of the eight centers participating in this snapshot are given in Table 1. In 2013, these centers had a total of 9,657 admissions of which 1,813 infants (19%) were born at < 32 weeks GA. Among admitted infants born < 32 weeks GA, 909 (50%) were inborn and 904 (50%) were transferred from another hospital, while the range of transfers by center was large (13–100%). The incidence on any BPD in 2013 for infants born < 32 weeks GA was 771 (43%). Although only two centers have BPD-specific units, six centers had designated BPD teams. All had a home infant ventilator program and involved pediatric pulmonology specialists in care while in the NICU and after discharge. In most centers, BPD care after NICU discharge was coordinated by pediatric pulmonologists, but in two centers care was coordinated by multidisciplinary teams led by neonatologists.

Snapshot Demographics

On the day of the snapshot, the total census across all eight centers and their affiliated units was 710 infants with a range of 75 to 132 infants per center. Of these 351 (49%) were born < 32 weeks GA, and 128 of these infants (36.5%) met the criteria for sBPD (Table 2). The infants with sBPD were born at an earlier mean GA (26.2 ± 2.6 vs. 27.5 ± 2.5 weeks; $p < 0.001$), had a lower mean birth weight (882 ± 414 vs. $1,073 \pm 372$ g; $p < 0.001$), and shorter mean birth length (32.9 ± 4.3 vs. 36 ± 4.3 cm, $p < 0.001$) than did the infants born at < 32 weeks without sBPD. The reported frequency of sBPD among infants born < 32 weeks GA varied significantly between centers (11–58%; $p < 0.001$).

Respiratory Support

Among infants with sBPD, 62% were receiving invasive PPV (IPPV) at 28 DOL, which ranged significantly between centers (13–89%; $p < 0.001$, Table 3). Use of IPPV among infants with sBPD had decreased to 41% by 36 weeks PMA, but there was still significant variation between centers (0–68%; $p = 0.001$). Use of HFNC among infants with sBPD also varied between centers ranging between 0 and 33% of infants at 28 DOL and 0 to 100% at 36 weeks PMA. There were no differences between centers in the frequency of use of 30% supplemental oxygen at either 28 DOL or 36 weeks PMA.

Procedures

On the day of the snapshot, 12% of infants with sBPD had tracheostomies, 14% had gastrostomies, and 7% had funduplications (Table 4). There were no differences among centers in the proportion of infants with sBPD that were managed with these procedures.

Medication Usage

There was significant variation between centers in the use of diuretics (28–87%; $p = 0.018$), inhaled corticosteroids (0–87%; $p < 0.001$), and inhaled β -agonists (0–67%; $p < 0.001$)

among infants with sBPD, but not in the use of systemic corticosteroids or antireflux medications (Table 5).

Pulmonary Hypertension

Diagnosis of PH supported by ECHO was present in 23% of infants with sBPD, but the frequency did not vary between centers (Table 4). Patients with PH did not differ by provided F_{IO_2} support at 28 DOL ($p = 0.57$) compared with those without PH, but did at 36 weeks PMA (F_{IO_2} : 50 vs. 37%; $p = 0.04$). We did not assess variation between centers for the PH therapies that we collected data on as the number of infants receiving them was very small. Specifically, inhaled nitric oxide was prescribed for 3% of the infants with sBPD on the date of the snapshot, calcium channel blockers for 1% and phosphodiesterase type 5 (PDE5) inhibitors for 9%. There was no patient treated with endothelin receptor blockers or prostacyclin (PGI₂) analogues. Among infants with sBPD and PH, 10 of the 26 infants (38%) were receiving at least one of the PH therapies mentioned above.

Discussion

BPD is one of the most common complications in patients born extremely prematurely and is an important cause of morbidity and mortality. Therapeutic advances such as antenatal steroids, postnatal surfactant, and improved respiratory support strategies have led to improved survival at lower GAs, yet the prevalence of BPD has not declined.^{8–10} Infants born < 32 weeks GA are at particularly high risk of developing BPD. On the day of data collection across all centers the proportion of infants with any BPD ranged from 20 to 77%, and with severe BPD from 11 to 58%. Our data highlights the high prevalence of the disease (36.5%) in tertiary referral NICUs. Moreover, at 28 DOL 62% of infants still required invasive respiratory support; and these infants remain at higher risk of pulmonary complications even if not requiring PPV at 36 weeks PMA as reported by other investigators.¹¹

Our results also highlight the many gaps in knowledge with respect to optimal management of sBPD reflected by the wide variation of respiratory support modalities, medication usage, and procedures amongst the eight centers. Although we did not observe differences among centers regarding the use of 30% supplemental oxygen at defined time points, there was significant variation in the frequency of invasive PPV use at 28 DOL, 36 weeks PMA between centers. The absence of evidence-based guidelines for managing the preterm infant with chronic respiratory failure likely explains the variability observed in the use of invasive ventilation.

Medical therapies such as systemic and inhaled corticosteroids, β -agonists, and diuretics are often used to modulate the course of established sBPD. However, randomized controlled trials (RCTs) in this population are rare, and studies evaluating the benefit of these therapies have yielded conflicting results.^{12–16} The most controversial still is the use of corticosteroid and developmental outcomes,^{17,18} although no studies have systematically assessed the effect of systemic corticosteroids in patients with sBPD, this concern may explain the systemic corticosteroid use of only 13% in infants with sBPD. It is important to point out that the data on utilization of systemic corticosteroids and other medications reflect

utilization at the time of the snapshot and did not assess utilization earlier in the individual infant's course. Bronchodilator use and inhaled corticosteroids varied significantly between centers, which may be related to local biases as well as the lack of feasible objective tools for measuring airway reactivity in this population. While studies evaluating the effect of diuretics in BPD have shown short-term improvements,^{12–14} there are no studies evaluating long-term outcomes such as length of hospital stay or need for ventilator support¹⁴ which may explain the variation in diuretic usage between our centers and reflects the need for further studies of these agents.

PH diagnosis was supported by ECHO in 23% of the infants with sBPD in our population, which is consistent with prior reports and highlights the importance of PH as comorbidity in infants with sBPD.^{15,16,19,20} In addition to the higher F_{IO_2} support observed among patients with PH, we also observed that substantial fractions (38%) of infants with PH were receiving specific therapies for PH. Given that prior reports have described a 2-year mortality rate ranging from 33 to 48% after diagnosing BPD-associated PH^{21,22} and the absence of U.S. Food and Drug Administration-approval for these therapies, clinical studies of these therapies are needed in this population.

Tracheostomy tube placement in BPD remains a complex decision with scant evidence to guide practice.^{23,24} Although not statistically significant, the rate of tracheostomy placement varied in sBPD patients between centers. Similar variation was noted in the number of infants who underwent gastrostomy tube placement or fundoplication. In the absence of clear evidence on which to base the use of these therapies, such variability is not surprising.

Our data were collected on a single day and were therefore not intended to define the incidence of sBPD, but rather to describe the point prevalence of the disease (36.5%) in tertiary referral NICUs. This high prevalence of sBPD within the study population may not reflect all NICU populations as the prevalence may have been influenced by many factors, including regional referral patterns for sBPD as indicated by the high percentage (50%) of infants transferred to these centers, as well as our definition of PPV which also included the newer modality of HFNC. The inclusion of HFNC may have led to classifying more infants as having sBPD; but this modality is used frequently as reflected by our data and in some cases is probably used as an equivalent for NCPAP. Although we did identify differences between centers for several key metrics, we cannot distinguish whether these differences reflect institutional versus specific provider differences in practice. Our descriptive study has several important strengths; including data collected using a standardized instrument on a large cohort of preterm infants from a geographically diverse group of NICUs within the United States.

In conclusion, our findings highlight that severe BPD remains a significant problem among infants born before 32 weeks GA. Furthermore, our study suggests that this population may not be as rare and difficult to study as previously thought. The variability of respiratory support and medical management strategies that we observed confirm the need for high level evidence preferably in the form of RCTs or studies utilizing comparative effectiveness research and the importance of multicenter collaborations in determining the optimal management approach to sBPD. With limited published data on the optimal management of

these patients, further work to define optimal management strategies to improve the outcomes of these patients is imperative.

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Table 1

Center characteristics for calendar year 2013

	1	2	3	4	5	6	7	8
Center statistics								
NICU bed capacity (<i>n</i>)	99	89	45	102	80	160	114	86
Mean daily census December 2013 (<i>n</i>)	92	77	41	93	58	129	80	96
Annual deliveries (<i>n</i>)	0	1,939	1,933	4,489	8,699	4,878	3,363	287
Total admissions (<i>n</i>)	856	1,329	754	1,331	1,162	1,304	1,763	1,158
Infants < 32 wk GA (<i>n</i>)	220	151	118	317	208	279	315	205
Outborn infants < 32 wk GA (%)	100	75	20	32	13	30	48	90
Infants < 32 wk GA with BPD (<i>n</i> , %)	143 (65%)	36 (24%)	63 (53%)	82 (26%)	73 (35%)	73 (26%)	243 (77%)	58 (28%)
Clinical statistics								
Procedures performed in infants with BPD								
Gastrostomies (<i>n</i> , % yearly total)	39 (54%)	9 (15%)	30 (67%)	23 (35%)	6 (60%)	29 (78%)	14 (29%)	28 (26%)
Fundoplication (<i>n</i> , % yearly total)	2 (100%)	2 (18%)	20 (74%)	10 (53%)	0 (0%)	2 (67%)	9 (45%)	23 (36%)
Tracheostomies (<i>n</i> , % yearly total)	7 (58%)	12 (80%)	5 (63%)	3 (43%)	4 (100%)	9 (64%)	8 (73%)	11 (50%)
Respiratory support								
Infants with BPD discharged with tracheostomy only (<i>n</i> , %)	7 (5%)	0 (0%)	0 (0%)	4 (5%)	0 (0%)	3 (4%)	11 (5%)	0 (0%)
Infants with BPD discharged with tracheostomy/ventilator (<i>n</i> , %)	0 (0%)	8 (22%)	5 ^a (8%)	1 (1%)	4 (5%)	6 (8%)	19 ^a (8%)	9 ^a (16%)
Center characteristics								
Specific BPD unit	Yes	Yes	No	No	No	No	No	No
Specific BPD team	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Peds Pulm routinely involved inpatient and after discharge	Yes	Yes	Yes	Yes	Yes ^b	Yes	Yes	Yes ^c
BPD-specific care after discharge provider	MDT	MDT	Peds Pulm	Peds Pulm	Peds Pulm	Peds Pulm	Peds Pulm	Peds Pulm
Home infant ventilator program	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations: BPD, bronchopulmonary dysplasia; GA, gestational age; MDT, multidisciplinary team led by neonatology; Peds Pulm, pediatric pulmonary.

^aCenter 3 is reporting on their primary facility of 45 beds; data in subsequent tables was collected from affiliated sites as well for an additional 55 beds.^bAll infants with ventilators/tracheostomies are transferred to step-down unit once stable on a home ventilator or before going home-based on institutional practices.^cOnly if severe BPD.

Table 2

Demographics of sBPD by center on the day of the “snapshot”

Mean $\pm$ SD (range) center	Frequency of sBPD ^a (%)	Birth weight (g)	Birth weight (percentile)	Birth length (cm)	Gestational age (wks)	Current postconceptional age (wks)
1	57.7% (30 out of 52)	739 $\pm$ 247 (400–1,576)	34 $\pm$ 28 (2–85)	31.1 $\pm$ 4.6 (20–43.5)	25.7 $\pm$ 2.4 (23–31)	47.2 $\pm$ 11.7 (35.6–85.9)
2	44.0% (11 out of 25)	1,015 $\pm$ 477 (520–2,250)	38 $\pm$ 29 (3–90)	34.9 $\pm$ 4.7 (28–42.5)	27.5 $\pm$ 2.6 (24–31)	48.0 $\pm$ 8.8 (36.9–60.1)
3	25.9% (15 out of 58)	728 $\pm$ 271 (380–1,520)	38 $\pm$ 28 (3–77)	32.2 $\pm$ 3.7 (27–41)	25.5 $\pm$ 2.6 (23–32)	48.8 $\pm$ 10.4 (37.3–78.0)
4	10.9% (6 out of 55)	742 $\pm$ 131 (550–920)	39 $\pm$ 28 (0–83)	31.3 $\pm$ 3.1 (26–35)	26.3 $\pm$ 2.6 (24–30.5)	43.6 $\pm$ 5.7 (37.9–50.8)
5	32.3% (10 out of 31)	927 $\pm$ 467 (490–2,070)	46 $\pm$ 26 (12–81)	32.9 $\pm$ 3.7 (27–39.5)	26.1 $\pm$ 2.6 (23–30)	41.8 $\pm$ 5.5 (35.9–51.6)
6	39.3% (22 out of 56)	950 $\pm$ 501 (515–2,670)	40 $\pm$ 29 (4–95)	32.5 $\pm$ 3.7 (26.5–42.5)	26.7 $\pm$ 2.4 (23–31)	48.0 $\pm$ 11.8 (35.7–68.7)
7	41.9% (18 out of 43)	1,175 $\pm$ 403 (590–2,040)	44 $\pm$ 28 (15–88)	37.0 $\pm$ 3.6 (32–45)	28.1 $\pm$ 2.6 (25–32)	39.8 $\pm$ 7.0 (35.6–66.0)
8	51.6% (16 out of 31)	802 $\pm$ 484 (450–2,330)	35 $\pm$ 30 (4–89)	31.5 $\pm$ 3.5 (35–38.5)	25.7 $\pm$ 2.5 (23–31)	46.2 $\pm$ 9.3 (36.0–67.1)
Entire sBPD population	36.5% (128 of 351)	882 $\pm$ 414 (380–2,670) (<i>n</i> = 127)	39 $\pm$ 28 (0–95) (<i>n</i> = 127)	32.9 $\pm$ 4.3 (20–45) (<i>n</i> = 113)	26.4 $\pm$ 2.6 (23–32)	45.8 $\pm$ 10.1 (35.6–85.9)
<i>p</i> -Value ^b	< 0.001	0.011	0.94	0.001	0.030	0.10

Abbreviations: BPD, bronchopulmonary dysplasia; *n*, number (provided to reflect when data points were not complete in all of the patients); sBPD severe BPD; SD, standard deviation.^aProportion of infants born at less than 32 weeks GA who have sBPD.^bChi-square test employed for frequency of sBPD; other comparisons between centers assessed with analysis of variance with Bonferroni corrections, which indicate that the mean birth weight at center 7 is heavier than at centers 1 and 3, the mean birth length at center 7 is longer than at centers 1, 3, and 6, and the mean gestational age is trending toward being older at center 7 compared with centers 1 and 3.

Table 3

Respiratory support for sBPD at selected time intervals on the day of the “snapshot”

Percentage (%)center	N	F _{IO2} 30% (% yes)				Invasive positive pressure ventilation ^a (% yes)		
		28 d old	36 wks PMA	Current		28 d old	36 wks PMA	Current
1	30	77%	64%	57%		59%	48%	10%
2	11	100%	70%	73%		63%	45%	36%
3	15	50%	63%	47%		53%	27%	20%
4	6	100%	50%	17%		67%	0%	0%
5	10	78%	11%	50%		89%	33%	20%
6	22	59%	59%	59%		82%	68%	50%
7	18	75%	59%	50%		13%	6%	28%
8	16	64%	50%	38%		81%	56%	50%
Entire sBPD population	128	73% (n = 93)	56% (n = 109)	52%		62% (n = 114)	41% (n = 121)	28% (n = 127)
Fisher exact <i>p</i> -value	–	0.39	0.23	0.44		<0.001	0.001	0.016

Abbreviations: BPD, bronchopulmonary dysplasia; *n*, number (provided to reflect when data points were not complete in all of the patients); sBPD severe BPD; SD, standard deviation.

^aInvasive ventilation is defined as any delivery of ventilation by either endotracheal tube or tracheostomy.

Table 4
Surgical procedures and pulmonary hypertension in sBPD on the day of the “snapshot”

Percentage (%) center	N	Tracheostomy (% yes)	Gastrostomy (% yes)	Fundoplication (% yes)	Pulmonary hypertension ^a (% yes)
1	30	14%	10%	3%	21%
2	11	27%	27%	0%	18%
3	15	7%	13%	7%	36%
4	6	0%	0%	0%	17%
5	10	0%	0%	0%	20%
6	22	14%	10%	10%	19%
7	18	12%	12%	12%	29%
8	16	13%	31%	19%	19%
Entire sBPD population	128	12% (n = 125)	14% (n = 125)	7% (n = 125)	23% (n = 114)
Fisher exact <i>p</i> -value	–	0.77	0.33	0.60	0.96

Abbreviations: BPD, bronchopulmonary dysplasia; *n*, number (provided to reflect when data points were not complete in all of the patients); sBPD severe BPD; SD, standard deviation.

^aDiagnosis of PH supported by echocardiogram.

Table 5

Selected medication use in sBPD on the day of the “snapshot”

Percentage (%)	center	N	Diuretics (% yes)	Inhaled beta-agonists (% yes)	Inhaled corticosteroids (% yes)	Systemic corticosteroids (% yes)	Antireflux medications (% yes)
1		30	43%	47%	47%	10%	23%
2		11	73%	36%	64%	27%	27%
3		15	87%	67%	87%	20%	40%
4		6	83%	0%	17%	0%	50%
5		10	60%	0%	0%	0%	30%
6		22	57%	33%	29%	14%	10%
7		18	28%	6%	6%	22%	6%
8		16	56%	25%	13%	7%	19%
Entire sBPD population		128	56% (<i>n</i> = 127)	32% (<i>n</i> = 127)	35% (<i>n</i> = 127)	13% (<i>n</i> = 126)	22% (<i>n</i> = 127)
Fisher exact <i>p</i> -Value		–	0.018	< 0.001	< 0.001	0.51	0.11

Abbreviations: BPD, bronchopulmonary dysplasia; *n*, number (provided to reflect when data points were not complete in all of the patients); sBPD severe BPD; SD, standard deviation.