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In-hospital Outcomes of Premature Infants with Severe Bronchopulmonary Dysplasia

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Abstract

Objective—To characterize in-hospital outcomes of premature infants diagnosed with severe bronchopulmonary dysplasia.

Study Design—Retrospective cohort study including premature infants with severe bronchopulmonary dysplasia discharged from 348 Pediatrix Medical Group neonatal intensive care units from 1997–2015.

Result—There were 10,752 infants with severe bronchopulmonary dysplasia, and 549/10,752 (5%) died prior to discharge. Infants who died were more likely to be male, small for gestational age, have received more medical interventions, and more frequently diagnosed with surgical necrotizing enterocolitis, culture-proven sepsis, and pulmonary hypertension following 36 weeks postmenstrual age compared to survivors. Approximately 70% of infants with severe bronchopulmonary dysplasia were discharged by 44 weeks postmenstrual age, and 86% were discharged by 48 weeks postmenstrual age.

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Conflicts of Interest

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Conclusion—A majority of infants diagnosed with severe bronchopulmonary dysplasia were discharged home by 44 weeks postmenstrual age. These results may inform discussions with families regarding the expected hospital course of infants diagnosed with severe bronchopulmonary dysplasia.

BACKGROUND

Bronchopulmonary dysplasia (BPD) is the most common and severe pulmonary complication of prematurity.[1] The incidence of BPD may be increasing due to improvement in the survival of infants at earlier gestational ages (GA).[2] The severity of BPD is correlated with long-term health outcomes. A consensus from the National Institutes of Health in 2001 proposed the classification of BPD into mild, moderate, and severe categories based on the level of respiratory support at 36 weeks postmenstrual age (PMA).[3] Compared to infants with mild or moderate BPD, infants with severe BPD are more likely to receive medications such as diuretics and bronchodilators, rehospitalized following discharge for pulmonary causes, and have more severe neurodevelopmental impairment at the 18–22 month follow up visit.[4–7]

Although infants with severe BPD have a longer initial hospitalization than their peers without BPD, antecedents, co-morbidities, and in-patient resource use in this population are not well-defined. In an effort to describe the clinical course of infants with severe BPD, we identified medical interventions and in-hospital clinical outcomes in infants born <−30 weeks GA diagnosed with severe BPD. We hypothesized that infants with severe BPD who died during primary hospitalization were more likely to be born at earlier GAs and require more medical interventions than those infants who survived to discharge.

METHODS

Data Source and Study Population

We obtained data from the Pediatrix Medical Group Clinical Data Warehouse, which prospectively captures clinical information entered into an electronic health record by clinicians at 348 neonatal intensive care units.[8] We extracted information on prenatal characteristics, demographics, exposure to medications, and interventions while in the hospital, as well as in-hospital clinical outcomes and level of respiratory support at time of death or discharge. We included all inborn infants <30 weeks of GA discharged between 1997 and 2015 and diagnosed with severe BPD. We excluded infants discharged prior to 36 weeks PMA and those with missing data on mortality.

Definitions

We defined severe BPD as those infants receiving positive pressure (defined as nasal continuous positive airway pressure (CPAP), high-flow nasal cannula (HFNC) (>1 L/min), nasal intermittent positive pressure ventilation (PPV), conventional ventilation or high-frequency ventilation) at 36 weeks PMA. We did not include infants receiving supplemental oxygen ≥30% via low-flow nasal cannula (LFNC, ≤ 1 L/min) in our definition as we wanted to identify the most severe cases of BPD and the actual oxygen concentration delivered via LFNC varies depending on the size of the nares, the amount of mouth breathing, and the

infant's tidal volume and inspiratory time.[9,10] Furthermore, data from the Pediatrix Medical Group Clinical Data Warehouse includes a single measurement of oxygen requirement for a given day, which would not conform to the current NICHD definition of severe BPD. We defined small for gestational age as <10th percentile for age at birth as described by Olsen.[11] We identified exposures to medical interventions including the use of diuretics (acetazolamide, amiloride, bumetanide, chlorothiazide, diazoxide, ethacrynic acid, furosemide, hydrocholorothiazide, metolazone, and spironolactone), sildenafil, stimulants (aminophylline, doxapram, caffeine, and theophylline), steroids (dexamethasone, prednisolone, and prednisone), inhaled medications (budesonide, albuterol, and levalbuterol), and inhaled nitric oxide. We examined the incidence of in-hospital outcomes including sepsis, defined as bacteremia with an organism not typically considered a contaminant, intraventricular hemorrhage grade III or IV, surgical NEC, pulmonary hypertension as a diagnosis by the clinician, gastrostomy tube placement, and tracheostomy prior to and following diagnosis of severe BPD.

In order to show the evolving clinical course throughout hospitalization, we reviewed the level of respiratory support in 4-week intervals for those infants who remained hospitalized following the diagnosis of severe BPD. We also included the number of infants who had died, had been discharged, or remained in-hospital at each of the 4-week intervals following diagnosis of BPD.

Statistical Analysis

The unit of observation for this study was the infant. We used standard summary statistics, including medians (interquartile ranges) and counts (percentages), to describe categorical study variables. We compared distributions of study variables across categories using Wilcoxon rank sum, Chi square, and Fisher's exact tests where appropriate. All analyses were performed using Stata SE 14.2 (StataCorp, College Station, TX) and assumed a significance limit of $\alpha = 0.05$. The study was approved by the Duke University Health System Institutional Review Board without the need for written informed consent as the data were collected without identifiers.

RESULTS

We identified 10,752 infants diagnosed with severe BPD at 36 weeks PMA. The number of infants with severe BPD who died prior to discharge was 549/10,752 (5%). At the time of diagnosis, 2525/10,752 (23%) were receiving mechanical ventilation, and 8227/10,752 (77%) were receiving HFNC, CPAP, or nasal intermittent positive-press ventilation. The median GA and birth weight of the cohort were 26 weeks (interquartile range; 25, 27) and 755 g (628, 920), respectively. Median GA and birth weight were lower in the infants who died compared with those who survived to discharge, GA 25 weeks (24, 27) vs. 26 weeks (25, 27), p = 0.003, and birth weight 650 g (560, 810) vs. 760 g (630, 925), p <0.001. Infants who died were more likely male and small for gestational age (Table 1). Infants that died were more likely to be exposed to diuretics, inhaled medications, sildenafil, stimulants, steroids and inhaled nitric oxide prior to 36 weeks PMA (Table 2). No statistically

significant difference was found in the exposure to surfactant or supplemental oxygen between the two groups.

Several events were diagnosed more frequently prior to 36 weeks PMA in infants who died compared to those who survived, including intraventricular hemorrhage, surgical NEC, pulmonary hypertension, and culture-proven sepsis (Table 3). Diagnosis of surgical NEC, pulmonary hypertension, and culture-proven sepsis after 36 weeks PMA occurred more frequently in infants who died compared to those who survived. Infants who died were more likely to receive mechanical ventilation after diagnosis than the group who survived to discharge (97% vs. 39%, $p < 0.001$) and received more days on the ventilator until death or discharge, median number of days 31, (11–64) vs 0, (0–4). Following diagnosis, 1019 infants (10%) who survived received a g-tube compared to 77 infants (14%) who died ($p = 0.002$), and 302 infants (3%) who survived received a tracheostomy compared to 64 infants (12%) who died ($p < 0.001$). Fifty-seven percent of infants discharged from the hospital received supplemental oxygen, and 3% received mechanical ventilation at the time of discharge (Supplementary Table 1).

An increasing proportion of infants remaining hospitalized received mechanical ventilation (Figure 1). While 24% of infants received some form of mechanical ventilation at 36 weeks PMA, this number increased to 48% in those infants remaining hospitalized at 56 weeks PMA. Seventy percent of infants with severe BPD were discharged by 44 weeks PMA and 86% were discharged by 48 weeks PMA (Table 4). The time period with the largest number of deaths occurred between 36 and 40 weeks PMA. Of the 2525 infants receiving mechanical ventilation at 36 weeks PMA, 1860 (74%) were discharged home prior to 52 weeks PMA, 336 (13%) died, and 329 (13%) remained hospitalized at 52 weeks PMA. Of the 8117 infants receiving HFNC or CPAP at 36 weeks PMA, 7907 (96%) were discharged prior to 52 weeks PMA, 108 (1%) died, and 212 (3%) remained hospitalized at 52 weeks PMA.

DISCUSSION

We found that the majority of infants diagnosed with severe BPD at 36 weeks PMA survive until discharge and that most are discharged by 44 weeks PMA. An important caveat is that mortality in this study does include infants who died prior to the diagnosis of BPD at 36 weeks PMA. While all of the infants included in our study received positive pressure at the time of diagnosis, the proportion of infants receiving some form of positive pressure decreased at 40 weeks PMA, and actually increased thereafter. For example, after 44 weeks PMA, an increasingly higher percentage of infants remaining hospitalized received mechanical ventilation, likely reflecting that the most critically ill infants had a longer duration of primary hospitalization. These results suggest that at the estimated date of delivery, about two-thirds of infants with severe BPD will remain hospitalized and a relatively small percentage of these hospitalized infants will receive mechanical ventilation. This information may help inform discussions with families regarding the expected hospital course of infants diagnosed with severe BPD.

We found that about half of infants diagnosed with severe BPD were exposed to postnatal dexamethasone, prednisone, or prednisolone. Approximately 40% of infants in our cohort received these steroids prior to 36 weeks PMA and those who subsequently died were more likely to receive steroids (49% vs. 37%). The proposed benefits of steroids in the infant include enhancement of endogenous surfactant and anti-oxidant production, amelioration of the inflammatory process contributing to the development of BPD, and reduction of pulmonary edema and bronchospasm, all of which may reduce the incidence of BPD. The most recent American Academy of Pediatrics guidelines on the use of postnatal steroids in premature infants at risk for BPD advise clinicians to, while consulting the infant's parents, balance the risks of using a short course of low-dose corticosteroids against the risks of evolving pulmonary disease and prolonged mechanical ventilation.[12]

We found that a lower percentage of infants who died (79%) were exposed to stimulant therapy prior to 36 weeks PMA compared to those infants who survived (93%). While this finding is surprising, we speculate that some of the infants who received prolonged mechanical ventilation may not have been started on stimulant therapy as extubation was not anticipated and central apnea cannot occur while on mechanical ventilation. Several studies have found that early administration of caffeine in premature infants is associated with an increase in survival without BPD.[13–15] The early use of caffeine should be strongly considered in infants at high risk for BPD regardless of respiratory support.

Premature infants with a diagnosis of BPD were found to require a high number of primary care provider office visits and prescription medications in the first year of life.[16] About 3% of infants in our study who were discharged home received mechanical ventilation, with approximately the same number receiving tracheostomy. More than half of infants with severe BPD discharged home received supplemental oxygen. Previous investigators found that premature infants with BPD who were discharged home with supplemental oxygen were more likely to receive respiratory medications, supplemental oxygen, and more frequent physician visits at 36 months of life compared with infants with BPD who were discharged home without supplemental oxygen.[17] Approximately one in ten infants in our study who survived to discharge received a gastrostomy tube during primary hospitalization. Infants with BPD who receive gastrostomy tubes were found to have longer primary hospitalizations, are more likely to receive ventilatory support and supplemental oxygen at the time of discharge, and are more likely to be rehospitalized in the first two years of life compared to infants with BPD who do not receive gastrostomy tubes.[18]

There are several limitations to our study. As the purpose of our study was to determine in-hospital outcomes in premature infants diagnosed with severe BPD, we did not include infants who died prior to 36 weeks PMA or infants who were transferred to other facilities outside the network. Our definition of severe BPD was based on the use of positive pressure at 36 weeks PMA. The inclusion of HFNC (considered >1 L/min via nasal cannula) in our definition of PPV does not directly measure distending pressure because the measured component is liter flow.[19,20] HFNC is an increasingly common modality used in neonatal intensive care units worldwide due to its perceived benefits in ease of use compared to nasal CPAP.[21,22] We included HFNC as PPV because we believe that the intent by the clinician was to provide PPV, even though the exact distending pressure is unmeasured. While infants

receiving LFNC (considered <1 L/min) with a fraction of inspired oxygen ≥0.3 at 36 weeks PMA would be considered to have severe BPD based on the 2001 National Institutes of Health consensus, we did not include these infants in our definition of BPD as the oxygen concentration which an infant receives via nasal cannula is not precise.[23] This is due to the entrainment of room air through the mouth and nose, which may result in the delivery of a lower fraction of inspired oxygen than what is recorded. A further limitation is that the diagnosis of pulmonary hypertension was based on documentation by clinicians and no echocardiogram images or reports were reviewed for this study.

In summary, we describe the in-hospital outcomes of premature infants born <30 weeks GA who were subsequently diagnosed with severe BPD. The majority were discharged home by 44 weeks PMA and a small percentage of these infants died. The infants receiving prolonged mechanical ventilation were more likely to remain hospitalized and of those infants who died, nearly all (>90%) died while receiving mechanical ventilation. While the incidence of severe BPD is relatively rare compared to the number of premature infants born each year worldwide, the substantial health care resources and familial stress associated with an increased morbidity and mortality, including prolonged hospitalization, demand further efforts to prevent and more effectively treat infants with severe BPD. Further studies using large sample sizes in collaboration with multiple clinical sites will be required to determine long-term pulmonary and neurodevelopmental outcomes in these infants and develop potential therapies to prevent and treat BPD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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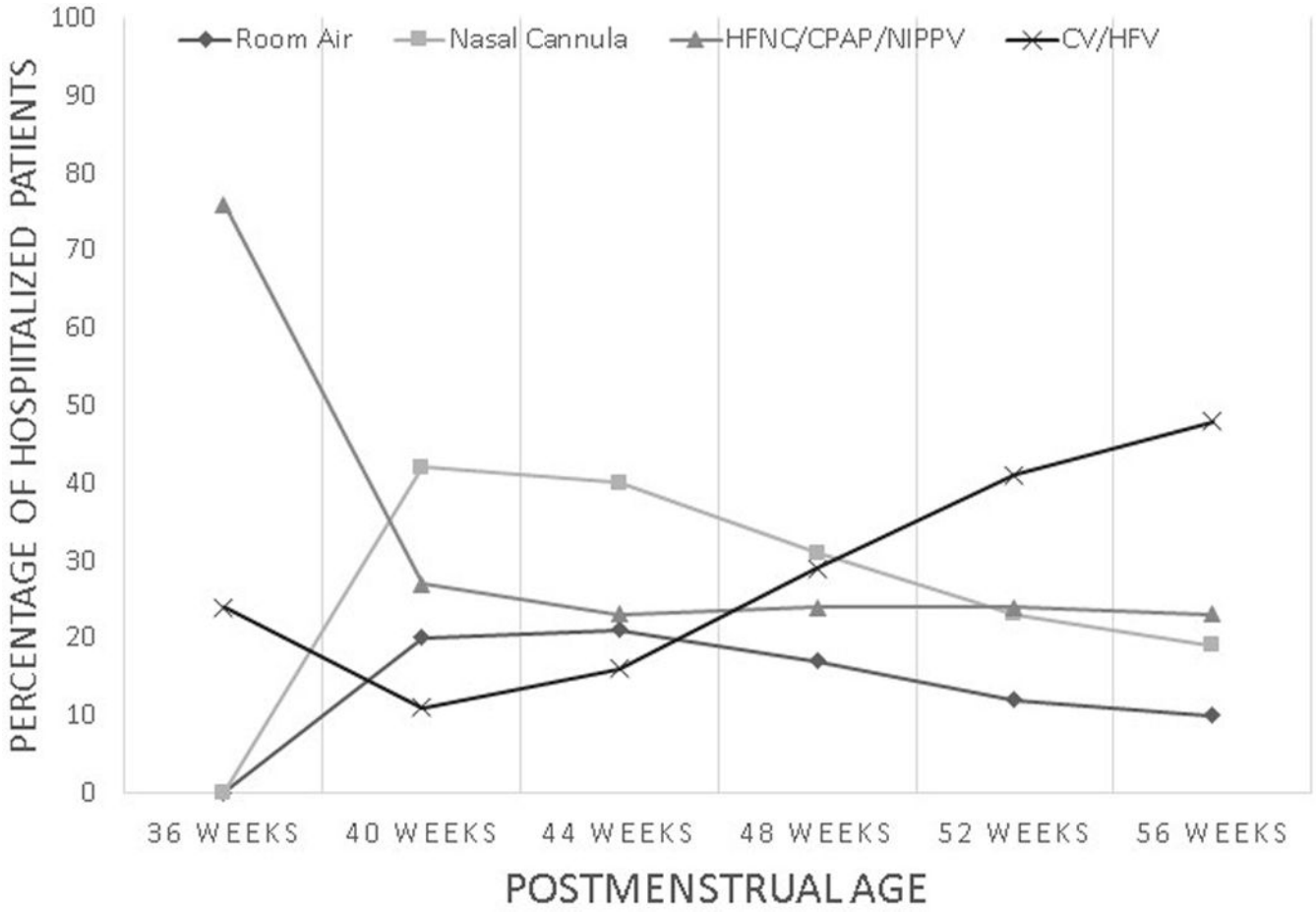

Figure 1. Respiratory support over time in hospitalized premature infants with severe BPD

Abbreviations: HFNC = high-flow nasal cannula; CPAP = continuous positive airway pressure; NIPPV = nasal-intermittent positive pressure ventilation; CV = conventional mechanical ventilation; HFV = high-frequency ventilation

Table 1

Cohort demographics

	Survived N= 10,203	**Died N= 549**	**P-value**
Antenatal steroids	8540 (84%)	445 (81%)	0.10
Antenatal antibiotics	4682 (46%)	239 (44%)	0.28
Cesarean section	7688 (76%)	418 (77%)	0.80
Male	5799 (57%)	341 (62%)	0.01
Gestational age (weeks)			< 0.001
≤ 25	4421 (43%)	279 (51%)	
26–28	4866 (48%)	211 (38%)	
29	916 (9%)	59 (11%)	
Birth weight (g)			<0.001
<1000	8365 (82%)	487 (89%)	
1000–1499	1777 (17%)	59 (11%)	
1500–2499	58 (< 1%)	3 (< 1%)	
SGA	2471 (24%)	225 (41%)	<0.001

SGA = small for gestational age

Table 2

Exposure to medications prior to 36 weeks postmenstrual age

	Survived N (%) = 10,203	Died N (%) = 549	P-value	Total Days of Exposure Median (IQR)	
				Lived	Died
Diuretics	8089 (79%)	482 (88%)	< 0.001	6 (1, 22)	14 (4–32)
Any Inhaled Medications *	5453 (53%)	359 (65%)	< 0.001	2 (0–27)	4 (0–29)
Sildenafil	57 (<1%)	29 (5%)	< 0.001	0 (0–0)	0 (0–0)
Stimulant	9500 (93%)	436 (79%)	< 0.001	49 (27–64)	26 (2–55)
Steroids	3776 (37%)	269 (49%)	< 0.001	0 (0–5)	0 (0–11)
Bronchodilator	982 (10%)	78 (14%)	< 0.001	0 (0–0)	0 (0–0)
Surfactant	8715 (85%)	456 (83%)	0.13	1 (1–2)	1 (1–2)
Inhaled Nitric Oxide	782 (8%)	115 (21%)	< 0.001	0 (0–0)	0 (0–0)

Abbreviations: IQR = interquartile range

* Inhaled medications include bronchodilators and steroids

Table 3

Outcomes prior to and after 36 weeks postmenstrual age

	Prior to 36 weeks PMA			After 36 weeks PMA		
	Survived N (%) = 10,203	**Died N (%) = 549**	**P-value**	**Survived N (%) = 10,203**	**Died N (%) = 549**	**P-value**
IVH	1112 (11%)	105 (19%)	< 0.001	20 (< 1%)	0	0.30
Surgical NEC	400 (4 %)	87 (16%)	< 0.001	26 (< 1%)	15 (3%)	< 0.001
Pulmonary HTN	777 (8%)	111 (20%)	< 0.001	318 (3%)	100 (18%)	< 0.001
Culture-Proven Sepsis *	2658 (26%)	228 (42%)	< 0.001	483 (5%)	140 (26%)	< 0.001

Abbreviations: IVH = Intraventricular hemorrhage; NEC = Necrotizing Enterocolitis; HTN = Hypertension

* Bacterial growth in urine, blood or CSF specimens with an organism not typically considered a contaminant

Table 4

Disposition of infants with severe BPD following time of diagnosis to 56 weeks PMA

	36 weeks PMA N (%)	40 weeks PMA N (%)	44 weeks PMA N (%)	48 weeks PMA N (%)	52 weeks PMA N (%)	56 weeks PMA N (%)
Total In-Hospital	10,752 (100%)	7531 (70%)	2983 (28%)	1164 (11%)	540 (5%)	272 (<1%)
Discharged *	0	3042 (28%)	7490 (70%)	9207 (86%)	9768 (91%)	9986 (93%)
Died **	0	179 (2%)	279 (2%)	381 (4%)	444 (4%)	498 (5%)

* Indicates how many infants discharged at the given point in time. Note that 221 infants were discharged after 56 weeks PMA (not shown)

** Indicates how many infants have died at the given point in time. Note that 51 infants died after 56 weeks PMA (not shown).