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ORIGINAL ARTICLE

In-hospital outcomes of premature infants with severe bronchopulmonary dysplasia

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OBJECTIVE: To characterize in-hospital outcomes of premature infants diagnosed with severe bronchopulmonary dysplasia (BPD).
STUDY DESIGN: Retrospective cohort study including premature infants with severe BPD discharged from 348 Pediatrix Medical Group neonatal intensive care units from 1997 to 2015.
RESULTS: There were 10 752 infants with severe BPD, and 549/10 752 (5%) died before 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 of postmenstrual age compared with survivors. Approximately 70% of infants with severe BPD were discharged by 44 weeks of postmenstrual age, and 86% were discharged by 48 weeks of postmenstrual age.
CONCLUSIONS: A majority of infants diagnosed with severe BPD were discharged home by 44 weeks of postmenstrual age. These results may inform discussions with families regarding the expected hospital course of infants diagnosed with severe BPD.

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INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common and severe pulmonary complication of prematurity.[1] The incidence of BPD may be increasing because of improvement in the survival of infants at earlier gestational ages (GAs).[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 of postmenstrual age (PMA).[3] Compared with infants with mild or moderate BPD, infants with severe BPD are more likely to be rehospitalized following discharge for pulmonary causes, receive medications such as diuretics and bronchodilators and have more severe neurodevelopmental impairment at the 18- to 22-month follow-up visit.[4–7]

Although infants with severe BPD have a longer initial hospitalization than their peers without BPD, antecedents, comorbidities 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 at <30 weeks of 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 that 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 the time of death or discharge. We included all inborn infants at <30 weeks of GA discharged between 1997 and 2015 and diagnosed with severe BPD. We excluded infants discharged before 36 weeks of 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, high-flow nasal cannula (HFNC) (>1 l min^{-1}), nasal intermittent positive pressure ventilation, conventional ventilation or high-frequency ventilation) at 36 weeks of PMA. We did not include infants receiving supplemental oxygen $\geqslant 30\%$ via low-flow nasal cannula ($\leqslant 1$ l min^{-1}) in our definition as we wanted to identify the most severe cases of BPD and the actual oxygen concentration delivered via low-flow nasal cannula 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, and this would not conform to the current NICHD (National Institute of Child Health and Human Development) definition of severe BPD. We defined small for gestational age as <10th percentile for age at birth as described by Olsen *et al.*[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 necrotizing enterocolitis, pulmonary hypertension as a diagnosis by the clinician, gastrostomy tube placement and tracheostomy before and following diagnosis of severe BPD.

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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, χ^2 and Fisher's exact tests where appropriate. All analyses were performed using Stata SE 14.2 (StataCorp, College Station, TX, USA) 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 of PMA. The number of infants with severe BPD who died before 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, continuous positive airway pressure or nasal intermittent positive-press ventilation. The median GA and birth weight of the cohort were 26 weeks (interquartile range: 25 to 27) and 755 g (628 to 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 to 27) vs 26 weeks (25 to 27), $P = 0.003$, and birth weight 650 g (560 to 810) vs 760 g (630 to 925), $P < 0.001$. Infants who died were more likely male and small for gestational age (Table 1). Infants who died were more likely to be exposed to diuretics, inhaled medications, sildenafil, stimulants, steroids and inhaled nitric oxide before 36 weeks of 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 before 36 weeks of PMA in infants who died compared with those who survived, including intraventricular hemorrhage, surgical necrotizing enterocolitis, pulmonary hypertension and culture-proven sepsis (Table 3). Diagnosis of surgical necrotizing enterocolitis, pulmonary hypertension and culture-proven sepsis after 36 weeks of PMA occurred more frequently in infants who died compared with 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 to 64) vs 0 (0 to 4). Following diagnosis, 1019 infants (10%) who survived received a g-tube compared with 77 infants (14%) who died ($P = 0.002$), and 302 infants (3%) who survived received a tracheostomy compared with 64 infants (12%) who died ($P < 0.001$). In all, 57% 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). Whereas 24% of infants received some form of mechanical ventilation at 36 weeks of PMA, this number increased to 48% in those infants remaining hospitalized at 56 weeks of PMA. Of the infants with severe BPD, 70% were discharged by 44 weeks of PMA and 86% were discharged by 48 weeks of PMA (Table 4). The time period with the largest number of deaths occurred between 36 and 40 weeks of PMA. Of the 2525 infants receiving mechanical ventilation at 36 weeks of PMA, 1860 (74%) were discharged home before 52 weeks of PMA, 336 (13%) died and 329 (13%) remained hospitalized at 52 weeks of PMA. Of the 8117 infants receiving HFNC or continuous positive airway pressure at 36 weeks of PMA, 7907 (96%) were discharged before 52 weeks of PMA, 108 (1%) died and 212 (3%) remained hospitalized at 52 weeks of PMA.

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

Abbreviation: SGA, small for gestational age.

DISCUSSION

We found that the majority of infants diagnosed with severe BPD at 36 weeks of PMA survive until discharge and that most are discharged by 44 weeks of PMA. An important caveat is that mortality in this study does include infants who died before the diagnosis of BPD at 36 weeks of PMA. Although 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 of PMA, and actually increased thereafter. For example, after 44 weeks of 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, approximately 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 before 36 weeks of 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 antioxidant 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 before 36 weeks of PMA compared with those infants who survived (93%). Although 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

Table 2. Exposure to medications before 36 weeks of 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[a]	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)

Abbreviation: IQR, interquartile range. [a]Inhaled medications include bronchodilators and steroids.

Table 3. Outcomes before and after 36 weeks of postmenstrual age

	Before 36 weeks of PMA			*After 36 weeks of 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[a]	2658 (26%)	228 (42%)	< 0.001	483 (5%)	140 (26%)	< 0.001

Abbreviations: HTN, hypertension; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PMA, postmenstrual age. [a]Bacterial growth in urine, blood or cerebrospinal fluid (CSF) specimens with an organism not typically considered a contaminant.

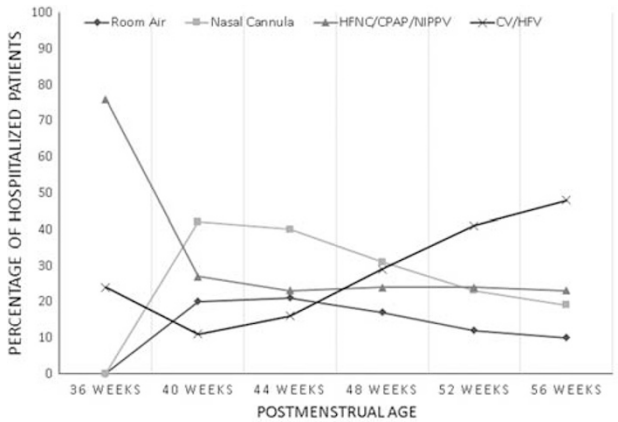

Figure 1. Respiratory support over time in hospitalized premature infants with severe bronchopulmonary dysplasia (BPD). CPAP, continuous positive airway pressure; CV, conventional mechanical ventilation; HFNC, high-flow nasal cannula; HFV, high-frequency ventilation; NIPPV, nasal intermittent positive pressure ventilation.

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] Approximately 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 1 in 10 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 2 years of life compared with 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 before 36 weeks of 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 of PMA. The inclusion of HFNC (considered $>1\ \mathrm{l\,min^{-1}}$ via nasal cannula) in our definition of positive pressure ventilation 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 because of its perceived benefits in ease of use compared with nasal continuous positive airway pressure.[21,22] We included HFNC as positive pressure ventilation because we believe that the intent by the clinician was to provide positive pressure ventilation, even though the exact distending pressure is unmeasured. Although infants receiving low-flow nasal cannula (considered $<1\ \mathrm{l\,min^{-1}}$) with a fraction of inspired oxygen $\geqslant 0.3$ at 36 weeks of 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 that an infant receives via nasal

Table 4. Disposition of infants with severe BPD following time of diagnosis to 56 weeks of PMA

	36 Weeks of PMA, N *(%)*	*40 Weeks of PMA,* N *(%)*	*44 Weeks of PMA,* N *(%)*	*48 Weeks of PMA,* N *(%)*	*52 Weeks of PMA,* N *(%)*	*56 Weeks of PMA,* N *(%)*
Total in-hospital	10 752 (100%)	7531 (70%)	2983 (28%)	1164 (11%)	540 (5%)	272 (3%)
Discharged[a]	0	3042 (28%)	7490 (70%)	9207 (86%)	9768 (91%)	9982 (93%)
Died[b]	0	179 (2%)	279 (2%)	381 (4%)	444 (4%)	498 (5%)

Abbreviations: BPD, bronchopulmonary dysplasia; PMA, postmenstrual age. [a]Indicates how many infants discharged at the given point in time. Note that 221 infants were discharged after 56 weeks of PMA (not shown). [b]Indicates how many infants have died at the given point in time. Note that 51 infants died after 56 weeks of PMA (not shown).

cannula is not precise.[23] This is because of the entrainment of room air through the mouth and nose that 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 of GA who were subsequently diagnosed with severe BPD. A majority were discharged home by 44 weeks of 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. Although the incidence of severe BPD is relatively rare compared with 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.

CONFLICT OF INTEREST

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Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)