Outpatient respiratory outcomes in children with BPD on supplemental oxygen

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Abstract

Introduction: Preterm children with bronchopulmonary dysplasia (BPD) frequently require supplemental oxygen in the outpatient setting. In this study, we sought to determine patient characteristics and demographics associated with need for supplemental oxygen at initial hospital discharge, timing to supplemental oxygen liberation, and associations between level of supplemental oxygen and likelihood of respiratory symptoms and acute care usage in the outpatient setting. **Methods:** A retrospective analysis of subjects with BPD on supplemental oxygen (O_2) was performed. Subjects were recruited from outpatient clinics at Johns Hopkins University and the Children's Hospital of Philadelphia between 2008 and 2021. Data were obtained by chart review and caregiver questionnaires. **Results**: Children with BPD receiving $>$ 1 liter of O_2 were more likely to have severe BPD, pulmonary hypertension and be older at initial hospital discharge. Children discharged on higher levels of supplemental O_2 were slower to wean to room air compared to lower O_2 groups ($p<0.001$). Additionally, weaning off supplemental O_2 in the outpatient setting was delayed in children with gastrostomy tubes and those prescribed inhaled corticosteroids, on public insurance or with lower estimated household incomes. Level of supplemental O_2 at discharge did not influence outpatient acute care usage or respiratory symptoms. **Conclusion**: BPD severity and level of supplemental oxygen use at discharge did not correlate with subsequent acute care usage or respiratory symptoms in children with BPD. Weaning of O_2 however was significantly associated with socioeconomic status and respiratory medication use, contributing to the variability in O_2 weaning in the outpatient setting.

Introduction

Preterm birth comprises 10.1% of all births in the United States.[1] With advances in neonatal care, survival rates of premature infants have improved, especially for those born at extremely low birth weights.[2] These low birth weight infants are at highest risk for developing bronchopulmonary dysplasia (BPD) and to minimize hypoxemia events, are more likely to be discharged to home on supplemental oxygen. In a single center study, approximately 1/3 of preterm infants with BPD who were followed in the outpatient setting were initially discharged to home on oxygen therapy.[3] Clinical practice guidelines from both the American Thoracic Society and British Thoracic Society recommend home oxygen therapy for infants with BPD with ongoing hypoxemia.[4 5] However, variations in supplemental oxygen use and weaning strategies in children with BPD,[6] may influence outpatient respiratory outcomes, particularly during the first three years of life.

BPD is characterized by alveolar hypoplasia and small airway disease. Achieving normal oxygen levels in children with BPD can help promote somatic growth, optimize developmental outcomes and minimize the development or worsening of pulmonary hypertension.[7]In the outpatient setting however, few guidelines for weaning supplemental oxygen in children with BPD exist; thus variability in respiratory outcomes and timing to liberation from supplemental oxygen is common. When comparing children with BPD on supplemental

oxygen at discharge to those on room air several studies have reported higher rates of hospitalizations and healthcare utilization in those discharged on supplemental oxygen.[8,9] However, another study found no differences in these outcomes between the two groups.[10]

In this study, we focused on children with BPD discharged on supplemental oxygen (O_2). The purpose of this study was to determine whether an association existed between level of supplemental oxygen use at discharge and subsequent outpatient acute care usage and respiratory symptoms in this study population. Secondly, we sought to identify patient characteristics and demographics that may be associated with the variability in the timing of liberation from supplemental oxygen in children with BPD, following initial hospital discharge.

Methods

A retrospective chart review was performed on subjects (n=417) recruited from outpatient BPD clinics at the Children's Hospital of Philadelphia and Johns Hopkins Children's Center between 2008-2021. All subjects were born at less than 37 weeks-gestation and were diagnosed with BPD by NIH consensus definition,[11] and were on home supplemental oxygen via nasal cannula; patients with tracheostomies or home ventilators were excluded. This study was approved by Johns Hopkins Institutional Review Board (Protocol #NA_00051884) and the Children's Hospital of Pediatrics Institutional Review Board (IRB# 20-017614) and all caregivers were consented.

Children using supplemental O_2 at initial hospital discharge were divided into four groups. Those who required [?]1/8 lpm of O_2 (group 1), those who required >1/8 lpm of oxygen but <1/2 lpm of O_2 (group 2), those who required [?]1/2 lpm O_2 but <1 lpm O_2 of oxygen (group 3), and those who required [?]1 lpm O_2 of oxygen (group 4). Demographic data and clinical characteristics were collected by chart review. Birthweight percentile was corrected by gestational age.[12] Race/ethnicity was obtained through caregiver report. Median household income was estimated using residential zip codes based on U.S. Census data.

Acute care usage and chronic respiratory symptom data was obtained via caregiver-completed questionnaires at outpatient visits when subjects were between 0 and 3 years of age.

Statistics: Chi square and ANOVA tests were performed to compare demographic data and clinical characteristics between oxygen groups (Table 1). Cox regressions adjusted for inter-site variation were performed to identify factors associated with earlier or later liberation from supplemental oxygen (Table 2). Associations between amount of oxygen at initial hospital discharge and acute care use/chronic respiratory symptoms were assessed for via logistic regression models adjusted for inter-site variation, potential demographic/clinical confounders, duration of oxygen use, number of questionnaires, and age of questionnaire assessments (Table 3). Results that were statistically significant had a P value less than or equal to 0.05. Stata IC 16 was used for data analysis.

Results

Subject Demographics

At initial hospital discharge, children who required higher levels of supplemental oxygen were more likely to have severe BPD, lower birthweight percentiles, and a diagnosis of pulmonary hypertension compared to those who required less supplemental oxygen (**Table 1**). Additionally, higher levels of supplemental oxygen at initial hospital discharge were associated with older age at discharge ($p<0.001$), gastrostomy tube placement ($p<0.001$), and use of diuretics ($p=0.005$), inhaled corticosteroids (ICS) ($p=0.005$), and pulmonary antihypertension medications ($p<0.001$). Race/ethnicity and public insurance were not associated with higher supplemental oxygen use at initial hospital discharge; however, there was some variation in oxygen amounts by median household income ($p=0.042$).

Timing of weaning of supplemental oxygen in BPD children in the outpatient setting

Liberation from supplemental oxygen was delayed in children who were initially discharged on higher amounts of supplemental oxygen ($p<0.001$) (**Figure 1**). The median age at liberation was 8.4 months for group 1, 10.8 months for group 2, 13.5 months for group 3, and 19.6 months for group 4.

Likelihood of weaning supplemental oxygen in a given month, in the outpatient setting

In a multivariate model, the likelihood of being weaned off supplemental oxygen in a given month was lower if the child was prescribed more supplemental oxygen initially, had a gastrostomy tube, had a lower estimated household income, or was prescribed inhaled corticosteroids (**Table 2**). Interestingly, severity of BPD at 36 weeks corrected age did not influence the likelihood of weaning off supplemental oxygen in a given month.

Acute care usage and respiratory outcomes, with regard to level of supplemental oxygen at initial hospital discharge .

We next examined correlations between outpatient respiratory outcomes and acute care usage with the level of supplemental oxygen use at initial hospital discharge. When examining differences by amount of oxygen at initial discharge, we found no significant differences in acute care usage, chronic respiratory symptoms, or rescue medication use (**Table 3**).

Discussion

The burden of respiratory morbidities in children with BPD can be lifelong [13] and identifying those at highest risk for long-term respiratory morbidities, is challenging. Children with BPD who require supplemental oxygen at initial hospital discharge have varying degrees of cardiopulmonary involvement and are likely at higher risk for chronic respiratory symptoms during the pre-school years when compared to children discharged off supplemental oxygen.[14]Identifying factors that predict outpatient acute care usage, chronic respiratory symptoms and timing to oxygen liberation could help modify respiratory morbidities in these children . This study focused on children with BPD discharged to home on supplemental oxygen to address these issues. Not unexpectantly, children discharged on higher levels of supplemental oxygen were more likely to have severe BPD and to carry the diagnosis of pulmonary hypertension. Additionally, those who required higher levels of supplemental oxygen at initial hospital discharge were more likely to have lower birthweight percentiles and to be older at initial hospital discharge. However, children discharged on higher levels of supplemental oxygen did not have a higher likelihood of acute care usage, chronic respiratory symptoms or need for respiratory medications during acute illnesses when compared to those discharged on lower levels of supplemental oxygen. The likelihood of weaning supplemental oxygen, in a given month, was significantly lower in children with gastrostomy tubes, children prescribed inhaled corticosteroids and in those who lived in homes with lower estimated incomes. Findings from this study suggest that although severity of BPD influences level of supplemental oxygen at initial hospital discharge, other factors after hospital discharge influence weaning of supplemental oxygen and respiratory morbidities, including socioeconomic status (SES) and ICS use, which could be modifiable factors.

In this study, several risk factors were associated with delayed weaning of supplemental oxygen. In particular, we found that weaning oxygen, per given month was less likely in children with lower estimated household incomes. This finding suggest that socioeconomic status can be a factor in liberating a child from supplemental oxygen in the outpatient setting. This finding raises the question of whether children with lower SES, have more difficulties in accessing care, once they are in the outpatient setting. However, a recent study did not support this.[15] Additional studies will be needed to determine if other health disparities or perceptions due to SES, influence variations in oxygen weaning strategies in children with BPD. We also found that higher use of ICS was associated with delayed weaning of supplemental oxygen. It is possible that ICS was used as an additive therapy in those who were more difficult to wean from supplemental oxygen, which may account for delayed weaning of supplemental oxygen. Other reasons may also affect weaning in the outpatient setting. Wong et. al., studied infants with moderate or severe BPD discharged on varying amounts of supplemental oxygen. They found that shorter NICU stays were associated with quicker oxygen weans at 9 and 12 months with no correlation to birthweight or gestational age.[16]Our findings indicate that factors after initial hospital discharge can influence weaning of supplemental oxygen in children with BPD.

In this study, no differences in acute care usage or respiratory symptoms were found between any of the oxygen groups in children with BPD. Higher levels of supplemental oxygen at discharge were not associated with increased rates of emergency room visits, hospitalizations, systemic steroid use, or antibiotic use for

respiratory conditions. There were also no differences in chronic respiratory symptoms or rescue medication use between the oxygen groups. It is possible that supplemental oxygen use in the outpatient setting lowers hospitalizations in BPD children by mitigating hypoxemia that can occur during acute respiratory illnesses, regardless of amount given. Greenough et. al., reported that children with BPD between the ages of 2 to 4 years who required supplemental oxygen did not have increased hospital admissions, compared to those on room air. [9]However, their study did see an increase in wheezing and use of inhalers. Lodha et. al., [10] also examined respiratory outcomes at 3 years of age in children without BPD, with BPD, and with BPD on supplemental oxygen. They reported that children with BPD on supplemental oxygen did not have higher rates of hospitalization or antibiotic use compared to the other groups. Unlike our study however, Lodha et. al., did not stratify by amount of supplemental oxygen use. Other studies however, have shown higher rates of rehospitalization for respiratory issues in infants with BPD requiring oxygen supplementation at home.[8,16] Our study suggest that being on any level of supplemental oxygen at initial discharge, could provide a buffer to support adequate oxygen levels during periods of illness, lessening the likelihood of hospitalization in children with more severe BPD.

A limitation of this study is the retrospective nature of the study design. Furthermore, this study included patients from two centers, in which the demographics of these cohorts predominately represent an urban population, which may not be generalizable to other patient populations, particularly those in rural areas. Additionally, both centers in this study have outpatient BPD clinics which may account for higher comfort in discharging children with BPD on higher levels of oxygen in the outpatient setting. Nevertheless, our study results suggest that the use of supplemental oxygen can help to mitigate differences in BPD severity with regard to acute care usage and reported respiratory symptoms in children with BPD in the outpatient setting.

In summary, among BPD children on supplemental oxygen in the outpatient setting, the level of oxygen supplementation at initial hospital discharge was not shown to correlate with acute care usage or respiratory symptoms. Weaning of supplemental O_2 however was significantly associated with household income and ICS use, indicating that these factors can influence timing of oxygen weaning by healthcare providers in the outpatient setting.

Table 1: Demographic and Clinical Characteristics by Oxygen Amount at Initial Hospital Discharge

Mean ± S.D. [Range]	Mean ± S.D. [Range]	**Entire Study Population** (n=417)	**Entire Study Population** (n=417)	**[?]0.125 LPM** (n = 149)	**>0.125 and <0.5 LPM** (n = 130)	**[?]0.5 and <1.0 LPM** (n=111)	**[?]1.0 LPM** (n=27)	*P* **valu**
Sex (% male)	**Sex** (% male)	55.6%	55.6%	55.7%	53.9%	63.1%	33.3%	**0.044**
Race (% non-white; n=404)	**Race** (% non-white; n=404)	59.7%	59.7%	59.5%	66.4%	54.3%	50.0%	0.20
Ethnicity (% Hispanic; n=415)	**Ethnicity** (% Hispanic; n=415)	5.5%	5.5%	5.4%	4.6%	4.6%	14.8%	0.18
Gestational age (weeks)	**Gestational age** (weeks)	26.4 ± 2.6 [22.9, 36.9]	26.4 ± 2.6 [22.9, 36.9]	26.3 ± 2.4 [22.9, 36.9]	26.5 ± 2.7 [23.0, 35.5]	26.2 ± 2.4 [23.0, 35.3]	26.8 ± 2.6 [23.4, 36.0]	0.69
Birthweight (grams; n=409)	**Birthweight** (grams; n=409)	858 ± 408 [380, 3370]	858 ± 408 [380, 3370]	868 ± 399 [380, 3370]	875 ± 455 [390, 3181]	829 ± 302 [415, 1790]	836 ± 590 [420, 2790]	0.82

Mean ± S.D. [Range]	Mean ± S.D. [Range]	**Entire Study Population** (n=417)	**Entire Study Population** (n=417)	**[?]0.125 LPM** (n = 149)	**>0.125 and <0.5 LPM** (n = 130)	**[?]0.5 and <1.0 LPM** (n=111)	**[?]1.0 LPM** (n=27)	*P* **valu**
Birthweight percentile (%; n=409)	**Birthweight percentile** (%; n=409)	40 ± 26 [1, 95]	40 ± 26 [1, 95]	42 ± 27 [1, 95]	39 ± 24 [1, 89]	42 ± 26 [1, 89]	25 ± 19 [2, 67]	**0.018**
BPD severity (%; n=387)	Mild	0.5%	0.5%	1.4%	0.0%	0.0%	0.0%	**<0.001**
	Moderate	Moderate	34.4%	47.5%	38.8%	17.8%	7.7%	
	Severe	65.1%	65.1%	51.1%	61.2%	82.2%	92.3%	
Gastrostomy tube (% yes)	**Gastrostomy tube** (% yes)	33.1%	33.1%	16.8%	33.1%	46.9%	66.7%	**<0.001**
Nissen fundoplication in subjects with gastrostomies (% yes; n =138)	**Nissen fundoplication in subjects with gastrostomies** (% yes; n =138)	65.2%	65.2%	52.0%	60.5%	71.2%	77.8%	0.22
Pulmonary hypertension after 36 weeks (% yes)	**Pulmonary hypertension after 36 weeks** (% yes)	27.8%	27.8%	16.1%	24.6%	40.5%	55.6%	**<0.001**
Pulmonary hypertension medications in subjects with pulmonary hypertension (% yes; n=116)	**Pulmonary hypertension medications in subjects with pulmonary hypertension** (% yes; n=116)	40.5%	40.5%	16.7%	25.0%	53.3%	73.3%	**<0.001**

Mean ± S.D. [Range]	Mean ± S.D. [Range]	**Entire Study Population** (n=417)	**Entire Study Population** (n=417)	**[?]0.125 LPM** (n = 149)	**>0.125 and <0.5 LPM** (n = 130)	**[?]0.5 and <1.0 LPM** (n=111)	**[?]1.0 LPM** (n=27)	*P* **valu**
Diuretics (% yes)	**Diuretics** (% yes)	65.5%	65.5%	54.4%	70.0%	73.0%	74.1%	**0.005**
Inhaled corti-cos-teroids (% yes)	**Inhaled corti-cos-teroids** (% yes)	74.8%	74.8%	65.8%	77.7%	79.3%	92.6%	**0.005**
Initial discharge age (months; n=416)	**Initial discharge age** (months; n=416)	4.7 ± 2.5 [0.1, 17.9]	4.7 ± 2.5 [0.1, 17.9]	4.0 ± 2.1 [0.5, 15.3]	4.7 ± 2.3 [0.1, 14.9]	5.3 ± 2.8 [1.0, 17.9]	5.8 ± 3.2 [0.2, 13.6]	**<0.001**
Median household income ($ in thousands; n=413)	**Median household income** ($ in thousands; n=413)	77.2 ± 27.9 [20.4, 156.8]	77.2 ± 27.9 [20.4, 156.8]	81.1 ± 27.8 [28.5, 156.8]	72.4 ± 26.7 [22.8, 156.8]	76.1 ± 28.6 [20.4, 145.8]	83.5 ± 28.9 [31.9, 148.9]	**0.042**
Public insur-ance (% yes)	**Public insur-ance** (% yes)	53.2%	53.2%	48.3%	53.1%	55.9%	70.4%	0.18

Figure 1. Kaplan-Meier plot with time to weaning from home supplemental oxygen by amount of oxygen at initial hospital discharge

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`image1.emf` available at https://authorea.com/users/462418/articles/613914-outpatient-respiratory-outcomes-in-children-with-bpd-on-supplemental-oxygen

Table 2: Likelihood of weaning oxygen in a given month by demographic data clinical characteristics

Amount of oxygen at initial discharge (LPM)	**Amount of oxygen at initial discharge** (LPM)
Sex (male=0; female=1)	**Sex** (male=0; female=1)
Race (white=0; nonwhite=1)	**Race** (white=0; nonwhite=1)
Ethnicity (non-Hispanic=0; Hispanic=1)	**Ethnicity** (non-Hispanic=0; Hispanic=1)
Gestational age (months)	**Gestational age** (months)
Birthweight (grams)	**Birthweight** (grams)
Birthweight percentile (%)	**Birthweight percentile** (%)
BPD severity (Reference=Mild)	Moderate
	Severe
Gastrostomy tube (no=0; yes=1)	**Gastrostomy tube** (no=0; yes=1)
Nissen fundoplication (no=0; yes=1)	**Nissen fundoplication** (no=0; yes=1)
Pulmonary hypertension after 36 weeks (no=0; yes=1)	**Pulmonary hypertension after 36 weeks** (no=0; yes=

Pulmonary anti-hypertensive medications (no=0; yes=1)	**Pulmonary anti-hypertensive medications** (no=0; ye
Diuretics (no=0; yes=1)	**Diuretics** (no=0; yes=1)
Inhaled corticosteroids (no=0; yes=1)	**Inhaled corticosteroids** (no=0; yes=1)
Discharge age (months)	**Discharge age** (months)
Median household income ($, in thousands)	**Median household income** ($, in thousands)
Public insurance (no=0; yes=1)	**Public insurance** (no=0; yes=1)

*Hazard ratios were generated through Cox regression and adjusted for inter-site variation with a dummy variable.

**Model was generated via backwards stepwise regression using variables significant in univariate modeling also with adjustment for site; final model n=412.

Table 3: Acute care usage between oxygen groups

	Adjusted odds ratio for outcome by initial oxygen amount (LPM)*	*P* **value**
Emergency department visit (no=0; yes=1)	0.42 [0.11, 1.62] (n = 229)	0.21
Hospital admission (no=0; yes=1)	0.95 [0.25, 3.64] (n = 230)	0.94
Systemic steroid use (no=0; yes=1)	1.53 [0.40, 5.76] (n = 230)	0.53
Antibiotic use (no=0; yes=1)	0.76 [0.21, 2.77] (n = 230)	0.68
Cough and/or wheeze (no=0; yes=1)	0.60 [0.18, 2.04] (n = 230)	0.41
Rescue medication use (no=0; yes=1)	0.59 [0.17, 2.00] (n = 228)	0.40
Shortness of breath with activity (no=0; yes=1)	0.64 [0.16, 2.61] (n = 208)	0.53
Nighttime symptoms (no=0; yes=1)	2.45 [0.62, 9.60] (n = 229)	0.20

*Odds ratios were generated through logistic regression and adjusted for duration of oxygen use, mean age for assessments of outcomes, center site, number of times outcomes were assessed, sex, birthweight percentile, severity of BPD (dummy variable), gastrostomy tube, pulmonary hypertension after 36 weeks, use of pulmonary hypertension medications, diuretic use, inhaled steroid use, and median household income.

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