Prematurity as an Independent Risk Factor for the Development of Pulmonary Disease

Julie L. Fierro, MD, MPH[1], Molly Passarella, MS[2,3], and Scott A. Lorch, MD, MSCE[2,3,4]

Objectives To determine if premature infants without bronchopulmonary dysplasia (BPD) are at similar risk for developing pulmonary morbidity as compared with those with BPD and if there are differences in management of care.

Study design We retrospectively abstracted information from our electronic medical record from January 1, 2006, to December 31, 2015, for primary care patients born at <30 weeks of gestation (n = 811). Multivariate models determined the impact of BPD on a diagnosis of respiratory disease, respiratory medications, subspecialty visits, and emergency department use or hospitalizations after adjusting for gestational age, sex, insurance type, and race.

Results Infants with BPD were more likely to be diagnosed with asthma than those without BPD (75% vs 60%; OR, 1.8; 95% CI, 1.27-2.54), but not all respiratory conditions (OR, 1.56; 95% CI, 0.7-3.51), and were more likely to be referred to a pulmonologist (relative risk, 5.98; 95% CI, 4.1-8.74). Infants with BPD were more likely to be hospitalized for respiratory conditions than those without BPD (50% vs 30%; relative risk, 2.44; 95% CI, 1.73-3.45).

Conclusions Although infants with BPD were more likely to have a diagnosis of asthma and be readmitted for respiratory conditions, 60% of infants without BPD were also diagnosed with asthma and 30% were readmitted. There were significant differences in the management of patients, including time to pulmonary referral and prescription rates for inhaled corticosteroids. Practitioners should consider all patients born prematurely at high risk for respiratory morbidity. *(J Pediatr 2019;213:110-4)*.

Preterm birth results in significant adverse health outcomes including bronchopulmonary dysplasia (BPD), a disease of disrupted or arrested lung development secondary to prematurity. A clinical diagnosis of BPD is made in preterm infants at 36 weeks postmenstrual age, with severity of disease based on the amount of supplemental oxygen and/or positive pressure required by the infant.[1] BPD develops in 10%-40% of very low birth weight and extremely low birth weight infants.[2] BPD is associated with significant pulmonary morbidity beyond the neonatal period, including the use of bronchodilators up to 2 years of age and a diagnosis of asthma later in childhood.[3] This impaired lung function has been shown to persist into middle childhood; for instance, patients with a diagnosis of BPD have abnormal baseline spirometry at 11 years of age compared with full-term controls.[4] Patients with BPD are also more likely to be rehospitalized after discharge from the neonatal intensive care unit and use outpatient services more frequently than premature patients without BPD.[5,6]

Infants born prematurely without BPD also have abnormal lung function and are high users of the healthcare system with frequent rehospitalizations for respiratory conditions.[7-10] In the postsurfactant era, a large proportion of patients born prematurely have cough and/or wheeze in the first year of life regardless of a diagnosis of BPD, suggesting that ongoing pulmonary morbidity is not exclusive to those patients with BPD.[11-13] However, these few studies are limited in that pulmonary morbidity was identified based on parental questionnaires. Additionally, there was no comparison of healthcare use and provider management of these patients to determine whether increased pulmonary morbidity and increased healthcare use were independent of a diagnosis of BPD.

Through the use of the electronic medical record (EMR), we sought to determine if premature infants without BPD were at comparable risk for ongoing pulmonary disease beyond the neonatal period. We also assessed the clinical management for respiratory conditions for patients with and without BPD and performed a subgroup analysis to determine differences in asthma management among patients with and without BPD.

BPD	Bronchopulmonary dysplasia
CHOP	Children's Hospital of Philadelphia
CLD	Chronic lung disease
HR	Hazard ratio
ICD-9	*International Classification of Diseases,* 9th edition
EMR	Electronic medical record

From the [1]Division of Pulmonology, Department of Pediatrics; [2]Division of Neonatology, Department of Pediatrics; and [3]Center for Perinatal and Pediatric Health Disparities Research, The Children's Hospital of Philadelphia; and [4]Leonard Davis Institute of Health Economics, The Wharton School, The University of Pennsylvania, Philadelphia, PA

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Methods

This was a retrospective cohort study of preterm infants with and without BPD seen in the primary care network at the Children's Hospital of Philadelphia (CHOP). The network includes 34 urban and suburban sites in Pennsylvania and New Jersey. Data were obtained via the institutional EMR. Patients born at <30 weeks of gestation who presented to care from January 1, 2006, to December 31, 2012, were included. Gestational age was measured with the gestational age field in the EMR and subsequently validated by chart review. There was a minimum of 3 years of data for each patient with ≤10 years of data available. Patients with BPD were identified via *International Classification of Diseases,* 9th edition (ICD-9) codes 518.89 (chronic lung disease [CLD]) and 770.7 (BPD). ICD-9 codes were assigned by the clinicians caring for these patients at the time of a given clinical encounter and confirmed by the attending physician or advanced practice nurse practitioner. Eligible patients included infants that had ≥1 well visit after 1 year of life, had a home zip code within the tristate area (Pennsylvania, New Jersey, Delaware), and remained within the CHOP network for a minimum of 3 years after birth. Patients were excluded if they had an inborn error of metabolism, major congenital anomalies, chromosomal anomalies, and genetic disorders caused by a single gene defect because these diagnoses may independently change health care use. The cohort was validated through chart review with study authors validating all charts for patients with a diagnosis of BPD or CLD of prematurity and 10% of charts for patients without BPD or CLD of prematurity.

We completed a subgroup analysis on patients with a diagnosis of asthma. These patients were identified via ICD-9 codes based on any one of the following diagnoses: asthma (493, 493.90), extrinsic asthma (493.00, 43.01, 493.02), intrinsic asthma (493.10), status asthmaticus (493.91, 493.11), asthma flare (493.92), chronic airway obstruction (496), bronchospasm (519.11), wheezing (786.07), exercise-induced asthma (493.81), and cough variant asthma (493.82). We identified 299 patients without BPD who had a diagnosis of asthma and 236 patients with BPD who had a diagnosis of asthma.

This study was approved by the CHOP Institutional Review Board. Patient information was documented by providers (attending physicians, fellows, residents, nurse practitioners, physician assistants, medical students) during ambulatory or inpatient healthcare encounters in the electronic record using the EPIC Hyperspace system (Verona, Wisconsin).

Information obtained via the EMR included patient characteristics, receipt of ≥1 dose of palivizumab immunization, encounter diagnoses, medications, encounters with a subspecialist, and diagnoses assigned during hospitalizations and emergency room visits. The outcomes of interest were a diagnosis of asthma or any respiratory disease, respiratory medications, encounters with subspecialties who manage respiratory conditions (a pulmonologist or an allergist), and emergency department encounters or hospitalizations for asthma or any respiratory disease. Encounters within the hospital network were noted within the EMR, and encounters outside of the network were captured through manual chart review of physician notes and letters.

Respiratory diagnoses were identified via manual review of ICD-9 codes of all encounter diagnoses, hospitalizations, and emergency room visit ICD-9 codes assigned to patients in each cohort. The ICD-9 codes included for all encounter diagnoses and for acute care visits (hospitalizations and emergency room visits) are in **Appendix 1** and **Appendix 2** (available at www.jpeds.com), respectively. Diagnoses included viral respiratory infections, pneumonia, asthma, airway abnormalities, laryngomalacia, tracheomalacia, and respiratory failure.

The medication record was searched using generic and trade names for respiratory and allergy medications that were prescribed at any time to the patient after discharge from the neonatal intensive care unit. These medications included rescue inhalers such as albuterol (Ventolin, Proair), levalbuterol (Xopenex), and ipratropium (Atrovent); inhaled corticosteroids such as fluticasone-salmeterol (Advair), beclomethasone diproporionate (Qvar), fluticasone propionate (Flovent), budesonide-formoterol fumarate (Symbicort), budesonide (Pulmicort), and mometasone furoate (Asmanex); respiratory medication equipment including aerochambers and nebulizer machines; oral and intravenous steroids; diuretics including chlorothiazide (Diuril), furosemide (Lasix), spironolactone (Aldactone); and montelukast (Singulair).

Statistical Analyses

Descriptive analysis included cohort demographics and frequency of encounter diagnoses, subspecialty visits, and acute care encounters. A subgroup analysis was completed for patients with asthma with an analysis of medication prescriptions, subspecialty visits, and acute care encounters. Univariate analysis including χ^2 and t tests were completed for each outcome of interest. Multivariate Poisson and logistic regression models were built to determine the impact of BPD on each outcome of interest while controlling for race, insurance type, gestational age, and sex.

Race, gestational age, and sex were identified via specified fields in the EPIC database. Insurance type was divided in to 7 categories based on the type of insurance used at the majority of visits. These included private insurance, Medicaid, self-pay, self-pay and Medicaid, self-pay and private, Medicaid and private, and a combination of self-pay, Medicaid, and private insurance.

A Cox proportional hazards model assessed the effect of a diagnosis of BPD on age at first visit to a subspecialist. A subgroup analysis on all patients with a diagnosis of asthma was completed. We used STATA version 15.0 (StataCorp, College Station, Texas) for all analyses.

Results

There were 811 infants in our cohort; 316 (39%) with a diagnosis of BPD and 495 (61%) without a diagnosis of BPD. Those with and without BPD were similar in terms of their distribution of sex, race, and insurance type (Table I). Patients with BPD were more premature at the time of delivery. The majority of patients with and without BPD received ≥1 dose of the palivizumab immunization; however, patients with BPD were more likely to receive the vaccine as compared with those without BPD ($P = .002$).

There were 236 patients (75%) with BPD and 299 patients (60%) without BPD diagnosed with asthma (OR, 1.8; 95% CI, 1.27-2.54). Overall, 97% of patients with BPD (306/316) and 94% of patients without BPD (466/495) were diagnosed with ≥1 respiratory comorbidity. There was no difference in diagnosis of a viral infection (OR, 1.03; 95% CI, 0.56-1.89) or pneumonia (OR, 1.14; 95% CI, 0.8-1.64) between the groups in the postdischarge period.

Nearly 50% of patients with BPD (153/316) were referred to a pulmonologist compared with 13% of patients without BPD (64/495; OR, 5.98; 95% CI, 4.1-8.74). There was no difference in referrals to an allergist (OR, 1.01; 95% CI, 0.61-1.68). For patients seen by a pulmonologist, those with BPD were seen for their first visit at a younger age compared with those without BPD (p50 = 8.5 months vs 3.3 years; hazard ratio [HR], 2.58; 95% CI, 1.86-3.57; Figure, A). There was no difference in age at first visit if a patient was seen by an Allergist (p50 = 2.5 years vs 1.9 years; HR, 0.88; 95% CI, 0.55-1.41; Figure, B).

Table I. Patient demographics

Characteristics	No BPD (n = 495)	BPD (n = 316)	*P* value
Sex			
Male	253 (51)	162 (51)	.97
Female	242 (49)	154 (49)	
Race			
White	162 (33)	86 (27)	.42
Black	263 (53)	190 (60)	
Hispanic	24 (4.8)	14 (4)	
Other	19 (3.8)	11 (3)	
Unknown	27 (5.5)	15 (5)	
Insurance type			
Private	221 (45)	121 (38)	.19
Medicaid	244 (49)	179 (57)	
Self-pay/private	8 (1.6)	6 (2)	
Medicaid/private	22 (4.4)	10 (3)	
Gestational age (weeks)			
22	1 (0.2)	1 (0.3)	0
23	4 (0.8)	19 (6)	
24	18 (4)	61 (19)	
25	32 (7)	49 (16)	
26	48 (10)	42 (13)	
27	83 (17)	62 (20)	
28	142 (29)	49 (16)	
29	167 (34)	33 (10)	
Palivizumab vaccine			
Received ≥1 dose	448 (91)	304 (96)	.002

Values are number (%).

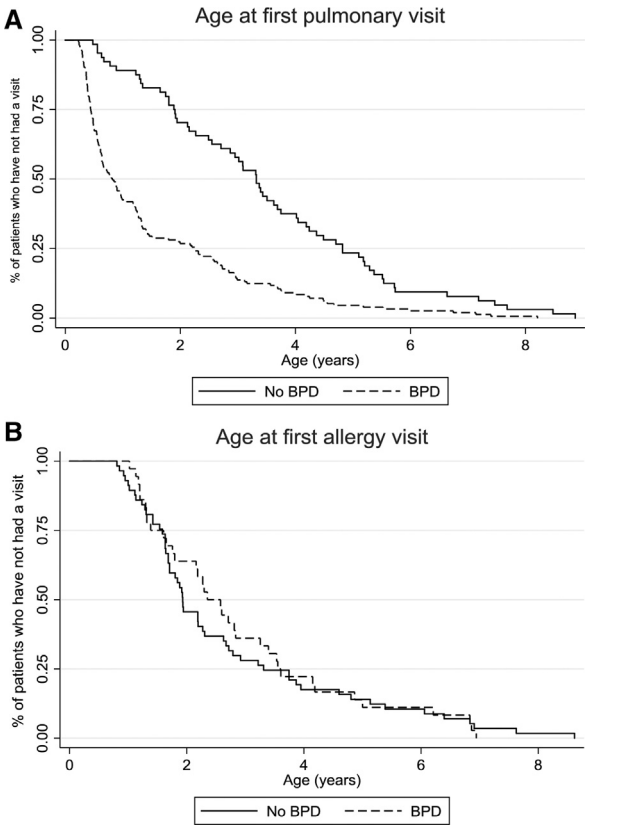

Figure. The age of the patients in years at their **A,** first pulmonary or **B,** allergy visit if a visit occurred. Each step down reflects 1 child getting a visit with a subspecialist. **A,** Patients with BPD saw a pulmonary specialist earlier than patients without BPD. Fifty percent of patients with BPD were seen by 8.5 months of life, whereas 50% of patients without BPD were seen by 3.3 years of life. **B,** There was overlap in the age at which patients were first seen by an allergy specialist. Fifty percent of patients with BPD were seen by 2.5 years of age, whereas 50% of patients without BPD were seen by 1.9 years of life.

There was no significant difference in the percentage of patients who had ≥1 emergency department visit for a respiratory condition for patients with and without BPD (OR, 1.41; 95% CI, 0.98-2.02), although patients with BPD had an increased overall number of emergency department visits for respiratory conditions overall (relative risk, 1.26; 95% CI, 1.10-1.43). Patients with BPD were more likely to be hospitalized for a respiratory condition (BPD vs no BPD: 52% vs 28%, OR, 2.44; 95% CI, 1.73-3.45; Table II). Patients with BPD also had longer lengths of stay for hospitalizations for respiratory disease (mean, 8.72 days; 95% CI, 7.7-9.73) vs those without BPD (mean, 5.53 days; 95% CI, 4.38-6.69; Table II).

Nearly all patients born prematurely with a diagnosis of asthma had a prescription for albuterol (Table III). There was no difference for patients with and without a history of BPD in prescriptions for asthma equipment (OR, 0.83;

Table II. Acute care visits for respiratory diseases

	Univariate analysis			Multivariate analysis
Variables	No BPD (n = 495)	BPD (n = 316)	*P* value	Multivariate analysis (95% CI)
At least 1 ED visit	181 (37%)	145 (46%)	.008	OR, 1.41 (0.98-2.02)
Mean number of ED visits	1.16 (95% CI, 0.96-1.36)	1.67 (95% CI, 1.36-1.98)	.003	RR, 1.26 (1.10-1.43)
At least 1 hospitalization	140 (28%)	165 (52%)	0	OR, 2.44 (1.73-3.45)
Mean number of hospitalizations	1.14 (95% CI, 0.88-1.40)	3.84 (95% CI, 2.9-4.77)	0	RR, 3.28 (2.94-3.65)
Length of stay for hospitalization (days)	Mean, 5.53 (4.38-6.69)	Mean, 8.72 (7.7-9.73)	0	RR, 1.64 (1.04-2.59)

ED, emergency department; *RR*, relative risk.

95% CI, 0.52-1.32) or oral and intravenous steroids (OR, 1.19; 95% CI, 0.78-1.82). However, patients with asthma and a BPD history were more likely to be prescribed an inhaled corticosteroid than patients with asthma and without BPD (77% vs 66%; OR, 2.33; 95% CI, 1.51-3.61; Table III).

Approximately 60% of patients with a diagnosis of asthma and BPD were referred to a pulmonologist vs 16% of asthma patients with BPD (OR, 7.09; 95% CI, 4.51-11.11), and patients with BPD also had their first visit at a younger age (p50 = 8.5 months vs 3 years; HR, 2.52; 95% CI, 1.73-3.67). There was no difference in referrals or age of first visit to an allergist (p50 = 2.6 years vs 1.9 years; HR, 0.86; 95% CI, 0.53-1.41).

Nearly one-third of patients with and without BPD who had a diagnosis of asthma were evaluated in the emergency department for an asthma exacerbation (OR, 1.06; 95% CI, 0.67-1.69). Patients with asthma with a history of BPD were more likely to be hospitalized for an asthma exacerbation (BPD vs no BPD, 50% vs 28%; OR, 2.2; 95% CI, 1.42-3.42). Those with BPD were also hospitalized for longer durations for an asthma exacerbation (mean, 3.67 days vs mean, 2.69 days, Appendix 3; available at www.jpeds.com).

Discussion

We found that prematurity without a diagnosis of BPD or CLD of prematurity was associated with pulmonary morbidity, with nearly 94% of patients without BPD and 97% of patients with BPD diagnosed with ≥1 pulmonary condition. However, the management of patients with vs without BPD differed for their respiratory conditions in terms of referrals to a pulmonologist and hospitalizations for respiratory disease. Although more patients with BPD were diagnosed with asthma, an equal proportion of patients were prescribed albuterol and oral steroids despite the fact that more patients with BPD were prescribed an inhaled corticosteroid. Although patients with BPD have abnormal lung function,[3,4] we suggest that prematurity, independent of a diagnosis of BPD, is also a driving factor for the development of ongoing pulmonary morbidity. Our study indicates that more study is needed to optimize the postdischarge respiratory management of patients born prematurely without a diagnosis of BPD.

Prior work has shown that patients born prematurely in the postsurfactant era, regardless of a diagnosis of BPD, have a high rate of cough, wheezing, and colds in the first year of life.[11-13] Our work further supports these findings by showing that the incidence of pulmonary morbidity is high among patients born prematurely regardless of the presence of BPD. Our data also support earlier work showing that patients with BPD are more likely to have a diagnosis of asthma.[3,14] However, we found an equal incidence of wheezing-related illnesses among patients born prematurely regardless of the presence of BPD, as demonstrated by a similar number of prescriptions for albuterol and oral steroids.

Patients with BPD were more likely to be referred to a pulmonologist and be referred at a younger age as compared with those with BPD. This finding was interesting, because we found an equivalent incidence of pulmonary morbidity between the groups. There have been no prior studies comparing outpatient pulmonary subspecialty follow-up for patients born prematurely with and without BPD. A study from the Neonatal Research Network showed that more than 50% of infants born at <28 weeks of gestation used more than 3 subspecialty outpatient services, and that the diagnosis of BPD was associated with more than 5 outpatient subspecialty services.[6] Other studies have shown that supplemental oxygen use among patients with BPD was associated with increased numbers of outpatient appointments and subspecialty encounters in their preschool years and school age as compared with BPD patients not discharged with a supplemental oxygen requirement.[15,16]

BPD has also been implicated as a risk factor for rehospitalization from respiratory disease.[17-19] Although we found

Table III. Medications for asthmatics

	Univariate analysis			Multivariate analysis
Medications	No BPD (n = 299)	BPD (n = 236)	*P* value	OR (95% CI)
Albuterol	297 (99)	235 (99)	.71	0.79 (0.06-10.14)
Asthma equipment	224 (75)	177 (75)	.98	0.83 (0.52-1.32)
Steroids	195 (65)	165 (70)	.25	1.19 (0.78-1.82)
Inhaled corticosteroid	180 (60)	182 (77)	0	2.33 (1.51-3.61)
Montelukast	45 (15)	40 (17)	.55	1.36 (0.8-2.32)
Allergy medication	169 (57)	146 (62)	.21	1.28 (0.85-1.92)
Diuretics	4 (1)	108 (46)	0	60.56 (21.01-174.7)

Values are number (%) unless otherwise indicated.

that patients with BPD were more likely to be hospitalized and had longer lengths of stay for respiratory diseases including asthma exacerbations, nearly 30% of patients without BPD were also hospitalized for a respiratory condition with an average length of stay of more than 5 days. Additionally, there was no significant difference in emergency room encounters for respiratory conditions or asthma among patients with and without BPD.

It is unclear what drives the divergence in postdischarge pulmonary management of premature infants with and without BPD. It is possible that patients with BPD are more ill than those without BPD.[10,12] Another possibility is that provider bias regarding the diagnosis of BPD induces providers to be more aggressive in how they manage these patients. However, we propose that the pulmonary consequences associated with prematurity should be seen as a spectrum of disease. BPD is one end of the barometer, but even without a diagnosis of BPD, patients born prematurely have ongoing pulmonary morbidity. Further work to quantify the degree of pulmonary morbidity with objective measures throughout childhood and adulthood are needed to better understand the full consequences of prematurity on lung development regardless of the diagnosis of BPD.

Limitations to our study included potential loss to follow-up; however, we attempted to control for this by only including patients who received care for a minimum of 3 years in our primary care network. There is also a potential for missing medications, subspecialty encounters, and/or acute care visits if patients went outside of the CHOP network and the information was not noted in the EMR. However, previous work suggests that these out-of-network encounters are infrequent and are noted by the primary care provider in the medical chart or via a discharge summary, and that these out-of-network referrals are driven primarily by geography. An additional limitation was our inability to determine the diagnostic criteria used by individual clinicians in diagnosing asthma. We sought to use a broad definition of asthma when creating this subgroup analysis; however, owing to the limitations of retrospective data review, we were unable to determine how patients were labeled as asthmatics.

We conclude that all survivors of extreme prematurity are at risk for pulmonary morbidity after discharge from the hospital. Patients with BPD were more likely to be diagnosed with asthma, prescribed an inhaled corticosteroid, referred to a pulmonologist, and hospitalized for a respiratory condition. However, rates of pulmonary morbidity were high in patients without BPD, and these patients had significant healthcare use, with 60% diagnosed with asthma and 30% hospitalized for a respiratory condition. Our work suggests that practitioners should be consider all patients born prematurely, regardless of the presence of BPD, at high risk for long-term respiratory morbidity. ■

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Reprint requests: Julie L. Fierro, MD, MPH, 3401 Civic Center Blvd, Philadelphia, PA 19104. E-mail: fierroj@email.chop.edu

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