Outpatient Inhaled Corticosteroid Use in Bronchopulmonary Dysplasia

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Abstract

Rationale: In the outpatient setting, inhaled corticosteroids (ICS) are frequently given to children with bronchopulmonary dysplasia (BPD) for treatment of respiratory and asthma associated symptoms. In this study we sought to determine if correlations existed between ICS use and ICS initiation and patient characteristics and outpatient respiratory outcomes. **Methods:** This study included children with the diagnosis of BPD (n=661) who were seen in outpatient pulmonary clinics at the Children's Hospital of Philadelphia between 2016-2021. Chart review was used to determine patient demographics, use and timing of ICS initiation, asthma diagnosis and acute care usage following initial hospital discharge. **Results**: At the first pulmonary visit, 9.2% of children had been prescribed an ICS at NICU discharge, 13.9% had been prescribed an ICS after NICU discharge but before their first pulmonary appointment, and 6.9% were prescribed an ICS at completion of initial pulmonary visit. Children started on an ICS as outpatients, had a higher likelihood of ER visits (adjusted OR: 2.68 $\pm$0.7), hospitalizations (4.81 $\pm$ 1.16) and a diagnosis of asthma (3.58 $\pm$ 0.84), compared to children never on an ICS. Of those diagnosed with asthma, children prescribed an ICS in the outpatient setting received the diagnosis at an earlier age. No associations between NICU BPD severity scores and ICS use were found. **Conclusions**: This study identifies an outpatient BPD phenotype associated with ICS use and ICS initiation independent of NICU severity score. Additionally, outpatient ICS initiation correlates with a subsequent diagnosis of asthma and acute care usage in children with BPD.

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Conclusions : This study identifies an outpatient BPD phenotype associated with ICS use and ICS initiation independent of NICU severity score. Additionally, outpatient ICS initiation correlates with a subsequent diagnosis of asthma and acute care usage in children with BPD.

Introduction

Bronchopulmonary dysplasia (BPD) is the most common cause of chronic lung disease of infancy, occurring primarily in extremely low birth weight (ELBW) newborns. (1, 2) Extreme preterm birth disrupts alveolar growth, frequently resulting in poor gas exchange due to alveolar hypoplasia. (3) As such, many ELBW infants require supplemental oxygen and/or positive pressure support during their initial hospitalization. Nevertheless, many ELBW survivors with BPD will undergo alveolar catch-up growth and be weaned off respiratory support, prior to initial hospital discharge or during their preschool years. (4, 5)

It has been recognized that children with BPD are commonly diagnosed with small airflow obstruction, and that abnormalities in airway flow can persist into adolescent and adult life. (4, 6) The development of small airflow obstruction in early life, can adversely influence lung function trajectories in later life (7) and can be a risk factor for the development of chronic obstructive lung disease (COPD) in adults. (8) The traditional marker of small airway disease is evidence of airflow obstruction on spirometry. However, since spirometry is difficult to perform reliably prior to 6 years of age, a non-invasive method for identifying young children with BPD who are at risk for a small airway phenotype is needed. Earlier identification of those at risk for a small airway phenotype may allow for more timely interventions that may improve lung function trajectories.

Although BPD severity is formally diagnosed based on respiratory support needs at 36 weeks post menstrual age (PMA), recent studies indicate that BPD severity scores assigned in the neonatal intensive care unit (NICU) may not predict respiratory outcomes in the outpatient setting. (9, 10) This lack of predictive value of outpatient respiratory outcomes based on inpatient BPD severity scores suggests the importance of establishing new criteria for assessing outpatient phenotypes in children with BPD. Currently, there are no established phenotypes or framework for classification of respiratory diseases associated with prematurity after NICU discharge.

Inhaled corticosteroids (ICSs) are commonly used to treat and control symptoms of small airflow obstruction in children with asthma. Children with BPD are also frequently prescribed ICSs, however their use and effectiveness in the outpatient setting is less well described.(11, 12). In this study we hypothesized that young children with BPD prescribed an ICS in the outpatient setting, will have different clinical characteristics and

a greater likelihood of adverse respiratory outcomes when compared to children who are not prescribed an ICS. Furthermore, we sought to determine if ICS use correlated with the timing and likelihood of an asthma diagnosis.

Understanding the use and timing of ICS initiation in the outpatient setting may be a proxy for identifying young children with BPD who have clinical features of small airway obstruction. Identifying these children earlier in life may allow for interventions that could improve respiratory outcomes. This study was preformed using electronic patient medical records from children with BPD seen in outpatient pulmonary clinics over a six-year period.

Methods

Study Population: Children with the diagnosis of BPD and seen in the Children's Hospital of Philadelphia outpatient pulmonary clinics between 2016-2021 were identified using electronic medical records (EMR). Inclusion criteria included birth prior to 34 weeks gestational age, a diagnosis of BPD by the 2001 National Heart, Lung, and Blood Institute (NHLBI) consensus statement, (13) and being 8 years of age or less at their first pulmonary clinic visit. Those who had tracheostomies and/or were ventilator-dependent were excluded. Inhaled corticosteroid (ICS) use and timing of initiation were determined by chart review. History of pulmonary hypertension was determined by chart review. Outcomes included asthma diagnosis and acute care usage before and after their first pulmonary visit. This study was approved by the Children's Hospital of Philadelphia Institutional Review Board (IRB# 20-017614) under exempt research. ICD-10 codes were used to identify children with the diagnosis of BPD with or without the diagnosis of asthma. These ICD codes were: P27.1, P27.1 + J45, P27.9 and P27.9 + J45.

Statistics: Descriptive means and frequencies were compared using t tests and chi square tests, respectively (Tables 1 and 3 and Supplemental Tables 1-3). Odds ratios for admissions and visits were derived from logistic regressions adjusted for potential confounders that were selected *a priori* , including gestational age, birth weight, supplemental oxygen use at NICU discharge, and duration of follow-up time (i.e., either time between NICU discharge and first pulmonary visit or time between first pulmonary visit and time of chart review) (Table 4). The odds ratio for a diagnosis of asthma was derived similarly, except age at last follow-up was substituted for duration of follow-up time. Kaplan-Meier analyses were used to assess differences between groups for time until the diagnosis of asthma (Figure 1). Stata IC 15 (StataCorp, LLC; College Station, TX) was used for all analyses. P values of less than 0.05 were defined as significant.

Results

Study Population

The study population included 661 subjects with the diagnosis of BPD. The majority of children were male (59.8%), with non-white children making up 43% of the study population. The mean gestational age was 26.3 ± 2.4 (mean ± SD) weeks and the mean birthweight was 884 ± 376 grams (**Table 1**). Most children (61.5%) had severe BPD and 12.6% had a history of pulmonary hypertension. Approximately half (50.9%) of the children were discharged from the NICU to home on supplemental oxygen.

Of the 661 subjects in the study population, 61 (9.2%) were discharged from the NICU on an ICS, 138 (20.9%) were initiated on an ICS as an outpatient, and 462 (69.9%) had not received any ICS therapy as an outpatient, at the conclusion of their first pediatric pulmonary outpatient visit (**Table 2**). Of note, for the 138 subjects who were initiated on ICS therapy as outpatients, 92 (66.7%) were initiated by a non-pulmonologist provider prior to the first pulmonary clinic visit, whereas 46 (33.3%) were initiated by a pulmonologist at completion of the first pulmonary clinic visit.

ICS Therapy Prescribed at NICU Discharge

Infants discharged from the NICU on ICS therapy (n=61) were born earlier (25.5 ± 1.9 versus 26.3 ± 2.4 weeks gestation; p <0.01) and weighed less at birth (761 ± 263 versus 896 ± 383 grams;p <0.008) than their counterparts who were not discharged on ICS therapy (n=600) (**Table 1**). Although ICS therapy

at NICU discharge was not associated with BPD severity (p =0.07) or pulmonary hypertension (p =0.08), infants on ICS therapy at discharge were more likely to be discharged on supplemental oxygen (78.7% versus 48.1%; p<0.001) and to have experienced a longer NICU length of stay (184 ± 88 versus 133 ± 68 days; p<0.001) compared to their counterparts. Interestingly, infants with a positive family history of asthma were less likely to be prescribed ICS at NICU discharge than those who were not (36.7% compared to 51.4%; p<0.029). These findings indicate that BPD infants prescribed ICSs at NICU discharge likely represent a distinct clinical BPD phenotype, compared to those who were not prescribed an ICS at NICU discharge.

Outpatient Use of ICS Therapy

Infants and children who were on ICS therapy as outpatients (n=192) did not differ by clinical characteristics, such as BPD severity or gestational age, compared to their counterparts who were not on outpatient ICS therapy (n=469) (**Table 3**). However, we observed that children on an ICS, at completion of their first pulmonary visit were more likely to have a family history of asthma (p =0.021) and to be on public insurance (p =0.031) compared to those who were not.

To determine if there were subgroup differences related to being started on ICS therapy at NICU discharge, we compared those started on ICS therapy as outpatients (n =138) to those never on outpatient ICS therapy (n=462, **Supplemental Table 1**). Similar to before, those initiated on ICS therapy as outpatients were more likely to have a family history of asthma (64.9% versus 47.5%;p <0.001) and to be on public insurance (68.6% versus 58.1%; p =0.028) than those who were not. Although the groups did not differ by BPD severity (p =0.27), those initiated on ICS therapy as outpatients were less likely to require home supplemental oxygen (33.3% versus 52.5%; p <0.001) and have shorter NICU lengths of stay (119 ± 63 versus 137 ± 68 days; p =0.005). Complete comparisons of all three subgroups for analysis can be found in**Supplemental Table 2** .

Respiratory Outcomes Stratified by ICS Therapy

Respiratory outcomes that were assessed, included having a diagnosis of asthma as well as acute care use before and after the first pulmonary clinic visit under the assumption that subjects receiving ICS therapy were all prescribed it by the conclusion of their pulmonary visit. In terms of acute care usage prior to the first pulmonary visit, subjects initiated on ICS therapy as outpatients had more absolute numbers of emergency department (ED) visits (p <0.001) and hospital admissions (p <0.001) than those on ICS therapy at NICU discharge or not started at all (**Supplemental Table 3**). There were no differences in acute care usage after first pulmonary clinic visit between the three groups.

The frequency of asthma diagnosis (73.4%) in those initiated on ICS therapy as outpatients was much higher than in those on ICS therapy at NICU discharge (51.9%) or not initiated at all (36.4%;p <0.001). However, given that differences in the age at the time of first pulmonary clinic visit existed (p <0.001), as well as duration of follow-up time (p =0.001) between the three groups, we also performed adjusted logistic regression to account for these differences and to adjust for potential confounders related to prematurity. Adjusted logistic regression revealed that children started on an ICS at any point as an outpatient had a higher likelihood of an ED visit (2.68±0.70;p <0.001) and/or rehospitalization (4.81±1.16;p <0.001) prior to their first outpatient pulmonary visit compared to children never on an ICS (**Table 4**). After any time following the first pulmonary visit, the likelihood of ED visits and re-hospitalizations for those started on ICS therapy as an outpatient, dropped to 1.73±0.35 (p =0.007) and 1.78±0.37 (p =0.006), respectively, when compared to children never on an ICS. There were no differences in the likelihood of ED visits or rehospitalizations between those on ICS therapy at NICU discharge versus those never on an ICS.

The likelihood of a diagnosis of asthma was higher in both children started on an ICS as an outpatient (3.58±0.84; p <0.001) and those prescribed an ICS continuously since NICU discharge (1.97±0.65; p =0.040) compared to those never on an ICS. Additionally, of those diagnosed with asthma in the outpatient setting, the time until asthma diagnosis was earliest in the children started on an ICS as an outpatient (p <0.001) (**Figure 1**).

Discussion

In this study, we used electronic patient medical records to determine if ICS use and ICS initiation correlated with patient characteristics and respiratory outcomes in infants and children with BPD in the outpatient setting. We found that by completion of the first pulmonary visit, 29% of children with BPD were on an ICS while 71% were not. The infants and children prescribed an ICS in the outpatient setting were found to have patient characteristics different from those who were not prescribed an ICS at all or those prescribed at NICU discharge. These findings suggest that there exist several distinct outpatient BPD phenotypes based on ICS use and initiation. For instance, the children prescribed an ICS as outpatients had a greater likelihood of acute care usage and were more likely to be diagnosed with asthma compared to those not on an ICS. Interestingly we found that ICS initiation in the outpatient setting was driven primarily by healthcare providers that were not pulmonologists. Another interesting observation was that we found no associations between BPD severity scores in the NICU and outpatient ICS phenotypes. In brief, our data indicates a correlation between a decision to initiate and the timing of ICS initiation (i.e., NICU discharge versus outpatient management) with patient demographics and outpatient respiratory outcomes; suggesting an emergence of several different outpatient BPD phenotypes defined in part, by ICS use.

Our study revealed that factors related to the prescription of ICS therapy at the time of NICU discharge were related to the degree of prematurity and respiratory disease. Notably, gestational age, birth weight, need for supplemental oxygen at discharge, length of NICU stay, and BPD severity, (which trended towards significance), were associated with ICS therapy prescribed at discharge. In contrast, children initiated on ICS therapy as outpatients were less likely to be on home supplemental oxygen and more likely to have shorter NICU lengths of stay, implying that a different set of factors may be contributing to decision-making for prescribing an ICS in the outpatient setting. Our outcome data, suggests that the more frequent ED visits and rehospitalizations observed between NICU discharge and the first outpatient pulmonary clinic visit, for a select group of infants and children, may be driving non-pulmonary providers to initiate outpatient ICS therapy.

After the first pulmonary visit, we found a decrease in the magnitude of the adjusted odds ratios for ED visits and rehospitalizations, in subjects prescribed outpatient ICS therapy prior to their first visit. Nevertheless, it should be noted, that the odds ratio for these outcomes still remained significantly above 1, when compared to subjects not on an ICS. This association implies that ICS therapy may only partially ameliorate the likelihood of adverse outpatient outcomes. Other factors, such as social determinants of health, neutrophilic-driven small airway inflammation or small airway dysanapsis may be greater drivers of outpatient respiratory outcomes once children are discharged from the NICU. Further studies are needed to examine these relationships.

In the longer term, we observed striking differences in the development of asthma associated with the timing of prescription of ICS therapy. While the frequency of a diagnosis of asthma is not associated with ICS therapy at the time of NICU discharge (p =0.45), it is associated with being on ICS therapy at the conclusion of the first pulmonary clinic visit (p <0.001). Moreover, over 70% of those prescribed ICS therapy after NICU discharge and before the first pulmonary clinic visit had a diagnosis of asthma, which may suggest the emergence of a new respiratory phenotype, that presents in the outpatient setting. Although our study is limited in identifying potential causes for the emergence of this phenotype, we would speculate that both genetic and environmental factors may be involved, given the associations we observed with a family history of asthma and public insurance coverage for the group of subjects placed on ICS therapy after NICU discharge.

This study did not address whether ICS use was beneficial in modifying respiratory outcomes in the BPD patient population prescribed an ICS. Indeed, a beneficial response to ICS in the BPD population has been shown to be variable.(11, 12) ICS has been shown to improve small airflow obstruction caused by eosinophilic inflammation, however their effectiveness in neutrophilic airway inflammation is less clear. (14) Several studies have suggested that small airway obstruction in children with BPD, is likely driven by a non-eosinophilic inflammatory process. (15-18). One study of ICS use in formerly preterm children between 6 and 12 years of age found that by 12 weeks, ICS use resulted in modest lung function improvement. (19)

Although a modest improvement in lung function was found in this study, results may have been different if participants had been enriched for a family history of asthma and asthma diagnosis. Another smaller study in children born <34 weeks-gestation found that the combination of an ICS coupled with a long-acting β agonist was superior to an ICS alone.(20) Larger studies will be needed to address which phenotypes of BPD children will potentially benefit from ICS use to mitigate respiratory morbidities and symptoms.

We also did not address why an ICS was prescribed (at NICU discharge or in the outpatient setting). Nevertheless, three different phenotypes emerged that were associated with distinct demographic features and outpatient respiratory outcomes, independent of BPD severity in the NICU. These different outpatient BPD phenotypes (as described by ICS use and initiation of ICS use) may be driven by genetic influences. (21) however, we cannot rule out a component of caregiver preference in deciding to initiate an ICS or not. In a single center study, we previously reported that children with BPD and a family history of asthma had a greater likelihood of ED visits, and systemic steroid use in the outpatient setting, suggesting that there may be a genetic component influencing ICS use. (22) A more precise understanding of outpatient BPD phenotypes may help with prognosticating respiratory outcomes and modifying long-term outcomes in children at risk for lifetime respiratory morbidities.

Limitations of this study include its retrospective nature and the use of electronic patient records which may contain inaccuracies based on ICD codes and encounter information. Furthermore, our results reflect a large urban center which may not be generalizable to other geographic areas. Furthermore, practice variations in use of ICS therapy in infants and children with BPD likely exist. Nevertheless, different demographic characteristics were found among the three groups based on ICS use and timing of initiation.

In summary, insights gained from this study may improve our understanding of outpatient clinical phenotypes in preterm children with BPD, further improving our understanding of their long-term respiratory outcomes. Furthermore, identifying specific cohorts of children with BPD who stand to benefit from ICS therapy will allow for more robust, evidence-based guidelines for outpatient ICS use in this population moving forward.

Figure Legends

Figure 1. Kaplan Meier curve showing that children with BPD who were started on ICS as outpatients were more likely to be diagnosed with asthma and to be diagnosed with asthma at an earlier age.

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