

Bronchopulmonary Dysplasia and Diuretic Use in the Outpatient Setting

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Abstract

Introduction: During NICU hospitalization, children born preterm with bronchopulmonary dysplasia (BPD) are frequently prescribed diuretics for treatment of respiratory symptoms. However, less is known about diuretic use and weaning in the outpatient setting. This study sought to characterize clinical features associated with outpatient diuretic use, and timing of diuretic weaning in children with BPD. **Methods:** Data was obtained by chart review from registry 1224 participants born < 32 weeks gestation, discharged between 2008-2023 and recruited from outpatient BPD clinics at Johns Hopkins Children's Center and the Children's Hospital of Philadelphia (97.4% diagnosed with BPD). Data was analyzed using Chi-square tests, t-tests, and ANOVA tests. **Results:** Children with BPD prescribed diuretics as outpatients (n=737), were more likely to have lower birth weights, earlier gestational age, and severe BPD compared to those not on diuretics (n=487). Of those prescribed diuretics, most children were on a thiazide alone (46.4%) or a thiazide and a potassium sparing agent (44.8%) with a minority on loop diuretics alone (3.3%) or loop diuretic combinations (4.7%). Most children weaned off diuretics by two years of age. Public insurance, earlier gestational age, technology dependence and loop diuretics were associated with slower diuretic weaning. **Conclusion:** Outpatient diuretic use is common in BPD with > 75% of children being weaned by two years of age. No difference was found in weaning of home oxygen between children on one versus no diuretic. Thiazides were most commonly prescribed with slower outpatient diuretic weaning associated with public insurance, technology dependence and loop diuretic use.

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Abstract

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Methods : Data was obtained by chart review from registry 1224 participants born < 32 weeks gestation, discharged between 2008-2023 and recruited from outpatient BPD clinics at Johns

Hopkins Children’s Center and the Children’s Hospital of Philadelphia (97.4% diagnosed with BPD). Data was analyzed using Chi-square tests, t-tests, and ANOVA tests.

Results: Children with BPD prescribed diuretics as outpatients (n=737), were more likely to have lower birth weights, earlier gestational age, and severe BPD compared to those not on diuretics (n=487). Of those prescribed diuretics, most children were on a thiazide alone (46.4%) or a thiazide and a potassium sparing agent (44.8%) with a minority on loop diuretics alone (3.3%) or loop diuretic combinations (4.7%). Most children weaned off diuretics by two years of age. Public insurance, earlier gestational age, technology dependence and loop diuretics were associated with slower diuretic weaning.

Conclusion: Outpatient diuretic use is common in BPD with > 75% of children being weaned by two years of age. No difference was found in weaning of home oxygen between children on one versus no diuretic. Thiazides were most commonly prescribed with slower outpatient diuretic weaning associated with public insurance, technology dependence and loop diuretic use.

Introduction

Bronchopulmonary dysplasia (BPD) is the most common cause of chronic lung disease during infancy. ⁽¹⁾ In infants with evolving or severe BPD, diuretics are often used by healthcare providers to improve gas-exchange abnormalities and mitigate pulmonary symptoms in the inpatient setting. ⁽²⁻⁴⁾ The mechanisms of action of acute and chronic diuretic use in preterm infants with BPD are not entirely understood. Diuretic use in preterm infants with lung disease may decrease pulmonary edema by promoting diuresis and reducing intravascular fluid in the lungs. Furosemide has also been reported to have a direct effect on the lungs through pulmonary vasodilation, which may help improve pulmonary congestion.^(5, 6)

Diuretics are also associated with side effects, including electrolyte abnormalities, calcium imbalances and nephrocalcinosis.^(7, 8) Indeed despite their frequent use in the NICU, others have only reported short-term benefits from diuretics in infants with BPD.⁽⁹⁾ Currently, no standardized guidelines for their use in the NICU exist, likely contributing to significant practice variation across institutions.⁽¹⁰⁾ Further, no guidelines exist for outpatient use or weaning of diuretics in children with BPD.

After initial hospital discharge, outpatient diuretic use is commonly continued in children with BPD, without clear guidance for use or weaning. Studies have revealed differences in weaning diuretics practices between subspecialists and lack of established guidelines for weaning diuretics in children with BPD on supplemental oxygen.^(11, 12) Several international societies have suggested diuretic weaning strategies in children with BPD, however consensus between the groups was not found. The American Thoracic Society guidelines suggest that infants with BPD discharged on diuretics should have their medication discontinued on an individual basis, since no standard methods currently exist to stop diuretics.⁽¹³⁾ The European Respiratory Society with very low certainty evidence gave a conditional recommendation for letting infants on diuretics outgrow their dose.⁽¹⁴⁾ The Thoracic Society of Australia and New Zealand however, offered no recommendations for long term diuretic therapy or weaning in patients with BPD.⁽¹⁵⁾

In this study we identified associations between patient characteristics in children with BPD and diuretic use and examined the type(s) of diuretics being prescribed after initial hospital discharge. We also examined how the number and type of prescribed diuretic(s) influenced supplemental oxygen weaning in children with BPD in the outpatient setting.

This analysis was performed through retrospective review of data from 1224 preterm children born < 32 weeks gestation. The vast majority of children carried the diagnosis of BPD (97.4%), were born between 2008-2023 and were recruited from outpatient BPD clinics across two tertiary care centers.

Methods

Data was obtained by retrospective chart review that included patients recruited from the Children’s Hospital of Philadelphia (CHOP) and Johns Hopkins Children’s Center outpatient BPD clinics, whose initial hospital discharge was between 2008-2023. All patients were born at or less than 32 weeks-gestation and severity of BPD was based on the 2001 NIH consensus definition.⁽¹⁶⁾ Participants with cyanotic congenital heart disease were excluded. Approval was obtained from the Children’s Hospital of Philadelphia Institutional Review Board (IRB # 20-017614_AM18) and Johns Hopkins IRB (Protocol #NA_00051884). All caregivers provided informed consent. Birthweight percentile was corrected by gestational age.⁽¹⁷⁾ Median household income was estimated through residential zip codes using U.S. Census data.

Chi square tests, t-tests, and ANOVA tests compared clinical characteristics and demographic data between participants on outpatient diuretics and those not on outpatient diuretics as well as between participants on one, two or three diuretic agents and between diuretic classes. Cox regressions were performed to identify characteristics associated with slower or faster weaning of diuretic therapy with shared frailty by study site to account for study site-related differences. Results with a P value less than or equal to 0.05 were considered statistically significant. Stata 15.0 was used for data analysis (StataCorp, College Station TX).

Results

Patient Characteristics: Children with reported use of diuretics at their first pulmonary outpatient visit (n=737) were more likely to have severe BPD ($p<0.001$), lower birthweight ($p=0.001$), and born at an earlier gestational age ($p=0.012$) compared to those not prescribed diuretics (n=487) (**Table 1**).

Subjects on outpatient diuretics were more likely to be older at the time of initial hospital discharge ($p<0.001$), however their first pulmonary appointment occurred at a younger age ($p<0.001$) compared to those not prescribed diuretic therapy at discharge. Further, being on diuretic(s) at the first outpatient pulmonary appointment was associated with an increased likelihood of home supplemental oxygen requirement ($p<0.001$), tracheostomy ($p=0.018$), ventilator dependence ($p=0.019$), gastrostomy tube ($p<0.001$), Nissen fundoplication ($p<0.001$), pulmonary hypertension ($p<0.001$) and being prescribed inhaled corticosteroids ($p<0.001$). No association was found between diuretic use at the first pulmonary outpatient visit and median household income, public insurance, race, or sex.

Diuretic use: In children prescribed diuretic therapy, most were either on one (50.1%) or two (47.4%) diuretics (**Table 2**). For patients receiving one diuretic, the majority were prescribed a thiazide diuretic (92.6%), whereas significantly fewer individuals were prescribed a loop diuretic alone (6.6%). Of those children with BPD receiving dual diuretic therapy, most were prescribed a thiazide and potassium sparing agent, (94.5%). Site differences were seen in the use of diuretic therapies (data not shown), however from both sites, thiazides were the predominant diuretic used in the outpatient setting (96.3% and 96.0% respectively).

We also examined differences in patient characteristics between children prescribed a potassium sparing diuretic (n=353) versus those not on a potassium sparing diuretic (n=384). We found that children on a potassium sparing diuretic were more likely to be seen in pulmonary clinic at an older age ($p=0.010$), and more likely to be prescribed an inhaled corticosteroid ($p<0.001$) and to have a Nissen fundoplication ($p=0.014$) (**Supplemental Table 1**). Interestingly, being prescribed a potassium sparing diuretic was not associated with requiring less electrolyte supplementation compared to those prescribed another class of diuretic.

In contrast, children in the outpatient setting on loop diuretics (n=62) were more likely to require electrolyte supplementation ($p<0.001$) versus those not on loop diuretics (n=675). (**Supplemental Table 2**). Children on a loop diuretic at their first outpatient pulmonary visit were more likely to have a later age of initial hospital discharge ($p<0.001$), to have a tracheostomy ($p<0.001$), to be ventilator dependent ($p<0.001$), to require home supplemental oxygen ($p=0.003$), to have a gastrostomy tube ($p<0.001$) and Nissen fundoplication ($p<0.001$), and to have pulmonary hypertension ($p<0.001$); characteristics aligning with more severe respiratory disease.

Only a minority of children were prescribed three diuretics at the time of their first pulmonary visit (n=19), and when compared to those on one or two diuretics they were more likely to be older at the time of their initial hospital discharge ($p<0.001$), to have a tracheostomy ($p<0.001$), to be ventilator dependent ($p<0.001$), to be on home supplemental oxygen ($p=0.014$), to have pulmonary hypertension ($p<0.001$), and to have a gastrostomy tube ($p<0.001$) and a Nissen fundoplication ($p<0.001$) (**Table 3**). Additionally, almost all subjects prescribed three diuretics received electrolyte supplementation.

Diuretic weaning: In a multivariate model, the likelihood of weaning off diuretics in a given month was slower in patients with a tracheostomy tube, home supplemental oxygen requirement, pulmonary hypertension, gastrostomy tube, prescribed inhaled corticosteroids, on public insurance, or born at an earlier gestational age (**Table 4**).

Interestingly, BPD severity did not influence the likelihood of weaning off diuretics in a given month whereas, children who were prescribed electrolyte supplementation had an increased likelihood of weaning off diuretics faster in a given month. Weaning of outpatient diuretics was guided by healthcare providers in over 80% of patients (**Table 3**). Over 50% of BPD infants prescribed outpatient diuretics were weaned off by 10 months chronological age with over 75% weaned off diuretic therapy by 15 months chronological age (**Figure 1**).

Diuretics and supplemental oxygen: For children with BPD on home supplemental oxygen (n=519), the

median age of oxygen weaning was 10.1, 10.2, 14.3 and 33.5 months respectively for children on zero, one, two and three diuretics. There were no statistical differences in time to wean off supplemental oxygen between those on one diuretic compared to those on no diuretics (**Figure 2**). Children with BPD on two diuretics and home supplemental oxygen took longer to liberate from home supplemental oxygen compared to those not prescribed a diuretic ($p < 0.001$).

Discussion

Although support for outpatient chronic diuretic use is lacking, many preterm children with BPD are prescribed diuretics after initial hospital discharge.^{(18) (19)} In this study, we characterized clinical features associated with outpatient diuretic use and timing of diuretic weaning, in children < 32 weeks gestation with the diagnosis of BPD. We found that children diagnosed with severe BPD in the NICU were more likely to be on a diuretic at their first pulmonary visit compared to those who were not. Additionally, lower birthweight and earlier gestational age were associated with outpatient diuretic use in children with BPD. In the outpatient setting, thiazides were the most commonly prescribed diuretic, with most children prescribed either a thiazide alone (46.4%) or a thiazide and a potassium sparing agent (44.8%). Interestingly, children on a potassium sparing agent were just as likely to be prescribed potassium supplementation as those on non-potassium sparing diuretics. Children who were prescribed loop diuretics or greater than two diuretics at their first outpatient pulmonary visit were more likely to have comorbidities, including tracheostomy, home ventilator use and pulmonary hypertension. Healthcare providers guided diuretic weaning in the majority of patients and most children in this study were weaned off diuretics by two years of age. Diuretic weaning was slower in children born at an earlier gestational age, who had comorbidities, and who were prescribed loop diuretics. Children on public insurance also had slower diuretic weaning, suggesting that socioeconomic barriers to weaning may exist in this group of children. There was no difference in supplemental oxygen weaning between those on one or no diuretic, suggesting that home use may not be necessary in some children with BPD weaning off home supplemental oxygen.

In our study, thiazide monotherapy or dual therapy with a thiazide and potassium sparing agent were the most commonly prescribed diuretic(s) in children with BPD at their first pulmonary outpatient visit. This finding supports other studies which found that these diuretics are commonly used in the outpatient setting to treat children with BPD.⁽²⁰⁾ In our study we found no significant differences in gestational age, birthweight, BPD severity, respiratory support requirements or pulmonary hypertension diagnosis between children on thiazide monotherapy or dual therapy with a potassium sparing agent. Furthermore, those on a potassium sparing agent were just as likely to be on electrolyte supplementation as those on other diuretics. Another study that examined diuretic use in NICUs across the United States also found only modest reductions in use of potassium chloride supplementation in infants with BPD on thiazides plus potassium sparing agents compared to those on thiazides alone.³ Our findings indicate that the combination of a thiazide plus a potassium sparing agent may not provide additional benefit over a thiazide alone, with regard to electrolyte imbalances.

In the NICU, loop diuretics are commonly used to treat infants with severe BPD.^{2,19} Slaughter et. al., found that furosemide was the most commonly used diuretic in the NICU, however thiazides in the NICU were used for the longest duration of use.¹⁹ In our study, we found that only 8.4% of children were on a loop diuretic at their first outpatient pulmonary visit. This finding supports a study by Bamat et. al., in which reported use of loop diuretics at NICU discharge ranged between 13.5% and 5.1% in children with grade 2 or 3 BPD.² Although infrequently used in our outpatient population of BDP children, those prescribed loop diuretics ($n=62$) were more likely to be technology dependent and to be older at NICU discharge compared to those on non-loop diuretics ($n=675$). Those on loop diuretics also had a higher likelihood of home oxygen dependency, gastric tube use and the diagnosis of pulmonary hypertension. These children were also more likely to require electrolyte supplementation. Our study indicates that loop diuretics, although commonly used in the NICU, are less likely to be prescribed in the outpatient setting in children with BPD; with their use primarily limited to those with significant disease co-morbidities and technology dependence. Our study also found that BPD severity in the NICU at 36 weeks post menstrual age (PMA) did not correlate with timing

of diuretic weaning in the outpatient setting, suggesting that NICU severity scores at 36 weeks gestation are not predictive of outpatient diuretic weaning. Not surprisingly however, we found that slower diuretic weaning was associated with children on home supplemental oxygen, loop diuretics, inhaled corticosteroids and technology dependence.

Of further interest, we found that children with BPD on public insurance in the outpatient setting were more likely to wean slower from diuretics, compared to children on private insurance. We previously found that children with BPD on public insurance were more likely to utilize acute care and have nighttime respiratory symptoms during the first 3 years of life, suggesting that these children may be sicker as outpatients and/or have impaired access to timely healthcare.(21) We also previously found that children on public insurance had delayed weaning of home supplemental oxygen compared to those on private insurance.(22) Social determinants of health may be a major factor that influences rate of weaning diuretics in the outpatient setting in children with BPD, causing prolonged and possibly unneeded exposure to diuretics. Although public insurance provides a safety net for children, those on public insurance may also have greater challenges due to poverty, access to care, or food insecurity. There is an ongoing need to understand the relationship between social determinants of health and outpatient outcomes and medication use in children with BPD.

Interestingly, in the subset of children on home supplemental oxygen we found no difference in oxygen weaning between those on no diuretics versus one diuretic. This suggest that children prescribed one diuretic may be unnecessarily exposed to a diuretic when weaning off home supplemental oxygen. However, we did find that weaning of home oxygen was slower in those children prescribed 2 or more diuretics. Our findings suggest that children prescribed two or more diuretics and who are on home supplemental oxygen, may either have greater lung disease severity and/or that healthcare providers are more reluctant to wean supplemental oxygen due to a perception of more severe lung disease.

Our study has limitations including the retrospective nature of the study and inclusion of only two sites. However, our study included both children both prescribed or not prescribed diuretics and those on and off home supplemental oxygen, providing us an opportunity to study differences in patient characteristics between these groups and to examine diuretic weaning practices in children on or off home supplemental oxygen. Although we noted practice variations between the two sites, thiazides were found to be the most frequently prescribed diuretic in the outpatient setting, in contrast to loop diuretics which have been reported to be the most commonly prescribed diuretic in the inpatient setting. The outpatient preference to use thiazides may reflect the better safety profile of thiazides compared to loop diuretics. Future prospective studies are needed to address outpatient practice variation across diverse geographic areas and to more comprehensively phenotype patients in the outpatient setting to further distinguish those who may benefit most from outpatient diuretic usage.

In summary, diuretic use is common in children with BPD in the outpatient setting. Patient characteristics are similar between those on one or two diuretics, whereas children on loop diuretics are more likely to be technology dependent and to have comorbidities, including pulmonary hypertension. Interestingly, there were no differences in weaning off home supplemental oxygen between those on one or no diuretic. Finally, we noted that children on public insurance are more likely to be weaned slower from diuretics in the outpatient setting. Further studies are needed to understand how outpatient diuretic use influences long-term respiratory outcomes in BPD and how social determinants of health can influence diuretic weaning. Understanding these associations will help optimize health outcomes and potentially lessen side-effects of outpatient diuretic use in children with BPD.

Figure Legends

Figure 1. Time to wean off diuretics in the outpatient setting. By 10 months chronological age over 50% of children were weaned off prescribed diuretics and by 15 months chronological age over 75% were weaned off prescribed diuretics.

Figure 2 . Time to wean off diuretics in children with a supplemental oxygen requirement. There were no statistical differences in time to wean off supplemental oxygen between children on one diuretic

compared to children on no diuretics. Children on two diuretics and home supplemental oxygen took longer to liberate from home supplemental

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