Management of diuretics in infants with bronchopulmonary dysplasia discharged on home oxygen.

Sara Dawson[1], Lynn D'Andrea[1], and Joanne Lagatta[1]

[1]Medical College of Wisconsin Department of Pediatrics

July 27, 2022

Abstract

Background: Infants with Bronchopulmonary Dysplasia (BPD) are often prescribed diuretics before the neonatal intensive care unit (NICU) discharge. It is unknown whether outpatient medication weaning strategies affect duration of home oxygen therapy. **Methods:** This was a secondary cohort analysis of infants born <32 weeks gestational age with BPD from 2015-2018 discharged from our NICU or regional NICUs, referred to our pulmonary clinic for home oxygen management. We compared three groups: those discharged with no diuretics, diuretics actively weaned (dose decreased) and diuretics passively weaned (dose not adjusted). **Results:** Out of 125 infants, 116 were included in the analysis. Forty-five infants were discharged without diuretics; 52 infants were discharged with diuretics that were actively weaned; 19 infants were discharged with diuretics that were passively weaned. Infants who were passively weaned spent the most time on home oxygen (median 28 weeks, IQR 16-52; p=0.011); there were no differences in home oxygen duration in infants actively weaned (median 13 weeks, IQR 10-26) versus not on diuretics (median 22 weeks, IQR 12-30, p=0.285). Multivariable adjustment for other illness characteristics associated with duration of home oxygen did not change this finding. **Conclusions:** Active weaning of diuretics did not prolong duration of home oxygen, in the setting of a standardized clinical guideline for weaning home oxygen in infants with BPD. These data can serve as baseline information to implement and test standardized strategies for outpatient medication management.

Title: Management of diuretics in infants with bronchopulmonary dysplasia discharged on home oxygen.

Sara K Dawson MD[1], Lynn A D'Andrea MD[1], Joanne M Lagatta MD MS[2]

[1]Department of Pediatrics, Division of Pulmonary and Sleep Medicine, Medical College of Wisconsin, and Children's Wisconsin, Milwaukee, Wisconsin, USA

[2] Department of Pediatrics, Division of Neonatology, Medical College of Wisconsin and Children's Wisconsin, Milwaukee, Wisconsin, USA

Address Correspondence: Sara Dawson, MD, Division of Pediatric Pulmonary Sleep Medicine, Medical College of Wisconsin, 9000 W. Wisconsin Ave MS#B620, Milwaukee WI 53226. Phone: 414-266-6730. Fax: 414-266-6742. Email: sdawson@mcw.edu

Funding Source :K23 HL136525 (JL), the Children's Research Institute (JL) and the Medical College of Wisconsin Department of Pediatrics (SD)

Financial Disclosure: All authors have no financial relationships relevant to this article to disclose

Conflict of Interest : The authors have no conflicts of interest to disclose

Key Words: Bronchopulmonary dysplasia, diuretics, inhaled corticosteroids, home oxygen therapy

Running title : medication management of infants on home oxygen

Background:

Infants with Bronchopulmonary Dysplasia (BPD) are often prescribed diuretics before the neonatal intensive care unit (NICU) discharge. It is unknown whether outpatient medication weaning strategies affect duration of home oxygen therapy.

Methods:

This was a secondary cohort analysis of infants born <32 weeks gestational age with BPD from 2015-2018 discharged from our NICU or regional NICUs, referred to our pulmonary clinic for home oxygen management. We compared three groups: those discharged with no diuretics, diuretics actively weaned (dose decreased) and diuretics passively weaned (dose not adjusted).

Results:

Out of 125 infants, 116 were included in the analysis. Forty-five infants were discharged without diuretics; 52 infants were discharged with diuretics that were actively weaned; 19 infants were discharged with diuretics that were passively weaned. Infants who were passively weaned spent the most time on home oxygen (median 28 weeks, IQR 16-52; p=0.011); there were no differences in home oxygen duration in infants actively weaned (median 13 weeks, IQR 10-26) versus not on diuretics (median 22 weeks, IQR 12-30, p=0.285). Multivariable adjustment for other illness characteristics associated with duration of home oxygen did not change this finding.

Conclusions:

Active weaning of diuretics did not prolong duration of home oxygen, in the setting of a standardized clinical guideline for weaning home oxygen in infants with BPD. These data can serve as baseline information to implement and test standardized strategies for outpatient medication management.

Introduction

Infants with bronchopulmonary dysplasia (BPD) are often discharged with home oxygen therapy.[1] Along with home oxygen therapy, infants are often discharged with diuretic medications. Evidence to support the use of diuretic therapy in BPD is controversial, with many questioning the need for this treatment.[2-4] After NICU discharge, data show that diuretic usage decrease over the first year of life. [4,5] The American Thoracic Society recently published recommendations for outpatient respiratory management which suggest against the routine use of diuretics, and recommend discontinuing them in the outpatient setting.[6]However, for infants on home oxygen therapy, it remains unclear how and when to discontinue diuretics, balancing the recommendations to wean medication against a potential logistic preference to wean from home oxygen first.

Our outpatient BPD clinic uses a structured guideline to wean from home oxygen using recorded home oximetry and monthly clinic visits.[7] Along with home oxygen weaning guidelines, we recently introduced guidelines for active weaning of diuretic medications for all infants who did not otherwise require them for cardiovascular indications. The objective of this study was to evaluate whether actively weaning diuretics, instead of an alternative approach of allowing the infant to passively outgrow their dose, would be associated with prolonged weaning from oxygen or trigger unexpected visits. We hypothesized that active weaning of diuretics in premature infants discharged on home oxygen would not prolong the duration of home oxygen therapy.

Methods

This was a secondary cohort analysis of infants born <32 weeks gestational age with BPD discharged with home oxygen from 2015-2018. Infants were either discharged from our level IV NICU or regional level III NICUs and referred to our pulmonary clinic after NICU discharge for home oxygen management. BPD was defined as respiratory support at 36 weeks post-menstrual age.[7-9] Infants with tracheostomies and surgical non-respiratory comorbidities were excluded; only one member of a multiple gestation was included. For the

larger prospective observational cohort study in our NICU caregivers were consented. The infants referred to our pulmonary clinic were considered exempt as a retrospective chart review.

Infants in our BPD clinic are seen 4-6 weeks after discharge from the NICU. Home oxygen is weaned using a structured algorithm, which has been previously published. [7] We also have a standardized guideline for the management of diuretics. Diuretic medications are either actively or passively weaned (Figure 1). We start active diuretic weaning during the first BPD clinic visit if the infant had a pre-discharge pCO2 less than 60 mmHg, no cardiac abnormalities, gaining weight appropriately and passes a room air trial in clinic. If the infant is on a therapeutic dose, we decrease the dose from twice a day to daily one week before the next clinic visit and discontinue at that visit if the infant is clinically stable. If the infant is on a subtherapeutic dose, we decrease the dose to daily at the first visit and tell the parents to discontinue a week before the next visit. Passively weaned means we allow the infant to gradually outgrow their dose. Weaning diuretics and home oxygen occur at the same time.

Our primary exposure variable of interest was diuretic weaning strategy. To test our primary hypothesis that active weaning of diuretics does not prolong duration of home oxygen therapy or trigger unexpected visits, we defined three groups: those discharged from the NICU without diuretics, those actively weaned from diuretics, and those who were passively weaned from diuretics without high-risk indications including patent ductus arteriosus, pulmonary hypertension on echocardiogram after 36 weeks corrected age, or other illness related reason. Infants passively weaned due to high-risk indications were excluded for this analysis.

Our primary outcome was duration of home oxygen in weeks after NICU discharge. Discontinuation of home oxygen was defined as passing a home overnight pulse oximetry study on room air, determined by manual chart review. Secondary outcomes included number of failed room air trials in clinic, overnight pulse oximetry trials, oxygen weaned off-protocol, need for sleep study, increased home oxygen above baseline and new or increased diuretics during emergency department, inpatient and clinic encounters, number of visits to BPD clinic and number of missed clinic visits. Off-protocol weaning included infants whose parents started room air trials, advanced room air trials quicker than instructed or took the infant off supplemental oxygen completely. This includes those who were ultimately told to continue the process they started and those that were told to go back to the original plan.

We reviewed charts for NICU illness variables including gestational age at birth, sex, birth weight, multiple gestation, antenatal steroids, surfactant, patent ductus arteriosus (PDA) ligation or medical therapy; number of days requiring ventilation, home oxygen liter flow at discharge, corrected gestational age at discharge, family history of asthma, and discharge with diuretics, bronchodilators, or inhaled corticosteroids. After NICU discharge we reviewed the chart for illness characteristics that might have affected decision-making regarding diuretic or oxygen weaning, which included emergency department visits, readmissions, pediatric intensive care admission, or receipt of systemic corticosteroids. Because inhaled corticosteroids are also frequently used in infants with BPD discharged with home oxygen therapy, both prescribed before and after NICU discharge, we categorized use of inhaled corticosteroids in three groups: no inhaled corticosteroids, prescribed at NICU discharge, and started after NICU discharge.

Statistical analysis

We compared illness differences between diuretic weaning groups, using chi squared or Fisher's exact tests for differences in proportions, and Kruskal-Wallis tests for differences in medians. To compare our primary outcome of duration of home oxygen therapy, we used Cox survival curves to describe differences between diuretic weaning groups. Differences in secondary outcomes were compared by chi-squared or Fisher's exact tests or Kruskal-Wallis tests. We similarly assessed whether other illness covariates were associated with differences in duration of home oxygen weaning. To evaluate the association between diuretics and duration of home oxygen therapy adjusted for other illness covariates, we used a series of Cox regression models of time to successful weaning from home oxygen, with failure set as failure to wean by 1 year after discharge. Model was run in steps with key covariate of diuretic management retained at each step: first, an unadjusted comparison of diuretic management; second, adjusted for potential NICU illness covariates that were

significantly associated in bivariable analysis with either diuretic weaning plan or duration of home oxygen therapy; third, adjusting for post-NICU significant covariates. Between the second and third steps, variables associated at a p>0.2 were dropped from the model. In the post-NICU-discharge model, emergency and readmission encounters were retained a priori because it was hypothesized that they significantly impacted clinical decision-making about medication management. Variables that were not directly part of the home oxygen weaning process, such as failed room air trials or overnight pulse ox studies, were not included in modeling. A p value of <0.05 was considered statistically significant for all analyses. The institutional Review Board of Children's Wisconsin approved this study.

Results

A total of 125 infants were seen in pulmonary clinic for home oxygen management after NICU discharge; 71 infants were discharged from our NICU and 54 infants were referred from local NICUs. Of the 125 infants, 123 had complete 1 year follow up. Diuretics were used at NICU discharge in 78 (62%) infants. Common medications included spironolactone/hydrochlorothiazide (53), chlorothiazide (11) and hydrochlorothiazide (14).

Active diuretic weaning was used in 52 infants; the median time to discontinuing diuretics for actively weaned infants was 12 weeks after NICU discharge (IQR 9-17 weeks). Passive weaning was used in 19 infants, with 12 who were passively weaned because they failed initial room air trial and 7 who were passively weaned for other etiologies. Their median time to discontinuing diuretics was 16 weeks after NICU discharge (IQR 14-21, p=0.025 compared to active weaning). An additional 7 infants were passively weaned due to secondary medical reasons including pulmonary hypertension (3), pulmonary vein stenosis (1), PDA (1) and recurrent hospitalization (2). These 7 infants were dropped from subsequent comparisons.

Illness characteristics of infants in diuretic weaning groups are displayed in Table 1. Compared to infants discharged without diuretics, infants discharged with actively-weaned diuretics were born at an earlier gestational age; received more surfactant, and days on mechanical ventilation; were discharged at a later corrected gestational age and with higher liter flow of home oxygen. After discharge, they were at higher risk for readmissions. There were fewer illness differences between infants actively versus passively weaned from diuretics. Notably, there were no significant differences between the three groups in family history of asthma or discharge with inhaled corticosteroids; after NICU discharge.

Figure 2 shows the primary outcome of duration of home oxygen. Actively weaning diuretics was not associated with longer duration of home oxygen compared to infants who were never discharged on diuretics. Passively weaned infants spent the most time on home oxygen. Table 2 shows differences in secondary outcomes related to home oxygen weaning. Compared to infants discharged without diuretics, infants with actively-weaned diuretics had more failed overnight pulse oximetry studies, but without differences in sleep studies done, number of clinic visits, missed appointments, or off protocol weaning attempts. Passive weaning of diuretics was more likely to be recommended for infants who failed room air trials in clinic. Seventy eight percent of infants on diuretics had their diuretics discontinued prior to the discontinuation of home oxygen (75% of those who were actively weaned; 25% of those who were passively weaned).

Table 3 shows associations between duration of home oxygen therapy and other illness characteristics in addition to diuretic weaning strategy. Longer duration of home oxygen was associated with lower birth weight, PDA ligation, more days of mechanical ventilation and higher liter flow of home oxygen at NICU discharge. After NICU discharge, longer duration of home oxygen was associated with use of inhaled and systemic corticosteroids, respiratory readmissions, and emergency department visits. Off protocol weaning of home oxygen therapy was also associated with longer duration of home oxygen. In multivariable regression analysis, passively-weaned diuretics were associated with longer duration of home oxygen therapy, adjusted for NICU and post-discharge illness characteristics. Other significant associations with home oxygen duration included post-discharge inhaled corticosteroids and infants who had their home oxygen weaned off-protocol (Table 4).

Discussion

This study examines the association between diuretic weaning strategy and duration of home oxygen in the year following discharge from the NICU in infants with BPD in the setting of guidelines for management of home oxygen. We found that actively weaning diuretics was not associated with longer duration of home oxygen, but passively weaning diuretics was associated with longer duration of home oxygen. We also found that infants started on inhaled corticosteroids after NICU discharge and whose parents weaned home oxygen off-protocol experienced a longer duration of home oxygen.

Infants with BPD discharged with home oxygen therapy are often also discharged with diuretics. It has been shown that diuretics in infants with BPD may improve pulmonary mechanics such as improved pulmonary compliance, lung function and oxygenation.[2,4,10-13]However, diuretics do not decrease oxygen dependence in the inpatient setting, and evidence is limited regarding the impact of long term treatment.[3,14-16] The American Thoracic Society (ATS) guidelines for outpatient management of diuretics suggest that infants with post-prematurity respiratory disease who were discharged home with diuretic therapy should have diuretics discontinued in a careful manner; the guidelines also recommend avoiding routine use of diuretics.[4,6,16] Partially due to the wide variation in both home oxygen and use of respiratory medication use between centers, there are few recommendations regarding how and when to wean diuretics specifically in conjunction with home oxygen therapy.[5,16] Bhandari et al. described an active medication taper in infants with stable BPD, though few infants in that study were also receiving home oxygen therapy. [17] Palm et al. found that most infants with home oxygen therapy have diuretics discontinued prior to home oxygen discontinuation, though this study did not address the specific method of diuretic weaning.[18] Using our guidelines, we were able to effectively start many infants' weaning process for supplemental oxygen and diuretics in the same visit.

We found that infants started on inhaled corticosteroids after NICU discharge had a longer duration of home oxygen therapy, similar to recent findings by White and colleagues among patients in a trial of recorded home oximetry.[4] As with diuretics, the prescribing pattern of inhaled corticosteroids varies between institutions.[18] Infants in our center are variably discharged home from the NICU on inhaled corticosteroids; in clinic we follow a guideline to prescribe inhaled corticosteroids only if the infant has recurrent coughing and wheezing, following the recent published ATS recommendations.[6] It is unlikely that the longer duration of home oxygen therapy was related to inhaled corticosteroids themselves but rather to intercurrent illness; we also noted that respiratory rehospitalizations, emergency department visits, and systemic corticosteroid bursts were associated with longer duration of home oxygen therapy. Nonetheless, our data provide reassurance that starting routine inhaled corticosteroids in infants with BPD discharged with home oxygen therapy does not appear beneficial in decreasing the length of home oxygen.

We found that infants whose parents did not follow the home oxygen weaning protocol ultimately had a longer duration of home oxygen. Off-protocol weaning issues included some parents taking infants off supplemental oxygen before being instructed to do so, or delays in implementing the home oxygen weaning process. Since half of infants with off-protocol weaning had either failed an overnight pulse oximetry study or had ED visits or admissions, it may be that these infants had a longer duration of home oxygen due to the severity of their illness, rather than the weaning process itself. Other infants and their families experienced delays in clinic appointments or ordering of home oximetry testing to discontinue oxygen, which contributed to the longer duration of home oxygen. For these infants and their families, implementing additional educational and clinical interventions to reduce the family impact of home oxygen therapy may have the potential to shorten the length of oxygen. This cohort was followed before our newer strategy of offering telehealth visits which helps families who have difficulty getting back and forth. It will be interesting in future studies how the utilization of remote health strategies effects the length of home oxygen.

Strengths of this study were the high degree of follow up and use of pre-specified clinical guidelines. This biggest limitation was that it was a single-center study. We were not able to control the exact time of appointments which may affect the exact duration of home oxygen and medications. We did evaluate other proxy measures of home oxygen weaning to try to mitigate this weakness. Some factors associated with prolonged home oxygen weaning are hard to evaluate as "independent" risk factors, such as use of systemic

corticosteroids, respiratory readmissions, and emergency department encounters, since these are all likely single events related to acute illness.

In the setting of a standardized clinical guideline for weaning home oxygen in infants with BPD, actively weaning diuretics was not associated with longer duration of home oxygen. We did find that beginning inhaled corticosteroids after NICU discharge and off-protocol weaning were associated with a longer duration of home oxygen. These data can serve as a baseline information to implement and test standardized strategies for diuretic weaning. These results also highlight the need for future studies regarding the use of inhaled corticosteroids in infants with BPD, telehealth visits, more remote health strategies for weaning home oxygen and parental education interventions effects on the duration of home oxygen.

References

1. Lagatta JM, Clark RH, Brousseau DC, Hoffmann RG, Spitzer AR. Varying patterns of home oxygen use in infants at 23-43 weeks' gestation discharged from United States neonatal intensive care units. *J Pediatr.* 2013;163(4):976-982 e972.

2. Bhandari A, Panitch H. An update on the post-NICU discharge management of bronchopulmonary dysplasia. *Semin Perinatol.*2018;42(7):471-477.

3. Stewart A, Brion LP, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. *Cochrane Database Syst Rev.* 2011(9):CD001817.

4. White H, Berenson A, Mannan J, Feldman HA, Rhein L, Group RHOS. Utilization trends of respiratory medication in premature infants discharged on home oxygen therapy. *Pediatr Pulmonol.*2020;55(6):1359-1365.

5. Ryan RM, Keller RL, Poindexter BB, et al. Respiratory Medications in Infants <29 Weeks during the First Year Postdischarge: The Prematurity and Respiratory Outcomes Program (PROP) Consortium. *J Pediatr.* 2019;208:148-155 e143.

6. Cristea AI, Ren CL, Amin R, et al. Outpatient Respiratory Management of Infants, Children, and Adolescents with Post-Prematurity Respiratory Disease: An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2021;204(12):e115-e133.

7. Dawson SK, D'Andrea LA, Lau R, Lagatta JM. Using a home oxygen weaning protocol and pCO2 to evaluate outcomes for infants with bronchopulmonary dysplasia discharged on home oxygen. *Pediatr Pulmonol.* 2020;55(12):3293-3303.

8. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001;163(7):1723-1729.

9. Jensen EA, Dysart K, Gantz MG, et al. The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. *Am J Respir Crit Care Med.* 2019;200(6):751-759.

10. Kao LC, Durand DJ, Phillips BL, Nickerson BG. Oral theophylline and diuretics improve pulmonary mechanics in infants with bronchopulmonary dysplasia. *J Pediatr.* 1987;111(3):439-444.

11. Kao LC, Warburton D, Cheng MH, Cedeno C, Platzker AC, Keens TG. Effect of oral diuretics on pulmonary mechanics in infants with chronic bronchopulmonary dysplasia: results of a double-blind crossover sequential trial. *Pediatrics.* 1984;74(1):37-44.

12. Baraldi E, Filippone M. Chronic lung disease after premature birth.*N Engl J Med.* 2007;357(19):1946-1955.

13. Allen J, Zwerdling R, Ehrenkranz R, et al. Statement on the care of the child with chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med.* 2003;168(3):356-396.

14. Kao LC, Durand DJ, McCrea RC, Birch M, Powers RJ, Nickerson BG. Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. *J Pediatr.*1994;124(5 Pt

1):772-781.

15. Walsh MC, Szefler S, Davis J, et al. Summary proceedings from the bronchopulmonary dysplasia group. *Pediatrics.* 2006;117(3 Pt 2):S52-56.

16. Slaughter JL, Stenger MR, Reagan PB. Variation in the use of diuretic therapy for infants with bronchopulmonary dysplasia.*Pediatrics.* 2013;131(4):716-723.

17. Bhandari A, Chow U, Hagadorn JI. Variability in duration of outpatient diuretic therapy in bronchopulmonary dysplasia: a clinical experience. *Am J Perinatol.* 2010;27(7):529-535.

18. Slaughter JL, Stenger MR, Reagan PB, Jadcherla SR. Utilization of inhaled corticosteroids for infants with bronchopulmonary dysplasia.*PLoS One.* 2014;9(9):e106838.

Figure 1: Diuretic weaning algorithm

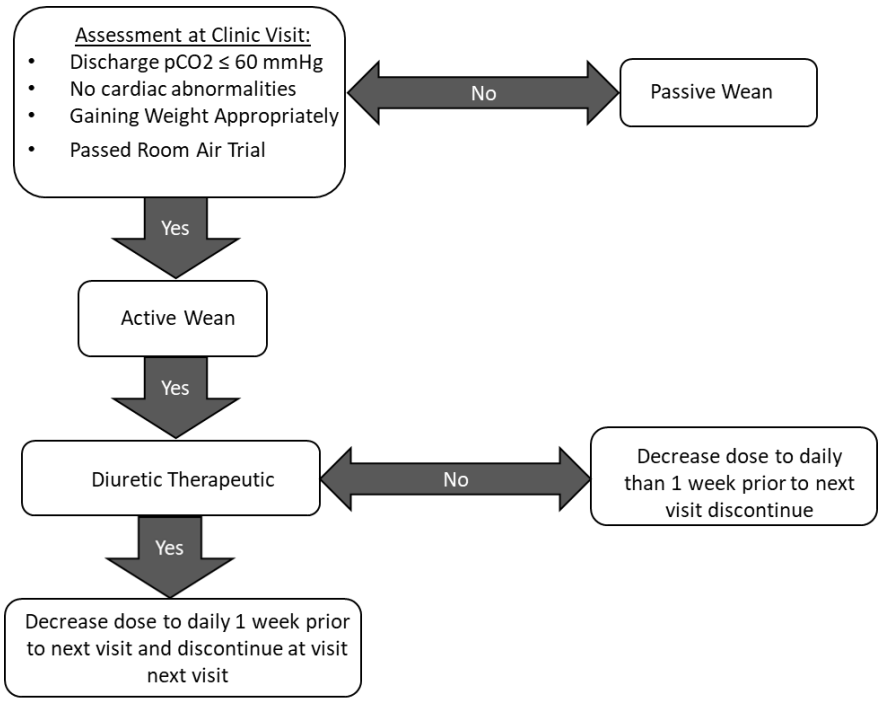


Figure 1: Algorithm for weaning diuretics. At the first BPD clinic visit if the infant had a pre-discharge pCO2 less than 60 mmHg, no cardiac abnormalities, gaining weight appropriately and passes room air trial in clinic. If the infant is on a therapeutic dose, we tell the parents to decrease the dose to daily one week before the next clinic visit and discontinue at that visit if the infant is clinically stable. If the infant is on a subtherapeutic dose, we decrease the dose to daily at the first visit and tell the parents to discontinue a week before the next visit. Passively weaned means we allow the infant to gradually outgrow their dose.

Figure 2: Actively Weaning Diuretics does not Increase duration of home oxygen

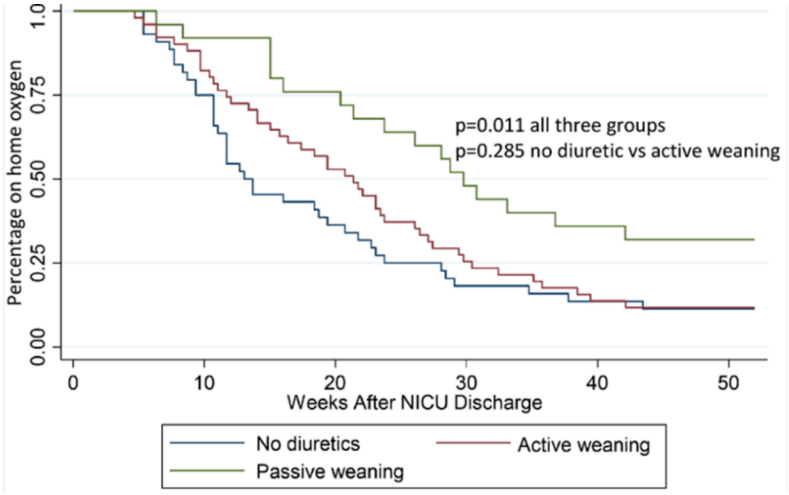
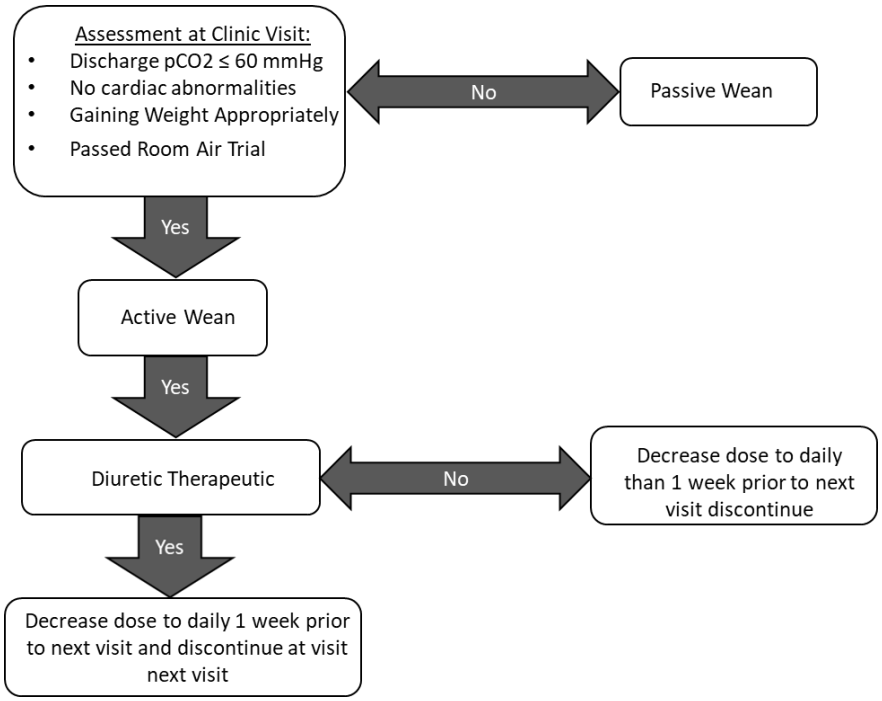
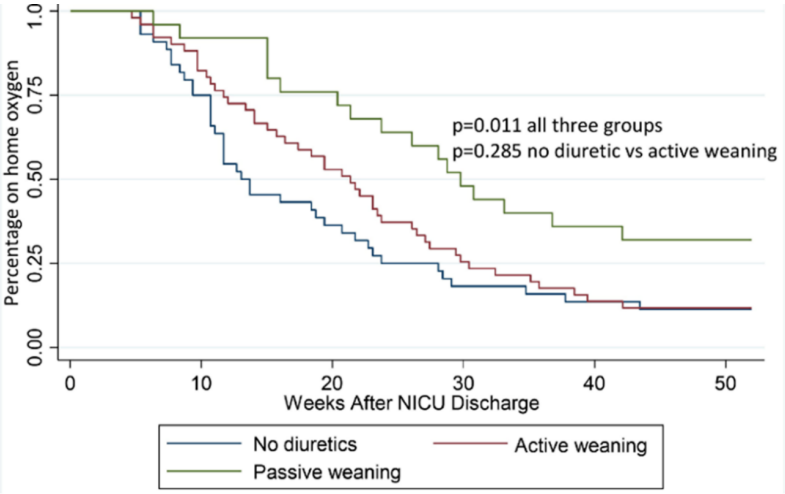


Figure 2: This figure shows the Cox survival curves to describe the differences between diuretics weaning groups. The y axis shows the percentage of infants discontinuing home oxygen; the x axis shows the number of weeks after NICU discharge on home oxygen.





Hosted file

`MedicationsManuscriptTablesV8.docx` available at https://authorea.com/users/336540/articles/578665-management-of-diuretics-in-infants-with-bronchopulmonary-dysplasia-discharged-on-home-oxygen