Wheezing in Preterm Infants and Children

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Abstract

Wheezing is a common outcome of preterm birth. This article will review the mechanisms, epidemiology, and treatment of wheezing in preterm children with and without a history of bronchopulmonary dysplasia

Introduction

Respiratory problems, such as wheezing and cough, are a common complication of preterm birth [1]. Numerous studies have identified environmental, host, and treatment factors associate with both increased and decreased risk of wheezing in preterm infants and children after discharge from the neonatal intensive care unit (NICU). Although wheezing in preterm children overlaps with pediatric asthma, it is clear that mechanisms of wheezing other than asthma contribute to this problem. Despite the large volume of data demonstrating the substantial morbidity imposed on preterm children by wheezing, there is a paucity of high-quality evidence to guide the treatment and prevention of wheezing in preterm children with and without bronchopulmonary dysplasia (BPD). In this article, we will review the epidemiology and pathophysiology of wheezing in preterm infants and children and the data on treatment in this patient population.

Mechanisms of Wheezing in BPD

Expiratory wheezing on physical exam is an audible manifestation of turbulent airflow through partially obstructed intrathoracic airways. In addition to virus-induced wheezing and asthma, other mechanisms can contribute to wheezing in preterm infants and children. Central airway collapse, such as tracheomalacia and bronchomalacia is common in preterm infants, especially those with severe BPD [2]. Sustained mechanical trauma to the small airways by long-term positive pressure ventilation has been presumed to be a major contributor to intermittent collapse and associated wheeze in BPD. However, despite a more recent trend toward less invasive respiratory support strategies in premature infants, measures of infant lung function have demonstrated the prevalence of lower airways obstruction has not changed over the last two decades [3]. An additional mechanism of diffuse airways collapse and wheeze in children with BPD may derive from the hallmark alveolar simplification and pulmonary hypoplasia seen in this disease process. Impaired alveolar development in BPD may result in loss of necessary airway tethering by the fibroelastic network of adjacent alveoli to maintain airway patency during exhalation [4]. Furthermore, both the airway epithelium and the surrounding smooth muscle of susceptible premature airways may become damaged by a complex inflammatory cascade triggered by two separate but related events: intermittent hypoxemia and sustained exposure to supplemental oxygen. During the very early newborn period some premature infants experience frequent episodes of hypoxemia, and the extent of these events has been shown to correlate with reports of wheezing and use of asthma medications two years later [5].Cellular and animal models suggest broad ranges of hyperoxia from supplemental oxygen administration during the postnatal period can result in significant airway smooth muscle proliferation as well as notable increase in methacholine-induced airway reactivity [6, 7]. Respiratory viral infections are the primary trigger for wheezing in term infants and children [8], and

there is evidence that preterm birth or its treatment are associated with altered immune responses to viral infection [9-11].

Epidemiology of Wheezing in Preterm Infants and Children

There have been numerous studies of wheezing in preterm infants and children after discharge from the NICU. Differences in study design, definitions of wheezing outcomes, and study populations make it difficult to make direct comparisons between studies. However, there are several common findings amongst all the studies. Wheezing is very common in preterm infants and children, especially in the first two years of life, with a reported prevalence ranging from 46% to 59% [12-15]. The prevalence of wheezing decreases over time, but is still higher in school aged preterm children compared to their term peers [16-22]. As summarized in Table 1, preterm children with a history of BPD are more likely to have symptoms of wheezing or be prescribed asthma medications such as bronchodilators (BD) or inhaled corticosteroids (ICS). However, there is still a substantial percentage of children without a history of BPD who wheeze or are prescribed these medications.

Risk factors for wheezing in the first 2-3 years of life in preterm infants are summarized in Table 2 and include many antenatal (parental) factors, host factors, and post-natal exposures. In the first three years of life antenatal and host risk factors include gestational age (GA), antenatal maternal tobacco use, parental asthma, intrauterine growth retardation, infant African-American race, and infant male sex [23, 24]. Post-natal risk factors included suboptimal growth or nutrition (low breastmilk exposure and growth failure at 36 weeks post-menstrual age), signs of significant early respiratory disease via associated interventions (delivery room surfactant, cumulative oxygen exposure), indomethacin prophylaxis, and public health insurance [23, 24]. BPD is associated with a higher incidence of wheezing compared to preterm children who did not develop BPD, but up to 59% of preterm children without the diagnosis of BPD also have wheezing [15]. Additional post-natal risk factors for wheeze in late pre-term infants included a marker or significant, early respiratory disease (mechanical ventilation) in addition to infant atopy (atopic dermatitis) and day care [13]. In term children, the ratio of the time to peak expiratory flow over total expiratory time (Tpef/Te) is a risk factor for wheezing in the first few years of life and asthma in childhood [25-27], but measurements of Tpef/Te in preterm children have not proven useful in predicting subsequent wheezing risk [14, 28, 29].

Follow up studies of preterm infants and children have also identified factors associated with a lower risk of wheezing (Table 3). There are several therapeutic interventions in the NICU that have been associated with a lower rate of subsequent respiratory problems. Early continuous positive airway pressure (CPAP) therapy was associated with decreased diagnosis of asthma, lower diagnosis of any respiratory condition, and decreased ER visits for respiratory cause in the first 2 years of life [15]. Both CPAP and low oxygen saturation goals were associated with lower wheeze apart from colds [15]. Late surfactant was associated with decreased home respiratory support while nitric oxide (NO) therapy was associated with decreased respiratory medication exposure within the first 12 months [12, 30]. Taken together, these demonstrate that at least early in life, therapeutic interventions may increase (mechanical ventilation)[13] or decrease the risk of early pulmonary morbidity. Other factors linked to lower risk of wheezing include higher birth weight, breastfeeding, and bacterial tracheal colonization [19, 20, 24, 31]. Palivizumab therapy has been associated with a lower risk of subsequent wheezing in the first few years of life, but its effect on wheezing and asthma in later childhood is not as clear [32-39]. Both low and high maternal body mass index have been associated with increased wheezing in preterm infants [19]. The mechanism in both cases is unclear. Growth has been associated with differing risks of wheezing. Fourth quartile weight velocity in the first year of life was associated with later wheezing risk in former 23-27 w GA infants, [31] while weight gain [?]3 percentiles in the first year of life was protective in 32-35 w GA infants [20].

Although the incidence of wheezing declines after the age of 3 years in preterm children, it still remains higher than that of term children during the school-age years [18, 19]. A history of maternal and paternal atopy and maternal smoking during pregnancy are associated with increased wheezing in older preterm children [18-20]. Higher maternal age (35-39 years) is also associated with increased wheezing risk [19]. Lower GA (24-32 w) is associated with an increased risk of wheeze at 7 and 11 years of life [19]. This contrasts with data

at age 3 and 5 when all preterm infants were noted to have increased wheeze compared to term infants [19]. Both infantile atopic dermatitis and childhood atopy or atopic dermatitis were associated with increased school-aged wheeze, indicating that risk factors for pediatric asthma also contribute to wheezing in preterm children [19, 20]. Antibiotic use in the first 3 years of life was also associated with increased school-aged wheeze, supporting the influence of a growing area of inquiry related to asthma and the microbiome [20]. Additional home or familial factors such as urban environment, formal childcare, post-natal smoke exposure, and public health insurance were also associated with an increased likelihood of wheezing [18-20, 31].

Although extremely low gestational age neonates born at <29 weeks GA (ELGANs) are at highest risk of wheezing following discharge from the NICU, infants born at [?]32 w GA, including late preterm infants (34-37 w GA) also demonstrate increased rates of wheezing compared to term infants [13, 20-22]. In the first three years of life, physician diagnosed wheeze in the last 12 months was present in 41-54% of 32-35 w GA infants, and in nearly half of this group wheezing was recurrent [13]. Similar to ELGANs, the wheezing prevalence decreased with time from ˜50% of infants the first three years [13] to 23% at age six [20] to 10-14% in 13-14 year olds [21]. A large study of preterm infants of all GA demonstrated increased wheeze in all preterm infants at 3 and 5 years, but only in those less than 32 weeks at 7 and 11 years of age [19]. This contrasts with studies of increased wheeze or asthma diagnosis of school aged former 32 to 35 w GA [20].

Caregiver-reported wheezing is subjective and potentially inaccurate. However, numerous studies have also reported that large percentages of preterm infants and children have are prescribed medications frequently used to treat wheezing, such as BD or ICS [12, 30, 40]. Nearly half of ELGANs receive a bronchodilator [12, 18, 31, 40] and approximately 25% receive ICS [12, 30, 40] in the first year after birth. While the increase in reported wheeze is increased only slightly among infants with BPD [15], the increase in respiratory medications among premature infants with BPD is much higher than premature infants without this diagnosis [15, 18, 31, 40]. Systemic corticosteroid use in the first 2 years has rarely been reported by BPD status, but studies that have analyzed this outcome measure haven not found statistically significant increased systemic corticosteroid use in children with BPD compared to those without BPD [15, 40]. Although the proportion of preterm children prescribed asthma medications declines with age, it remains higher in preterm children compared to term children even at 11 years, and by this age there is no difference in medication use between children with a BPD compared to those without BPD [16]. In addition to high rates of respiratory medication use, 16-39% of preterm children also require hospitalization in the first 2 years of life for respiratory illnesses.[12, 14, 15, 29, 30] The risk is also present in infants born at 32-35 w GA, as 6% are hospitalized for respiratory reasons in the first year of life [13]. Infants with BPD are at higher risk for hospitalization than those without BPD [15]. These data on medication use and hospitalizations provide further evidence of the substantial impact that wheezing has on the health of preterm children.

Numerous studies have shown that wheezing occurs commonly amongst preterm infants and children. However, as discussed previously, wheezing associated with preterm birth does not necessarily represent asthma. Biomarkers that are elevated in atopic asthma, such as the fraction of exhaled NO (FeNO) are not elevated in children with a history of BPD [41, 42]. Using a time-oriented logistic regression model to analyze data from a 10 year follow up study of ELGANs, Jackson, et al found that although BPD was a risk factor for preschool wheezing, it was not for asthma [31]. While wheezing due to preterm birth occurs through mechanisms independent of those for asthma, there is certainly a degree of overlap, as evidenced by the observation that well-establish asthma risk factors, such as atopic dermatitis, are also associated with increased wheezing in preterm children [13, 19, 20].

Treatment of Wheezing in Preterm Infants and Children

Medications used to treat wheezing or asthma such as BDs and ICS in term infants and children have frequently been used in preterm infants and children [40]. However, as discussed above the underlying pathophysiology of wheezing in preterm children is different from that of asthma. For example, FeNO tends to be low in BPD, whereas it is elevated in children with atopic asthma [41]. Furthermore, many children with BPD can have tracheobronchomalacia, which could worsen with BD therapy [43]. The immune response to viral infection is altered in preterm infants and children [9-11]. In addition, some medications used to

treat BPD, such as diuretics, may have effects on airway resistance, which is increased in the setting of wheezing [44].

Follow up studies of preterm infants have shown a high prevalence of BD use after discharge from the NICU, but there are few studies that have assessed its use as chronic daily therapy in BPD. Yuksel, et al administered terbutaline or placebo for 2 weeks to 10 preterm infants with a mean age of 12.5 months using a non-randomized, cross-over study design [45]. The primary outcome measures were a self-designed, non-validated symptom score and functional residual capacity (FRC) measured by helium dilution. They found that terbutaline therapy was associated with a significant improvement in symptom scores, but paradoxically led to an increase in FRC. In a study of older preterm children given daily inhaled terbutaline for 4 weeks, no significant change in the forced expiratory volume in 1 second (FEV1) was observed, although peak expiratory flow did increase significantly.

Although data supporting the effect chronic daily inhaled BD therapy on improving lung function are lacking, there have been numerous studies of the effects of single dose BD therapy on lung function, and between 24-97% of preterm children have demonstrated a significant BD response as measured by improvement in FEV1 [46]. Taken together, these data suggest that chronic daily BD therapy is probably not beneficial in children with BPD. However, intermittent use of short-acting beta agonists may have a role in treatment of acute wheezing episodes in this patient population.

ICS are commonly used to treat asthma in children, but their role in preventing wheezing in preterm infants and children is less clear. Randomized clinical trials of ICS therapy in preterm children have been conducted in both preterm infants and children [47-50]. Unfortunately, the strength of these studies has been limited by small study cohorts and the lack of standardized, validated clinical symptom scores. Overall, these studies have failed to show a consistent effect of ICS therapy on improving clinically important outcomes, and routine use of ICS in preterm children is not indicated. However, ICS may be helpful in preterm children with a history suggestive of asthma.

Diuretics are commonly administered to preterm infants in the NICU, and both furosemide and thiazide/spironolactone combination therapy have demonstrated in RCTs to increase pulmonary compliance and reduce airway resistance [51]. Long-term use of these medications, especially furosemide, can be associated with several side effects, including nephrolithiasis, hearing loss, and metabolic bone disease [52]. Diuretic therapy in preterm infants after discharge from the NICU has not been shown to reduce the risk of wheezing or other respiratory symptoms. They may be useful though for acute management of wheezing and hypoxemia in infants with BPD.

Summary

Wheezing is a common outcome of preterm birth, and its mechanism in preterm children differs from that of asthma in term children. Risk factors for wheezing as well as factors associated with a lower risk of wheezing have been identified through multiple cohort studies of preterm infants and children. Despite the high prevalence of wheezing in the preterm population, there is little high-quality evidence to guide its treatment. Inhaled BDs improve lung function in preterm children, but the effect of ICS on preventing wheezing episodes is unclear. Further research is needed to develop better methods to predict wheezing risk in preterm infants and treatment to prevent episodes of wheezing.

References

1. Islam JY, Keller RL, Aschner JL, Hartert TV, Moore PE. Understanding the Short- and Long-Term Respiratory Outcomes of Prematurity and Bronchopulmonary Dysplasia. *Am J Respir Crit Care Med* 2015; 192: 134-156.

2. Hysinger E, Friedman N, Jensen E, Zhang H, Piccione J. Bronchoscopy in neonates with severe bronchopulmonary dysplasia in the NICU. *J Perinatol* 2019; 39: 263-268.

3. Doyle LW, Carse E, Adams AM, Ranganathan S, Opie G, Cheong JLY. Ventilation in Extremely Preterm

Infants and Respiratory Function at 8 Years. *N Engl J Med* 2017; 377: 329-337.

4. Colin AA, McEvoy C, Castile RG. Respiratory morbidity and lung function in preterm infants of 32 to 36 weeks' gestational age.*Pediatrics* 2010; 126: 115-128.

5. Di Fiore JM, Dylag AM, Honomichl RD, Hibbs AM, Martin RJ, Tatsuoka C, Raffay TM. Early inspired oxygen and intermittent hypoxemic events in extremely premature infants are associated with asthma medication use at 2 years of age. *J Perinatol* 2019; 39: 203-211.

6. Wang H, Jafri A, Martin RJ, Nnanabu J, Farver C, Prakash YS, MacFarlane PM. Severity of neonatal hyperoxia determines structural and functional changes in developing mouse airway. *Am J Physiol Lung Cell Mol Physiol* 2014; 307: L295-301.

7. Dylag AM, Mayer CA, Raffay TM, Martin RJ, Jafri A, MacFarlane PM. Long-term effects of recurrent intermittent hypoxia and hyperoxia on respiratory system mechanics in neonatal mice. *Pediatr Res* 2017; 81: 565-571.

8. Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. *J Allergy Clin Immunol* 2017; 140: 895-906.

9. Cui TX, Maheshwer B, Hong JY, Goldsmith AM, Bentley JK, Popova AP. Hyperoxic Exposure of Immature Mice Increases the Inflammatory Response to Subsequent Rhinovirus Infection: Association with Danger Signals.*J Immunol* 2016; 196: 4692-4705.

10. Pryhuber GS. Postnatal Infections and Immunology Affecting Chronic Lung Disease of Prematurity. *Clin Perinatol* 2015; 42: 697-718.

11. Scheible KM, Emo J, Laniewski N, Baran AM, Peterson DR, Holden-Wiltse J, Bandyopadhyay S, Straw AG, Huyck H, Ashton JM, Tripi KS, Arul K, Werner E, Scalise T, Maffett D, Caserta M, Ryan RM, Reynolds AM, Ren CL, Topham DJ, Mariani TJ, Pryhuber GS. T cell developmental arrest in former premature infants increases risk of respiratory morbidity later in infancy. *JCI Insight* 2018; 3.

12. Hibbs AM, Walsh MC, Martin RJ, Truog WE, Lorch SA, Alessandrini E, Cnaan A, Palermo L, Wadlinger SR, Coburn CE, Ballard PL, Ballard RA. One-year respiratory outcomes of preterm infants enrolled in the Nitric Oxide (to prevent) Chronic Lung Disease trial. *J Pediatr* 2008; 153: 525-529.

13. Moreno-Galdó A, Pérez-Yarza EG, Ramilo O, Rubí T, Escribano A, Torres A, Sardón O, Oliva C, Pérez G, Cortell I, Rovira-Amigo S, Pastor-Vivero MD, Pérez-Frías J, Velasco V, Torres J, Figuerola J, Barrio MI, García-Hernández G, Mejías A. Recurrent wheezing during the first 3 years of life in a birth cohort of moderate-to-late preterm infants. *Pediatr Allergy Immunol* 2020; 31: 124-132.

14. Proietti E, Riedel T, Fuchs O, Pramana I, Singer F, Schmidt A, Kuehni C, Latzin P, Frey U. Can infant lung function predict respiratory morbidity during the first year of life in preterm infants? *Eur Respir J* 2014; 43: 1642-1651.

15. Stevens TP, Finer NN, Carlo WA, Szilagyi PG, Phelps DL, Walsh MC, Gantz MG, Laptook AR, Yoder BA, Faix RG, Newman JE, Das A, Do BT, Schibler K, Rich W, Newman NS, Ehrenkranz RA, Peralta-Carcelen M, Vohr BR, Wilson-Costello DE, Yolton K, Heyne RJ, Evans PW, Vaucher YE, Adams-Chapman I, McGowan EC, Bodnar A, Pappas A, Hintz SR, Acarregui MJ, Fuller J, Goldstein RF, Bauer CR, O'Shea TM, Myers GJ, Higgins RD. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). *J Pediatr* 2014; 165: 240-249.e244.

16. Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V, Thomas S, Stocks J. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. *Am J Respir Crit Care Med* 2010; 182: 237-245.

17. Hacking DF, Gibson AM, Robertson C, Doyle LW. Respiratory function at age 8-9 after extremely low birthweight or preterm birth in Victoria in 1997. *Pediatr Pulmonol* 2013; 48: 449-455.

18. Hennessy EM, Bracewell MA, Wood N, Wolke D, Costeloe K, Gibson A, Marlow N. Respiratory health in pre-school and school age children following extremely preterm birth. *Arch Dis Child* 2008; 93: 1037-1043.

19. Kotecha SJ, Watkins WJ, Lowe J, Granell R, Henderson AJ, Kotecha S. Comparison of the Associations of Early-Life Factors on Wheezing Phenotypes in Preterm-Born Children and Term-Born Children. *Am J Epidemiol* 2019; 188: 527-536.

20. Morata-Alba J, Romero-Rubio MT, Castillo-Corullón S, Escribano-Montaner A. Respiratory morbidity, atopy and asthma at school age in preterm infants aged 32-35 weeks. *Eur J Pediatr* 2019; 178: 973-982.

21. Vrijlandt E, Reijneveld SA, Aris-Meijer JL, Bos AF. Respiratory Health in Adolescents Born Moderately-Late Preterm in a Community-Based Cohort. *J Pediatr* 2018; 203: 429-436.

22. Yaacoby-Bianu K, Plonsky MT, Gur M, Bar-Yoseph R, Kugelman A, Bentur L. Effect of late preterm birth on lung clearance index and respiratory physiology in school-age children. *Pediatr Pulmonol* 2019; 54: 1250-1256.

23. Dylag AM, Kopin HG, O'Reilly MA, Wang H, Davis SD, Ren CL, Pryhuber GS. Early Neonatal Oxygen Exposure Predicts Pulmonary Morbidity and Functional Deficits at 1 Year. *J Pediatr* 2020; 223: 20-28.e22.

24. Keller RL, Feng R, DeMauro SB, Ferkol T, Hardie W, Rogers EE, Stevens TP, Voynow JA, Bellamy SL, Shaw PA, Moore PE. Bronchopulmonary Dysplasia and Perinatal Characteristics Predict 1-Year Respiratory Outcomes in Newborns Born at Extremely Low Gestational Age: A Prospective Cohort Study. *J Pediatr* 2017; 187: 89-97.e83.

25. Håland G, Carlsen KCL, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med* 2006; 355.

26. Martinez FD, Morgan WJ, Wright AL, Holberg C, Taussig LM. Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Group Health Medical Associates. *Am Rev Respir Dis* 1991; 143.

27. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988; 319.

28. Bentsen MH, Markestad T, Øymar K, Halvorsen T. Lung function at term in extremely preterm-born infants: a regional prospective cohort study.*BMJ Open* 2017; 7: e016868.

29. Ren CL, Feng R, Davis SD, Eichenwald E, Jobe A, Moore PE, Panitch HB, Sharp JK, Kisling J, Clem C, Kemp JS. Tidal Breathing Measurements at Discharge and Clinical Outcomes in Extremely Low Gestational Age Neonates. *Ann Am Thorac Soc* 2018; 15: 1311-1319.

30. Keller RL, Eichenwald EC, Hibbs AM, Rogers EE, Wai KC, Black DM, Ballard PL, Asselin JM, Truog WE, Merrill JD, Mammel MC, Steinhorn RH, Ryan RM, Durand DJ, Bendel CM, Bendel-Stenzel EM, Courtney SE, Dhanireddy R, Hudak ML, Koch FR, Mayock DE, McKay VJ, Helderman J, Porta NF, Wadhawan R, Palermo L, Ballard RA. The Randomized, Controlled Trial of Late Surfactant: Effects on Respiratory Outcomes at 1-Year Corrected Age. *J Pediatr* 2017; 183: 19-25.e12.

31. Jackson WM, O'Shea TM, Allred EN, Laughon MM, Gower WA, Leviton A. Risk factors for chronic lung disease and asthma differ among children born extremely preterm. *Pediatr Pulmonol* 2018; 53: 1533-1540.

32. Amitai N, Stafler P, Blau H, Kaplan E, Mussaffi H, Levine H, Steuer G, Bar-Yishay E, Klinger G, Mei-Zahav M, Prais D. Palivizumab Following Extremely Premature Birth Does Not Affect Pulmonary Outcomes in Adolescence. *Chest* 2020; 158: 660-669.

33. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, Bont L. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013; 368: 1791-1799.

34. Mochizuki H, Kusuda S, Okada K, Yoshihara S, Furuya H, Simões EAF. Palivizumab Prophylaxis in Preterm Infants and Subsequent Recurrent Wheezing. Six-Year Follow-up Study. *Am J Respir Crit Care Med*2017; 196: 29-38.

35. Prais D, Kaplan E, Klinger G, Mussaffi H, Mei-Zahav M, Bar-Yishay E, Stafler P, Steuer G, Sirota L, Blau H. Short- and Long-term Pulmonary Outcome of Palivizumab in Children Born Extremely Prematurely. *Chest* 2016; 149: 801-808.

36. Simões EA, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick L, Groothuis JR. The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. *J Allergy Clin Immunol* 2010; 126: 256-262.

37. Simoes EA, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, Kimpen JL. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. *J Pediatr* 2007; 151: 34-42, 42.e31.

38. Wenzel SE, Gibbs RL, Lehr MV, Simoes EA. Respiratory outcomes in high-risk children 7 to 10 years after prophylaxis with respiratory syncytial virus immune globulin. *Am J Med* 2002; 112: 627-633.

39. Yoshihara S, Kusuda S, Mochizuki H, Okada K, Nishima S, Simões EA. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. *Pediatrics* 2013; 132: 811-818.

40. Ryan RM, Keller RL, Poindexter BB, D'Angio CT, Shaw PA, Bellamy SL, Moore PE, McPherson C, Greenberg JM. 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.

41. Baraldi E, Bonetto G, Zacchello F, Filippone M. Low exhaled nitric oxide in school-age children with bronchopulmonary dysplasia and airflow limitation. *Am J Respir Crit Care Med* 2005; 171: 68-72.

42. Mieskonen ST, Malmberg LP, Kari MA, Pelkonen AS, Turpeinen MT, Hallman NM, Sovijärvi AR. Exhaled nitric oxide at school age in prematurely born infants with neonatal chronic lung disease. *Pediatr Pulmonol* 2002; 33: 347-355.

43. Panitch HB, Keklikian EN, Motley RA, Wolfson MR, Schidlow DV. Effect of altering smooth muscle tone on maximal expiratory flows in patients with tracheomalacia. *Pediatr Pulmonol* 1990; 9: 170-176.

44. Kao LC, Durand DJ, Nickerson BG. Effects of inhaled metaproterenol and atropine on the pulmonary mechanics of infants with bronchopulmonary dysplasia. *Pediatr Pulmonol* 1989; 6: 74-80.

45. Yuksel B, Greenough A, Maconochie I. Effective bronchodilator treatment by a simple spacer device for wheezy premature infants. *Arch Dis Child* 1990; 65: 782-785.

46. Kotecha SJ, Edwards MO, Watkins WJ, Lowe J, Henderson AJ, Kotecha S. Effect of bronchodilators on forced expiratory volume in 1 s in preterm-born participants aged 5 and over: a systematic review. *Neonatology* 2015; 107: 231-240.

47. Beresford MW, Primhak R, Subhedar NV, Shaw NJ. Randomised double blind placebo controlled trial of inhaled fluticasone propionate in infants with chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2002; 87: F62-63.

48. Kugelman A, Peniakov M, Zangen S, Shiff Y, Riskin A, Iofe A, Shoris I, Bader D, Arnon S. Inhaled hydrofluoalkane-beclomethasone dipropionate in bronchopulmonary dysplasia. A double-blind, randomized, controlled pilot study. *J Perinatol* 2017; 37: 197-202.

49. Pelkonen AS, Hakulinen AL, Hallman M, Turpeinen M. Effect of inhaled budesonide therapy on lung function in schoolchildren born preterm. *Respir Med* 2001; 95: 565-570.

50. Yuksel B, Greenough A. Randomised trial of inhaled steroids in preterm infants with respiratory symptoms at follow up. *Thorax*1992; 47: 910-913.

51. 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: 37-44.

52. Pacifici GM. Clinical pharmacology of furosemide in neonates: a review. *Pharmaceuticals (Basel)* 2013; 6: 1094-1129.

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