Curr Pediatr Res2021; 25 (6): 616-622 *ISSN 0971-9032*
www.currentpediatrics.com

Wheezing in preschool children: New perspective.

Suhas Kulkarni*, Anil Kurane

Department of Pediatrics, DY Patil Medical College, Kolhapur, Maharashtra, India

Abstract

In recent years the understanding about the mechanism of development of wheezing in children has improved and various management strategies were tried by different researchers. A search was made in PubMed by putting search term 'Recurrent Wheezing in Children Diagnosis and Management' and 'Recurrent Wheezing in Children'.

The respiratory syncytial virus induced bronchiolitis and rhinovirus infection in preschool children may lead to recurrent wheezing in preschool children. In infant immune system is immature and depends mainly on TLR ligation and maternal derived antibodies. Anti-inflammatory cytokines such as IL-10 and TGF beta are more common. RSV NS1 and NS2 proteins target RLR and TLR 3 dependent signaling and suppress the cellular response to RSV replication .This can lead to Th2 like response leading to asthma and allergy. CDHR3 acts as receptor in rhinovirus C infection. RV infection causes increase in IL 25 and IL 33 both induce Th2 type of immunity by increasing IL5 and IL 13.

Daily Inhaled Corticosteroids (ICS) have been found useful in preventing exacerbations. Evidence is inconclusive about intermittent inhaled corticosteroids, intermittent montelukast and daily montelukast in recurrent wheezing. Azithromycin started early may decrease duration of wheezing episode. About intravenous magnesium sulfate and hypertonic saline evidence is inconclusive.

Vitamin D supplementation in preterm babies for 6 months and avoidance of cow's milk for first three days of life may be useful in prevention of recurrent wheezing in preschool children.

Keywords: Wheezing, Preschool children, Perspective.

Accepted on June 21, 2021

Introduction

The first study about wheezing in children was carried out at Tucson by Martinez et al. and was published in 1995.In this prospective study they investigated the factors affecting wheezing in children before the age of three years and they were again examined at the age of six years to know the relation to wheezing at that age. 50% of the children wheeze at least once before the first 6 years of life. The burden of wheezing in children is huge [1,2].

Phenotypic classification of wheezing was attempted by Tucson study. According to it early wheezers, persistent wheezers and late onset wheezers were defined. PIAMA study (prevention and Incidence of Asthma and Mite Allergy) demonstrated 5 phenotypes [3]. The ALSPAC (Avon Longitudinal Study of Parents and Children) identified 6 phenotypes [4]. 5 respiratory phenotypes were identified by the URECA (Urban Environment and Childhood Asthma) study .It was based on frequency of wheezing episodes and atopic status [5]. In 2008 the European respiratory society developed a new classification of wheezing episode; virus induced wheezing and multi trigger wheezing [6]. In recent years the understanding about the mechanism of development of wheezing in children has improved and various management strategies were tried by different researchers. Hence this systematic review has been written for the pediatricians to give comprehensive information about these developments.

Search strategy

A search was made in PubMed by putting search term 'Recurrent Wheezing in Children Diagnosis and Management' and 'Recurrent Wheezing in Children'. Filters placed were 5 years, randomized clinical trials, review articles, English language, full text .The first search yield 25 articles and second term lead to 177 articles. Out of these relevant articles were selected which were mainly randomized control trials, novel developments in research laboratory and review articles. Also key articles from history about wheezing in children and cross references from these articles were reviewed.

Definition

Bronchiolitis is characterized by inflammation of small bronchioles and surrounding tissue in children up to 2 years of age and is caused by viral infection of the lower airways [7].

Wheezing: It is defined as whistling sound during expiration accompanied by dyspnea [8]. Diagnosis of wheezing is done if the obstruction is reversible and the disease fail to complete the diagnostic criteria for bronchiolitis and asthma.

Asthma: Is a chronic disorder characterized by airway inflammation, increased mucous secretion and bronchial hyper responsiveness.

Etiology

Bronchiolitis is caused by viruses. Recent papers indicate that bronchiolitis has three clusters of patients. The first group comprises of infants suffering from bronchiolitis caused by respiratory syncytial virus in which obstruction of the airways occur and in many children it is associated with recurrent wheezing. Second group consists of children with atopic background who develop bronchiolitis due to rhinovirus and is more likely to develop asthma in later life. The third group comprises of wheeze due to viruses other than rhinovirus and RSV which lead to occasional severe wheezing [9].

The detection of viruses by Polymerase Chain Reaction (PCR) diagnostics has changed the understanding about the etiology. RSV has been isolated from 50% to 80% of the hospitalized patients with bronchiolitis. Rhinovirus has been the second virus isolated. The rhinovirus has been isolated above the age of 12 months. The other viruses isolated are bocavirus, human metapneumovirus, parainfluenzae virus, adenovirus, and corona virus and influenza virus [9].

Wheezing in Preschool Children

Respiratory tract infections due to viruses at an earlier age lead to recurrent wheezing. The respiratory syncytial virus induced bronchiolitis may lead to recurrent wheezing in children less than six years of age. Frequent wheezing in preschool children can also be followed by infection with rhinovirus [10,11].

The recurrent wheezing secondary to viral infections may progress to asthma. Many long term prospective studies have demonstrated association between RSV induced bronchiolitis and asthma at the age of 6 years. Tucson respiratory study demonstrated relation between RSV induced bronchiolitis and asthma up to age of 11 years [1]. The Childhood Origin of Asthma Study (COAST) concluded that asthma risk by age of 6 years is increased if children had rhinovirus induced wheezing during first three years [9,8,12].

Several models have been developed for prediction of development of asthma in children with wheezing in childhood. The Asthma Predictive Index (API) was developed after Tucson study. It has been modified now and labeled as mAPI. If a child three years or younger has at least four wheezing episodes in last year in addition to that presence of one major or two minor criteria [13].

In a study by Lee et al in Korea API was used to predict asthma and was compared with other laboratory tests such as FeNo, spirometry, methacholine challenge test and allergic sensitization. They concluded that Asthma Predictive Index was associated with better prediction of asthma than other investigations. This study was a cross sectional study [14].

Pathophysiology of Wheezing in Children and Asthma

The symptoms and signs of asthma such as respiratory distress, chest tightness, wheezing, productive cough and episodes of broncho constriction develop due to chronic inflammatory condition of the bronchial airway. Epithelium of the airway normally clears the inhaled allergens, bacteria, viruses and noxious agents and does not allow them to penetrate the epithelium. The airway epithelium is covered by mucus which contains antimicrobial peptides and antibodies which helps in mucociliary clearance. The viscous and elastic properties of mucous gel depend on mucins MUCA5 and MUCB [15,16]. Mucous is a continuous layer on the epithelium.It is transported toward oral cavity by beating of ciliated cells [17].

The Pathophysiology of asthma involves impairment of mucociliary clearance leading to mucous plug formation. Mucous viscocity is increased in asthma due to eosinophils secreting peroxidase thus disturbing mucociliary function. Glycocalyx or Peri Ciliary Layer (PCL) is sponge like layer attached to cell membrane and it is made up of glycolipids and glycoproteins. The layer prevents adenoviruses from getting into the airway epithelium. The small size Boca viruses and rhinoviruses pass through the periciliary layer to epithelial plasma membrane.

Intercellular epithelial junctions in airway epithelium lead to resistance against viruses, bacteria, fungi and noxious chemical substances. These junctions are Adherence Junctions (AJs), hemidesmosomes and Tight Junctions (TJs).In asthma patients this barrier function is disrupted. In bronchial biopsies patchy disruption of TJs and reduction in proteins required for formation of TJs *e.g*. E cadherin have been observed. Studies with primary bronchial epithelial cells which were kept in Air Liquid Interface (ALI) culture also support these studies [16].

In healthy children more than 6 months of age, RSV infection leads to increase in Interferon type I and type III. This response is generated by Toll Like Receptor-3(TLR-3), Retinoic Acid Induced Gene (RIG) like helicase family RNA helicase (RLR) and Mitochondria-associated membranes. In the nucleus IRF-3 and NF-kB bring together respective transcriptional complexes leading to increase in interferon I and III. In children below six months and susceptible children the RSV NS1 and NS2 proteins act on RLR and TLR 3 dependent signaling and suppress the cellular response to RSV replication. This can lead to Th2 like response leading to asthma and allergy [18].

In infant immune system is immature and depends mainly on TLR and maternal derived antibodies. Cytokines which suppress inflammation such as IL-10 and TGF beta are more common. T helpers 1 (Th1) cytokines develop slowly.Cytokines IL 6 and IL 23 which induce IL 17 are found in TLR stimulated neonatal cells. In mice studies it is shown that IL 33 cytokine and innate Lymphoid Cells (ILC) 2 are more common in lung in early neonatal age and them because Th2 type of response [19]. The impaired activation of innate immunity and IL17 leads to mucous hyper secretion and severe disease. As B cell function is also inadequate in babies, they are protected only by high circulating neutralizing antibodies from mother [9,20].

In rhinovirus infection, RV type 1 cause lower respiratory tract infection and rhinovirus type c causes severe wheezing in children. CDHR3 acts as receptor in rhinovirus C infection. RV infection causes increase in IL 25 and IL 33 both induce Th2

type of immunity by increasing IL5 and IL 13. RV infection reduces type I Interferon expression in airway and cause inflammation of Th2 type [9].

Genetics and Wheezing

17q21 has been asthma locus detected which is associated with childhood wheezing.In these children wheezing induced by rhinovirus is associated with asthma in later years of life [21]. Cadherin related family member 3(CDHR3) was associated with childhood asthma. Later on it was discovered that it acts as receptor for Rhinovirus C.It was not associated with RSV infection [22].

Micro-biome and Wheezing

The various microbes present on the body are together called as micro biome. This can enhance development of immunity. The micro biome starts developing since birth. Certain microbial colonization patterns may be associated with wheezing and development of asthma. Antibiotic treatment during childhood wheezing episodes has been found to decrease the duration of symptoms. In RSV induced bronchiolitis treatment with azithromycin decreased the subsequent risk of respiratory problems [23].The development of micro biome depends on antibiotics, delivery mode and diet [24].

Diagnosis of Wheezing by Pulmonary Function Testing

Lung function tests such as spirometry are performed in children above 6 years of age. Lung function testing in children below 6 years has been tried by different methods. Presently the techniques used are interrupt or technique and forced oscillation technique.These techniques do not require forceful manoeuvre and child can breathe at tidal volume [25].

The forced oscillation technique

The impulse oscillometry technique is simple, non-invasive technique. It can be performed easily while taking tidal breathing. An external pressure wave is given to the airway at the mouth and analysis of pressure-flow relationship is examined in terms of (Zrs) impedence of the respiratory system. The resistance to flow involves frictional losses (Rrs) and elastic and inertial load (Xrs). It requires minimum cooperation from the children. The measurement therefore can be performed in children three years of age onwards and it can be performed in pulmonary laboratory, clinic, bedside, in school. Various reference equations for preschool children have been reported. The sensitivity of Impulse oscillometry has been reported 90% and specificity up to 53% to differentiate healthy children from asthma [26].

Interruptor Technique

Interrupter technique: In interrupter technique, if the airflow is obstructed suddenly at the mouth, the alveolar pressure and Pressure in mouth (Pmo) becomes equal. Rint is calculated as this (equilibrated) pressure divided by the airflow measured immediately before interruption. Reference values are available for interrupter technique. Interruptor resistance dose response relationship with salbutamol has been shown recently in wheezy children [27].

Treatment

Treatment algorithm of recurrent wheezing episodes in preschool children is not yet fully finalized. The important problem is in deciding whether the treatment is useful in some children or whether patient has outgrown the disease as age has advanced. As there is improved understanding in pathogenesis of recurrent wheezing, specific treatment strategies as per the etiology may emerge in future?

Inhaled Short Acting Beta 2 Agonist (SABA) is the first line of treatment in all wheezing episodes. A review by Yusuf F et al concluded that beta 2 receptors are present in smaller children. The mechanism of wheezing in bronchiolitis is due to mucous obstruction and edema of airway at the level of bronchioles hence bronchodilators are not effective in bronchiolitis [28]. Cochrane review by Gadomski et al. concluded that in children with bronchiolitis use of beta 2 agonists do not help in clinical improvement and in duration of hospitalization [29]. The Global Initiative for Asthma (GINA) guideline 2020 recommends use of beta 2 agonist intermittently in children below 5 years with wheezing [30].

Inhaled levosalbutamol has been shown to be better tolerated and had less side effect profile and caregiver's satisfaction score was also good in a review [31]. Inhaled hypertonic saline has been suggested by some researchers in acute episode of wheezing in children. Randomized controlled trial conducted by Kanjanapradap et al. showed that 2.5 mg salbutamol with 3% hypertonic saline decreased the length of hospital stay, need for oxygen and improved asthma severity score. But the sample size in this RCT was 47 [32]. The same was not seen in randomized control trial by BS Sharma et al in which sample size was 248 [33].

Intermittent use of Inhaled Corticosteroids

Kaiser et al. in subgroup analysis of children with intermittent asthma or viral triggered wheezing concluded that treatment with intermittent high dose Inhaled Cortico Steroids (ICS) resulted in reduced exacerbations (RR 0.65;95% CI 0.51-0.81 NNT 6) [34].

Study by Ducharme et al. showed that high dose fluticasone propionate administered as three inhalations by inhaler at the onset of Upper Respiratory Tract Infection (URTI) decreased the requirement of rescue oral corticosteroids. Gain in height was less in children with high dose fluticasone [35].

Intermittent use of high dose budesonide 1mg twice daily for 7 days at the onset of upper respiratory tract symptoms versus daily 0.5 mg at night was done. There was no significant difference between daily versus intermittent group [36]. Study by Clevenna et al. did not show any difference in nebulized beclomethasone group and placebo group and parent

satisfaction was almost similar. They concluded that nebulized beclomethasone does not prevent virus induced wheezing [37].

In a systematic review by Jose et al. identified 29 trials, out of which 6 trials with 3204 children were considered. In these trials primary outcomes were decreased episodes of wheezing, number of exacerbations and daily symptom score. The secondary outcomes were need for rescue systemic corticosteroids, hospitalizations. They concluded that in children with wheezing or asthma requiring controller therapy daily ICS is more effective than daily oral Montelukast for symptom control and decreasing exacerbations [38]. Daily ICS was shown to be helpful in preventing exacerbations in recurrent wheezing in children in the meta-analysis by Kaiser et al. [34].

Oral Corticosteroids

A randomized placebo controlled trial was conducted by Foster et al.Oral prednisolone and placebo was given to wheezing children in emergency department. Prednisolone 1mg/kg for 3 days was found to be effective in decreasing median length of stay in hospital. No side effects were observed [39].In a randomized control trial by Kostinen et al. oral prednisolone or placebo was given at the start of rhinovirus infection and time to initiate asthma control medication was checked. In overall analysis it did not show significant results. In subgroup analysis, in children with more than 7000 copies of viruses the risk to initiate asthma control measures was low in the children given prednisolone. So they conclude that with severe rhinovirus induced wheezing with high viral load prednisolone may be effective [40].

Intermittent Leukotriene Receptor Antagonist

Nwokoro et al. conducted a randomized controlled trial in 10 months to 5 years children and analyzed ALOX5 gene polymorphism and intermittent Montelukast. They concluded that intermittent Montelukast is not useful in decreasing unscheduled medical attendances for wheezing episodes[41].Cochrane review by Brodlie et al. after considering 5 trials for intermittent Montelukast opined that it does not decrease the wheezing episodes. For continuous use of Montelukast only one trial was considered and daily Montelukast did not show any reduction in rescue oral steroids as compared to placebo [42]. In a meta-analysis by Hussein et al. intermittent Montelukast did not decrease medical visits for wheezing and use of rescue steroids [43].

Antibiotics

In a randomized controlled trial Azithromycin in dose of 10 mg/kg/day or placebo was started from third day in children with wheezing. Children with pneumonia were excluded. Azithromycin significantly reduced the duration of wheezing episodes as compared to placebo group.The duration was decreased by 63% in azithromycin group. Time to next episode was not decreased [44]. Whether this effect was due to combination of viral and bacterial infections in wheezing episode or anti-inflammatory effect of azithromycin is yet to be finalized. In a study by Bacharier et al. 607 children were included 307were randomly given azithromycin 12 mg/kg/day for five days and 300 children were given placebo. Progression to LRTI was found in 35 children in Azithromycin group and 57 children in placebo group. Early use of azithromycin decreases the incidence of LRTI in these children with recurrent wheezing [45].In a systematic review by Pincheira et al. primary outcomes were need to hospitalization and time of asthma symptom resolution. It was found that there was no difference in hospitalization but time to symptom resolution was significantly less. The time to next wheezing episode did not change [46].

Magnesium Sulfate

As magnesium sulfate has been found useful in children with acute exacerbation of asthma, Pruikkonen et al. tried it in severe wheezing episode. Children 6 months to 4 years with Respiratory Distress Assessment Score (RDAI) more than or equal to 6 points were included in the study. Children were treated with salbutamol. They were randomly assigned to intravenous magnesium sulfate (40 mg/kg) group or to 0.9% sodium chloride group which was given as a placebo infusion for 20 minutes. Change in severity score was 4.7±2.6 in magnesium sulfate group and 4.2 ± 4.2 in placebo group. Hence it was decided that intravenous magnesium sulfate is not useful in management of wheezing episodes in children [47].

Spacers *vs.* Nebulizers

A prospective randomized control trial in pediatric emergency department was conducted by Mitselou et al. about use of nebulizer for delivery of bronchodilator versus spacer with metered dose inhaler. There was no difference in device acceptance by parents. There was no difference in heart rate, respiratory rate and oxygen saturation initially and after treatment in both the groups [48].

Prevention of Recurrent Wheezing

Supplementation of vitamin D 400 IU/day was given from birth to 6 months of age to 300 preterm born infants.In infants who were supplemented the incidence of recurrent wheezing was 31.1% (42 out of 135 infants) in non-supplemented group it was 41.8% (56 out of 134). Relative risk was 0.66 (95% CI, 0.47 to 0.94) p=0.02.It was concluded that supplementation with vitamin D leads to reduced risk of recurrent wheeze by 12 months.

In a randomized trial 312 infants were included. Immediately after birth breast feeding or cow's milk formula was given for first 3 days of life and children were followed for 2 years. Asthma and recurrent wheeze developed in 27 out of 151 in cow's milk formula patients as against 15 breast milk fed infants.The conclusion was if cow's milk formula is avoided for the first three days of life the risk of recurrent wheezing and development of asthma is decreased significantly [49].

Summary

- Viral respiratory tract infections by respiratory syncytial virus and rhinovirus in early life can lead to recurrent wheezing.
- They seem to modify the response to Th2 type of inflammation in respiratory epithelium and cause recurrent wheezing episodes.
- Daily Inhaled Corticosteroids (ICS) have been found useful in preventing exacerbations.
- Evidence is inconclusive about intermittent inhaled corticosteroids, intermittent montelukast and daily montelukast in recurrent wheezing.
- Azithromycin started early may decrease duration of wheezing episode.
- Intravenous magnesium sulfate and hypertonic saline evidence is inconclusive.
- Vitamin D supplementation in preterm babies for 6 months and avoidance of cow's milk for first three days of life may be helpful in decreasing recurrent wheezing in preschool children.

Conclusion

The respiratory syncytial virus induced bronchiolitis and rhinovirus infection in preschool children may lead to recurrent wheezing in preschool children. In infant immune system is immature and depends mainly on TLR ligation and maternal derived antibodies. Anti-inflammatory cytokines such as IL-10 and TGF beta are more common. RSV NS1 and NS2 proteins target RLR and TLR 3 dependent signaling and suppress the cellular response to RSV replication .This can lead to Th2 like response leading to asthma and allergy. CDHR3 acts as receptor in rhinovirus C infection. RV infection causes increase in IL 25 and IL 33 both induce Th2 type of immunity by increasing IL5 and IL 13.

References

1. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. N Engl J Med 1995; 19;332(3):133-8.
2. Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. Pediatric Pulmonology 2007;42(8): 723-8.
3. Brunekreef B, Smit J, De Jongste J, et al. The Prevention And Incidence Of Asthma And Mite Allergy (PIAMA) birth cohort study: Design and first results. Pediatr Allergy Immunol 2002;13:55-60.
4. Golding J, Pembrey M, Jones R. ALSPAC-The avon longitudinal study of parents and children study methodology. Paediatr Perinat Epidemiol 2001; 15(1): 74-87.
5. Gern JE. The urban environment and childhood asthma study. J Allergy Clin Immunol 2010; 125(3):545-9.
6. Brand PL, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: An evidence-based approach. Eur Respir J 2008; 32(4):1096-110.
7. Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. J Allergy Clin Immunol. 2017; 140(4):895-906.
8. Cloutier MM, Baptist AP, Blake KV, et al. 2020 Focused updates to the asthma management guidelines: a report from the national asthma education and prevention program coordinating committee expert panel working group. J Allergy Clin Immunol 2020; 146(6):1217-70.
9. Jartti T, Smits HH, Bønnelykke K, et al. Bronchiolitis needs a revisit: Distinguishing between virus entities and their treatments. Allergy 2019; 74(1):40-52.
10. Van Der Gugten AC, Van Der Zalm MM, Uiterwaal CS, et al. Human rhinovirus and wheezing: Short and long-term associations in children. Pediatr Infect Dis J 2013; 32(8): 827-33.
11. Takeyama A, Hashimoto K, Sato M, et al. Clinical and epidemiologic factors related to subsequent wheezing after virus-induced lower respiratory tract infections in hospitalized pediatric patients younger than 3 years. Eur J Pediatr. 2014; 173(7):959-66.
12. Stokes JR, Bacharier LB. Prevention and treatment of recurrent viral-induced wheezing in the preschool child. Ann. Allergy Asthma Immunol 2020; 125(2):156-62.
13. Castro-Rodriguez JA. The asthma predictive index: Early diagnosis of asthma. Curr Opin Allergy Clin Immunol 2011; 11(3):157-61.
14. Lee DH, Kwon JW, Kim HY, et al. Asthma predictive index as a useful diagnostic tool in preschool children: A cross-sectional study in Korea. Clin Exp Pediatr 2020; 63(3):104.
15. Thornton DJ, Rousseau K, McGuckin MA. Structure and function of the polymericmucins in airways mucus. Annu Rev Physiol 2008;70:459-86.
16. Frey A, Lunding LP, Ehlers JC, et al. More than just a barrier: the immune functions of the airway epithelium in asthma pathogenesis. Frontiers in Immunol 2020;11:761.
17. Houtmeyers E, Gosselink R, Gayan-Ramirez G, et al. Regulation of mucociliary clearance in health and disease. Eurb Respir J 1999;13(5):1177-88.
18. San-Juan-Vergara H, Peeples ME. Importance of virus characteristics in respiratory syncytial virus-induced disease. Immunol Allergy Clin North Am 2019;39(3): 321-334.
19. Thomas B, Rutman A, Hirst RA, et al. Ciliary dysfunction and ultra-structural abnormalities are features of severe asthma. J Allergy Clin Immunol 2010;126(4):722-9.
20. Gon Y, Hashimoto S. Role of airway epithelial barrier dysfunction in pathogenesis of asthma. Allergol Int 2018;67(1):12-7.
21. Çalışkan M, Bochkov YA, Kreiner-Møller E, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. N Engl J Med 2013;368 (15):1398-407.
22. Bønnelykke K, Coleman AT, Evans MD, et al. Cadherin-related family member 3 genetics and rhinovirus c

respiratory illnesses. Am J Respir Crit Care Med 2018;197(5):589-594.
23. Beigelman A, Isaacson-Schmid M, Sajol G, et al. Randomized trial to evaluate azithromycin's effects on serum and upper airway IL-8 levels and recurrent wheezing in infants with respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol 2015;135(5):1171-8.e1.
24. Bokulich NA, Chung J, Battaglia T, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci Transl Med 2016;8(343):343ra82.
25. Fenu G, Calogero C, Lombardi E. Lung Function Tests in Preschool Children. Turk Thorac J 2015;16(4):185-188.
26. Rosenfeld M, Allen J, Arets BH, et al. An official american thoracic society workshop report: Optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheezing in children less than 6 years of age. Ann Am Thorac Soc 2013;10:S1–11.
27. Beydon N, Nguyen TT, Amsallem F, et al. Interrupter resistance to measure dose-response to salbutamol in wheezy preschool children. Pediatr Pulmonol 2018;53(9): 1252-1259.
28. Yusuf F, Prayle AP, Yanney MP. β2-agonists do not work in children under 2 years of age: Myth or maxim?. Breathe 2015;15 (4):273-276.
29. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 2014(6).
30. https://ginasthma.org/gina-reports/
31. Gupta, Mukesh Singh. Evidence based review on levosalbutamol. Indian J Pediatr 2007;74:161-7.
32. Kanjanapradap T, Deerojanawong J, Sritippayawan S, et al. Does nebulized hypertonic saline shorten hospitalization in young children with acute viral wheezing? Pediatr Pulmonol 2018;53(2):138-144.
33. Sharma BS, Gupta MK, Rafik SP. Hypertonic (3%) saline vs. 0.9% saline nebulization for acute viral bronchiolitis: A randomized controlled trial. Indian J Pediatr 2013;50(8): 743-7.
34. Kaiser SV, Huynh T, Bacharier LB, et al. Preventing exacerbations in preschoolers with recurrent wheeze: A meta-analysis. Pediatrics 2016;137(6).
35. Ducharme FM, Lemire C, Noya FJ, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med 2009;360(4):339-53.
36. Zeiger RS, Mauger D, Bacharier LB, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med 2011;365(21): 1990-2001.
37. Clavenna A, Sequi M, Cartabia M, et al. Study Group. Effectiveness of nebulized beclomethasone in preventing viral wheezing: RCT Pediatrics 2014;133(3):e505-12.
38. Castro-Rodriguez JA, Rodriguez-Martinez CE, Ducharme FM. Daily inhaled corticosteroids or montelukast for preschoolers with asthma or recurrent wheezing: A systematic review. Pediatric Pulmonology 2018;53(12): 1670-7.
39. Foster SJ, Cooper MN, Oosterhof S, et al. Oral prednisolone in preschool children with virus-associated wheeze: A prospective, randomized, double-blind, placebo-controlled trial. Lancet Respir Med 2018;6(2):97-106.
40. Koistinen A, Lukkarinen M, Turunen R, et al. Prednisolone for the first rhinovirus-induced wheezing and 4-year asthma risk: A randomized trial. Pediatr Allergy Immunol 2017;28(6):557-63.
41. Nwokoro C, Pandya H, Turner S, et al. Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): Amulticentre, randomized, placebo-controlled trial. The Lancet Respiratory Medicine 2014;2(10):796-803.
42. Brodlie M, Gupta A, Rodriguez-Martinez CE, et al. Leukotriene receptor antagonists as maintenance and intermittent therapy for episodic viral wheeze in children. Cochrane Database Syst Rev 2015(10).
43. Hussein HR, Gupta A, Broughton S, et al. A meta-analysis of montelukast for recurrent wheeze in preschool children. Eur J Pediatr 2017;176(7):963-9.
44. Stokholm J, Chawes BL, Vissing NH, et al. Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: A randomized, double-blind, placebo-controlled trial. The Lancet Respiratory Medicine 2016;4(1):19-26.
45. Bacharier, LB, Guilbert, TW, Mauger DT, et al. Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial 2015;314(19), pp.2034-2044.
46. Pincheira MA, Bacharier LB, Castro-Rodriguez JA. Efficacy of macrolides on acute asthma or wheezing exacerbations in children with recurrent wheezing: A systematic review and meta-analysis. Pediatric Drugs 2020; 22(2):217-28.
47. Pruikkonen H, Tapiainen T, Kallio M, et al. Intravenous magnesium sulfate for acute wheezing in young children: a randomized double-blind trial. EurRespir J 2018;51(2): 1701579.
48. Mitselou N, Hedlin G, Hederos CA. Spacers versus nebulizers in treatment of acute asthma–a prospective randomized study in preschool children. Journal of Asthma 2016; 53(10):1059-62.
49. Tachimoto H, Imanari E, Mezawa H, et al. Effect of avoiding cow's milk formula at birth on prevention of asthma or recurrent wheeze among young children: Extended follow-up from the ABC randomized clinical trial. JAMA Network open 2020;3(10): e2018534-e2018534.

*Corresponding to:

Dr. Suhas Kulkarni

Department of Pediatrics

DY Patil Medical College

Kolhapur

Maharashtra
India

Tel: +919822320663
E-mail: drspk_2000@yahoo.com