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Review Article

Wheezing in Pre School Children-Approach to Diagnosis and Management-Review

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Abstract

Wheezing in infancy and childhood is a common condition; however, it is not a single disorder and can be due to causes other than asthma. Not all wheezing is asthma. Wheezing-associated respiratory illnesses in children are often described as asthma, however while most children with asthma show symptoms of wheezing, not all wheezing is related to asthma. Wheezing, coughing and breathlessness are common in young children, and can all be symptoms of conditions other than asthma. Even with all these wheezy children, we still do not know the answers to a number of basic questions. What is the cause and type of the wheezing illness in an individual child? What does it portend for the future of this child? Bronchiolitis refers to a first episode of wheezing, with respiratory distress triggered by a viral infection. Episodic viral wheezing refers to discrete episodes of wheezing without intermittent symptoms. Unremitting wheezing or Multiple-trigger wheeze refers to distinct episodes of wheezing with intermittent symptoms, such as coughing or wheezing at night or in response to exercise, crying, laughter, mist, or cold air. Wheezing Phenotype during the first 6 years of life 1. Transient early wheezers 2. Late wheezers 3. Persistent wheezers. Environmental conditions that increase the rate of bacterial and viral infections are risk factors for transient wheezing, but its relationship to asthma remains unclear. Children with frequent simple colds and other common childhood infections in infancy are less likely to develop persistent wheezing in later childhood. Many preschool children with viral induced wheezing will outgrow these symptoms, and do not have asthma. Until recently, however, international asthma management guidelines did not provide separate recommendations for preschool children. Generally, asthma is identified by the presence of cough, wheeze and breathing difficulty, together with features of atopy (or a family history of atopy or asthma) and impaired lung function evidenced by spirometry. It is important to explain to parents/carers that wheezing in an infant or preschooler does not mean the child will have asthma or allergies by primary school age. In preschool-aged children with recurrent wheeze (e.g. four or more episodes per year), consider using the Asthma Predictive Index, to estimate whether children are likely to have asthma during primary school years. Asthma Prediction Index has some major criteria and minor criteria. Major criteria are diagnosis of asthma in one or both parent, Diagnosis of atopic dermatitis during the first 3 year of life, Sensitization against > 1 allergen, Minor criteria- Milk, egg, or peanut sensitization. Associated with respiratory infections, Eosinophilia > 4%. In the first 3 years of life if anyone who have 1 major criteria, or 2 minor criteria is present in one episode, the possibility of asthma in 6 - 13 years is 59% but 2 episodes possibility is 77%. Investigation - Chest X - Ray, spirometry, CT scan of Chest and Fiberoptic Bronchoscope. It is usually not necessary if history of "classic" asthma or, patient response to salbutamol and or steroid; then only spirometry should be done. But need other investigation when Chronic cough (> 1 month), recurrent pneumonia, persistent signs or symptoms are seen despite therapy. Investigations are only needed when in doubt about the diagnosis.

Based on the limited evidence available, inhaled short-acting b2-agonists by metered-dose. Inhaler/spacer combination is recommended for symptomatic relief. Educating parents regarding causative factors and treatment is useful. Exposure to tobacco smoke should be avoided; allergen avoidance may be considered when sensitization has been established.

Inhaled corticosteroids remain first-line treatment for multiple-trigger wheeze but may also be considered in patients with episodic viral wheeze with frequent or severe episodes, or when the clinician suspects that interval symptoms are being under reported. Any controller therapy should be viewed as a treatment trial, with scheduled close follow up to monitor treatment effect. Some group recommends discontinuing treatment if there is no benefit and taking favorable natural history into account when making decisions about long-term therapy. Oral corticosteroids are not indicated in mild-to-moderate acute wheeze episodes and should be reserved for severe exacerbations in hospitalized patients.

Keywords: *Wheezing, Corticosteroid inhaler, Montelucast, Preschool Children*

Introduction

Wheezing in infancy and childhood is a common condition; however, it is not a single disorder and can be due to causes other than asthma. Not all wheezing is asthma. Wheezing-associated respiratory illnesses in children are often described as asthma, however while most children with asthma show symptoms of wheezing, not all wheezing is related to asthma. In more than half of the children who wheeze within their first three years, the wheezing is transient and does not increase the risk of later asthma. Around the world, thousands of times a day, an infant 6 to 8 months old with a runny nose, a cough, and wheezing arrives in a pediatrician's office or an outpatient clinic. In western countries about 1 in 3 children has at least one episode of wheezing before 3 years of age [1-3].

Wheezing, coughing and breathlessness are common in young children, and can all be symptoms of conditions other than asthma Even with all these wheezy children, we still do not know the answers to a number of basic questions. What is the cause and type of the wheezing illness in an individual child? What does it portend for the future of this child? What is the best way to approach and investigate wheezing in a preschooler? How should it be treated?

Methods

Data extraction

By performing a searched in Pub Med and the Cochrane Library and EMBASE with the keywords: (asthma * or wheeze*) AND (diagnostic approach and treatment as inhaled corticosteroids or corticosteroids or leukotriene or montelukast or long-acting beta agonists), limited for clinical trials or systematic reviews and for infants or preschool children. Literature searches were performed in order to identify material relating to preschool wheeze. Relevant study areas were identified, and, for each area, a literature search was carried out based on a predefined series of key clinical questions. and the strategies included filters to limit the results by study type (reviews, randomized controlled trials and other types of experimental research) and age range (0 - 5 years). In most cases, the results were limited to English language material. The evidence from the retrieved relevant papers was graded, according to recent recommendations [4], as high-, moderate-, low- or very low-grade evidence based on the following criteria: study design and quality (systematic reviews and randomized controlled trials: high quality; observational studies: low quality; any other type of article: very low quality), consistency of the data and relevance. The present manuscript was organized into three main sections: Definitions, diagnostic approach and Treatment.

Results

Bronchiolitis refers to a first episode of wheezing, with respiratory distress triggered by a viral infection. Wheezing during discrete time periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes. Episodic viral wheez-

ing (EVW) refers to discrete episodes of wheezing without intermittent symptoms. Unremitting wheezing or multiple-trigger wheezing (MTW) refers to distinct episodes of wheezing with intermittent symptoms, such as coughing or wheezing at night or in response to exercise, crying, laughter, mist, or cold air. The distinction between EVW and MTW is not clear in all patients some children retain a consistent pattern of EVW or MTW, but symptom patterns change over time in many patients and their airway pathology remains unclear Wheezing Phenotype during the first 6 years of life 1. Transient early wheezers 2. Late wheezers. 3. Persistent wheezers [1].

The fact that the incidence of all preschool wheezing disorders has increased (including viral wheeze) makes it probable that factors unrelated to atopy are implicated in the changing epidemiology of wheeze in childhood [5]. Young children who present with symptoms of wheeze may either have viral-associated respiratory problems that may not persist into later childhood or may have an asthmatic pattern of airway inflammation that may subsequently develop into asthma [6]. Results from longitudinal studies indicate that the term Basthma^includes different phenotypes: Tucson birth cohort study identified three phenotypes of childhood wheezing, namely transient early wheezing, nonatopic wheezing, and persistent‘atopic’wheezing [7,8].

The best way to discriminate phenotypes in young children is yet to be found. European Task Force has proposed to use the terms episodic (viral) wheeze (EVW) to describe children who wheeze intermittently and are well between episodes, and multiple-trigger wheeze (MTW) for children who wheeze both during and outside these discrete episodes No tests/markers to differentiate between EVW/MTW. Problems with history differentiating between the two. Patients may change their phenotype and this phenotypic classification does not take severity into account, inter current illness between viral colds may be under reported [8].

The term asthma should probably not be used in preschool children because data regarding underlying inflammation is lacking. Use of the terms transient, late-onset and persistent wheeze should probably be limited to population-based cohort studies and should not be used clinically. There are no data suggesting this phenotype is associated with eosinophilic inflammation or with increased atopic sensitization, the two factors that might be associated with steroid responsiveness [8]. Phenotype-specific treatment has been recommended even though phenotypes are not mutually exclusive [9]. Whether early childhood wheezing and asthma represent the ends of a spectrum of a single entity or they represent two distinct heterogeneous disorders is a subject of long debate. There are two groups of articles appearing in journals, few stressing the importance of preschool wheeze, ignoring the early onset asthma and others concentrating on the management issues of asthma, ignoring the wheezing phenotypes.

Since the provisional diagnosis of wheeze plays an important role both from the management and parental appraisal point of view, a proper study validating the above issues is the need of the hour and some consensus should be arrived, atleast in the issues relating to terminology.Paul and Bhatt suggestions about wheezing below 5 year are mentioned below [3]:

a) Instead of terminologies like‘wheezing below 5y’, ‘pre-school wheezing’ or wheezing/asthma phenotypes an uniform non-threatening terminology (like‘early wheezer’) should be used to reduce the confusion.

b) Since the first viral wheeze is diagnosed as bronchiolitis, the subsequent wheezy episodes may be termed as‘episodic wheeze’if it is viral induced. This may further be subdivided as mild/moderate/severe depending on the severity and the frequency.

c) ‘Multitrigger wheeze’(instead of multiple trigger) may be used when the wheezy attacks are caused by various triggers (exercise, allergen exposure, passive smoking and exposure to cold air) in addition to viral infections [10].

d) When associated with personal or family history of atopy, a significant proportion of children with multitrigger wheeze may develop asthma, hence‘atopic multitrigger wheeze’ is an important phenotype which should be identified early.

e) Though it may be difficult to diagnose asthma, recurrent wheeze frequently precedes the diagnosis of asthma, and asthma is estimated to occur in more than 20% of infants with wheeze [11]. So if all the qualifying features for asthma and a response to a therapeutic trial with inhaled corticosteroids are present an early diagnosis of‘asthma’ should be made and this will prevent unnecessary inves-tigations and antibiotic usage. The points like differentiation of preschool wheeze from asthma, management of acute wheeze and non - pharma-cological conditions are well discussed. The article cautioned about red flag indicator features related to atypical wheezing conditions like symptoms since birth, growth faltering, clubbing, associated stridor and these situations warrant further investigations [2].

Transient wheezes are commonest form of wheeze, decrease lung function at birth, no airway hyper responsiveness, non-atopic, no immunoreceptors to virus, resolves by 3 years. Persistent non-atopic wheezes are lung function abnormal at birth, reduced in later life. non-atopic, airway hyper-responsiveness, peak flow variability, RSV induced wheeze due to alteration in airway tone. Better outcome than persistent atopic wheezes. Persistent atopic wheezes are lung function normal at birth but deteriorate with recurrent symptom, increased symptoms with increasing age, airway liability, atopic, abnormal immune responses to viruses., Risk factor: maternal asthma, maternal smoking, persistent rhinitis, eczema less than one year of age [12,13].

Environmental conditions that increase the rate of bacterial and viral infections are risk factors for transient wheezing, but its relationship to asthma remains unclear. Children with frequent simple colds and other common childhood infections in infancy are less likely to develop persistent wheezing in later childhood. Many preschool children with viral induced wheezing will outgrow these symptoms, and do not have asthma. Generally, asthma is identified by the presence of cough, wheeze and breathing difficulty, together with features of atopy (or a family history of atopy or asthma) and impaired lung function evidenced by spirometry. It is important to explain to parents/careers that wheezing in an infant or preschooler does not mean the child will have asthma or allergies by primary school age. In preschool-aged children with recurrent wheeze (e.g. four or more episodes per year), consider using the Asthma Predictive Index, to estimate whether children are likely to have asthma during primary school years [14,15].

Asthma Prediction Index has some major criteria and minor criteria. Major criteria are Diagnosis of asthma in one or both parent, Diagnosis of atopic dermatitis during the first 3 year of life, Sensitization against > 1 allergen, Minor criteria - Milk, egg, or peanut sensitization. Wheezing not associated with respiratory infections. Eosinophilia (> 4%). In the first 3 years of life if anyone who have 1 major criteria or 2 minor criteria is present in one episode, the possibility of asthma in 6 - 13 years is 59% but 2 episodes possibility is 77% [14,15]. Various asthma predictive indexes (APIs) have been developed in the last years to identify children at risk of asthma in preschool age. Epidemiologic studies have employed various risk factors associated with the development of asthma such as parental history of atopy, wheezing history, IgE levels and cytokines profiles.

API is a validated clinical model for childhood asthma defined on a cohort of children who wheeze at least one time during the first 3 years of life.

The primary criteria to identify the score are ≥ 4 episodes of wheezing in 1 year and the secondary are clinician diagnose of parental eczema or asthma, allergic sensitization to aeroallergen, wheezing unrelated to cold, eosinophilia ≥ 4 percent. A positive index was defined as at least major criterion plus at least one major or two minor criteria.

API sensitivity is low, suggesting that the test is poor for predicting later asthma development. Nevertheless, API has a high negative predictive value, meaning that it can identify children who have a low probability to develop asthma with a negative test [15].

A modified version (mAPI) was tested in a cohort of high risk children with a family history of allergy and/or asthma. A positive mAPI increased the probability to identify patient at risk to develop future asthma. In past 12 months, 4 wheezing episodes (> 24h), with at least 1 physician-confirmed, plus major criteria are 1. Parental history of asthma 2. Atopic dermatitis. 3. Sensitization to > 1 aeroallergen. Minor criteria are Allergic sensitization to milk, egg or peanut 2. Wheezing apart from colds. 3 Eosinophilia > 5% [14,15].

Differential diagnosis of Wheezing in Infants and Young Children

1. Viral wheezing 2. Asthma 3. Chronic aspiration (Gastro esophageal reflux diseases, GERD or swallowing dysfunction, silent aspiration may also be the cause of persistent wheezing in many infants and young children who do not respond to bronchodilator and steroid treatments. 3. Infections (*Pertussis, Mycoplasma, Chlamydia*, TB) 4. Broncho pulmonary dysplasia, BPD 5. Foreign body 6. Anaphylaxis 7. Cystic fibrosis (CF) 8. Vascular tracheal compression 9. Tracheobronchial malformations 10. Mediastinal masses 11. Bronchiolitis obliterans 12. Immune deficiency 13. Primary ciliary dyskinesia 14. Heart failure [15].

Diagnostic Approach

1. Adequate clinical history 2. Careful physical examination and 3. Appropriate use of further investigations.

The purpose of history-taking and physical examination is to confirm that the preschool child has a wheezing disorder, to identify the pattern of symptoms, the severity of the condition and any possible trigger factors, and to look for features suggestive of another diagnosis or associated condition.

Clinical History

History-taking is the main diagnostic instrument in the assessment of preschool wheeze in those who are not wheezing during the consultation. Accurately identifying wheeze from the history can be difficult since the term is used by parents and healthcare workers to describe a variety of symptoms [16,17-19]. Children with doctor-confirmed wheeze exhibit greater airways resistance than children with only reported wheeze [20], even though interobserver agreement between doctors is poor [21]. A video questionnaire may help parents to distinguish wheeze from upper airway noises [22]. Symptom scoring systems have been insufficiently validated to justify general use, and validated questionnaires for this purpose in this particular age group are needed. Noisy breathing is common among infants aged, 6 months but only a small proportion have wheeze [16]. Reported noisy breathing that responds to bronchodilator therapy is likely to be genuine wheeze and to be caused, at least in part, by constriction of airway smooth muscle [23].

During history taking you have to ask either parents or patients some questions like. Is there a pattern to the wheezing? Episodic; asthma, Persistent: congenital or genetic cause. Is the wheezing associated with a cough? Gastro-esophageal reflux diseases (GERD), Sleep apnea, Asthma, Allergies. Is the wheezing associated with feeding and vomiting? GERD. Is the wheezing associated with multiple respiratory illnesses? Cystic fibrosis/Immunodeficiency. Is the wheezing associated with a specific season? Allergies: fall and spring, Croup: fall to winter, Human metapneumovirus: December through April, RSV: fall to spring. Does the wheezing get better or worse when the patient changes position? Tracheomalacia/Anomalies of the great vessels should be considered. Wheezing after exercise may be exercise induced asthma [24].

Physical Examination (P.E)

No evidence is available regarding the usefulness of physical examination in wheeze assessment. Textbook states that the degree of airway narrowing can only be estimated crudely and indirectly, by assessing work of breathing (chest retractions, nasal flaring and use of accessory respiratory muscles) and by auscultation of the chest to assess the ratio of expiration to inspiration and the degree of wheeze [24,25]. Upper airway obstruction (in particular, nasal congestion) can contribute to respiratory distress. The aim of further physical examination is the identification of unusual or atypical features that would suggest another underlying condition [25].

P.E. often non-specific (often normal in asthma) 2. Shape of the chest, mobility, percussion 3. Ronchi, crackles, stridor, wheezing, regional differences in ventilation 4. Abnormal voice/crying 5. Productive/dry cough, metallic cough 6. Digital clubbing or cyanosis 7. Failure to thrive 8. Inspiratory stridor 9. extra thoracic airways-Polyphonic wheezing-diffuse obstruction 10. Monophonic wheezing in peripheral obstruction [24].

Investigation

The diagnosis of a preschool wheezing disorder can be made by history-taking alone. The type, invasiveness and number of any investigation largely depend upon the degree of morbidity and the doubt about the diagnosis [24]. This is a matter of clinical judgment. Most clinicians would agree that investigations are only justified when symptoms are present from birth, airway obstruction is abnormally severe, recovery is very slow or incomplete (resulting in prolonged or repeated hospital admission in the first few years of life), episodes continue in the absence of a viral infection or, sometimes, in cases when parents are very anxious [24]. There is little research evidence to guide the choice of investigations. Among infants and preschool children with severe persistent symptoms who were investigated according to a fixed diagnostic protocol, a considerable number of pathological findings were observed suggesting that invasive investigations are justified in this category [26,27].

Most infants with a first wheezing (even those with recurrent wheezing) do not need any investigations. All children with persistent cough should have their sweat electrolytes measured. The sweat test remains the standard diagnostic test for Cystic Fibrosis (CF), although CF gene mutation studies are being used increasingly. However, the necessity for CF screening is race-dependent. Other investigations include bacteriological studies on sputum if this can be produced; viral and mycoplasmal antibody levels; tuberculin skin testing; and in selected cases, immune function tests. All children should have a full blood count and white cell differential: persistent lymphopenia or neutropenia may be present even when the child is well [24,28].

Chest X-Ray, spirometry, CT scan of Chest and Fiber-optic Bronchoscope

Chest-X-Ray 1. Usually not necessary if history of "classic" asthma or, patient response to salbutamol and or steroid. Then only spirometry should be done but in preschool children, it is difficult, only possible in school aged children. But need other investigation when 1. Chronic cough (> 1 month) 2. recurrent pneumonia 3. persistent signs or symptoms despite therapy. CT scan of Chest is indicated if 1. persistently abnormal CXR 2. persistent signs or symptoms despite therapy 3. recurrent pneumonia. Sweat Test and CFTR Gene for Cystic Fibrosis Fiber optic Bronchoscope for biopsy and Congenital anomalies and also for broncoalveoler lavage fluid, infants with persistent wheezing may also have airway abnormalities that can be detected with bronchoscopy. [28] Some infant and preschool children need lung function test, though not available in every country and it is under evaluation. Studies showed that reduced forced expiratory flows were associated with wheeze. However, spirometry may not be possible in preschool children due to the difficulties in cooperating during the test [24]. To document airway hyper responsiveness, young children-friendly method like tidal breath method such as interrupter resistance (Rint), Forced Oscillation Test (FOT) and Impulse Oscillation Test (IOT) preferably with challenge by exercise followed by bronchodilator can be considered [29]. Cardiac ECHO, barium esophagography, angio-CT, angio-MR for CHD and anomalous blood vessel), Nasal brushing, FeNO for eosinophic airway inflammation and primary ciliary dyskinesia. Sleep study also do for obstructive sleep apnoea syndrome, OSAS [24,30].

Microbiological investigations

With current viral culture and PCR technology, a wide range of respiratory viruses can be identified, including the most common causative viruses [31]. There is no evidence, however, that this contributes to management, either in the short term (the acute episode) or in the long term, and it is recommended only for research purposes.

Tests of sensitization to allergens

The reported prevalence of sensitization in preschool children with wheeze in population studies varies widely [32-34]. Limited evidence is available regarding the prevalence of sensitization in preschool children presenting to healthcare workers with wheeze. One study comparing children aged 2 - 5 years with doctor-confirmed wheeze who were responding favorably to a bronchodilator to healthy non-wheezing children found that 32% of wheezy children gave positive skin-prick test results to one or more aeroallergens, compared to 11% of healthy children (likelihood ratio 2.9) [34]. Sensitization to inhalant allergens in 1-4-year-old children from general practice increases the likelihood of the presence of asthma at the age of 6 years by a factor of two to three [35]. Sensitization to hen's egg at the age of 1 year is a reasonable marker for allergic sensitization to aeroallergens at the age of 3 years, with a specificity of .90% and sensitivity of .30% [36]. Total serum immunoglobulin E measurements in early life are not predictive of outcome [37]. Although elevated eosinophilic cationic protein levels in preschool wheezes are associated with symptom persistence [38], the degree of overlap between groups renders such measurements useless for clinical purposes. Blood eosinophilia can be used as part of an asthma predictive index, but the predictive value of this index (in Particular, that of a positive result) is low [13].

Radiological examinations

There is no evidence that chest radiographs help in the diagnosis or treatment of preschool children with acute or recurrent wheezing [39]. Improvements in diagnostic imaging techniques may improve understanding of the mechanisms and long-term outcome of early childhood wheezing disorders by providing details about airway structure, airway wall thickness and airway caliber. At present, however, specialized imaging should be restricted to unusual or severe disease [24]. The plain chest x-ray is valuable in assessing the severity and distribution of lung involvement. Wide-spread changes such as bronchial wall thickening or inflammation involving several lobes suggest a systemic disorder such as cystic fibrosis (CF), ciliary dyskinesia, or an immunodeficiency disorder. Focal changes are more common if there is congenital abnormality, an inhaled foreign body or bronchial obstruction for some other reason. High resolution computerized tomography (HRCT) is more sensitive than plain radiographs at revealing bronchiectasis: it has largely replaced bronchography. It can also show localized areas of gas-trapping (hyperinflation) and interstitial fibrosis not evident on the chest x-ray, for example in children with bronchiolitis obliterans. CT scanning and magnetic resonance imaging are both helpful for assessing congenial anatomic abnormalities, such as sequestration or cystic adenomatoid malformations. Isotope scans provide useful evidence about regional ventilation and perfusion [24].

Measurement of gastro-esophageal reflux

Although gastro-esophageal reflux is common among infants and preschool children with chronic or recurrent respiratory symptoms [40], a beneficial effect of demonstrating and treating gastro-esophageal reflux in infants with wheeze has not been shown. Esophageal pH monitoring and a swallowing function study when reflux and silent aspiration are suspected, and the sensitivity and specificity of upper gastrointestinal series were insufficient to warrant its use as an alternative to 24-hour esophageal pH monitoring, and that video-fluoroscopic swallowing study confers several potential benefits [24].

Lung function test

There are no studies supporting the usefulness of pulmonary function tests in children with nonspecific symptoms, or in distinguishing between episodic and multiple-trigger wheeze. In the individual patient, however, determination of lung function (and bronchodilator response) in preschool children can help in the discrimination of common wheezing disorders from other conditions [41,42].

Exhaled nitric oxide and other assessments of airways inflammation

Elevated exhaled nitric oxide fractions (FeNO) have been found in wheezing infants, especially when they are atopic [43,44], and these normalize during treatment with ICSs [45] and montelukast [46,47]. FeNO in infants are affected by environmental exposures and genetic predisposition to atopy [48]. Reference values for FeNO are only available for children aged 0 - 4 years [49]. For uncooperative children aged, 4 years, measurement of FeNO has not been standardized and there is no evidence supporting the usefulness of measuring or monitoring FeNO in this age group. In one study found an association between high exhaled nitric oxide levels and a positive asthma predictive index in infants and toddlers with recurrent wheezing [13]. other tests of inflammation, such as analysis of induced sputum, have not been studied at all in preschool children.

Lung biopsy and bronchoalveolar lavage fluid study

Few studies have applied bronchoalveolar lavage or bronchial biopsy in preschool wheezing disorders. Most such investigations have been performed in children with severe or unusual clinical features, limiting the generalisability of findings. Both the degree of inflammation and the composition of the infiltrate have been variable, with neutrophils dominating in some studies, eosinophils in others and no evidence of either in others [50]. The only consistent finding was thickening of the reticular basement membrane in wheezy children [50], but not in infants (median age 12 months), even when reversible airflow obstruction and atopy were demonstrated [14]. A recent study showed that, by a median age of 29 months, some children with confirmed wheeze exhibit eosinophilic airway inflammation and reticular

basement membrane thickening, implying an age window at 12 - 30 months during which interventions aimed at preventing established airway inflammation might be possible [51]. Further studies of airway inflammation using bronchoalveolar lavage and bronchial biopsy in large groups of representative patients with episodic and multiple-trigger wheeze are urgently needed in order to improve understanding of the pathophysiology of preschool wheezing disorders. Unfortunately, such studies are hindered by ethical and practical constraints. At present, such invasive investigations should only be used in unusual cases in specialized centers.

Treatment

Treatment is based on reducing inflammation, maintaining pulmonary function and quality of life, preventing exacerbations and providing drugs free from adverse events or with minimal adverse events. National and international guidelines recommend inhaled corticosteroids as the first-choice treatment and, as alternative, leukotriene receptor antagonists. Long-acting β2 agonists are not recommended for this age group because there is a lack of studies proving their efficacy and safety the recommendation is to treat for 8 to 12 weeks and, if the response is negative, increase the medication dose, change the drug combination or review the diagnosis. [52]. There is consistent strong evidence that passive exposure to environmental tobacco smoke is harmful, in terms of both induction and exacerbation of preschool wheezes and should be firmly discouraged.

Allergen avoidance

Early life exposure to allergens (including aeroallergens and ingested food allergens) may lead to allergic sensitization and so potentially increase the risk of subsequent asthma, particularly in children at high risk (that is, children with a family history of asthma or atopy, particularly a parental history). It is unclear whether the risk of developing asthma in children is reduced by interventions to reduce exposure to single allergens (monofaceted), or whether multifaceted interventions targeting the reduction of more than one type of allergen exposure simultaneously will lead to a better outcome or be more effective.

Healthcare professionals should not recommend house dust mite aeroallergen avoidance for the primary prevention of asthma Healthcare professionals should not offer advice on pet ownership as a strategy for preventing childhood asthma. Maternal food allergen avoidance during pregnancy and lactation is not recommended as a strategy for preventing childhood asthma.

Breastfeeding should be encouraged for its many benefits, including a potential protective effect in relation to early asthma.

Weight reduction is recommended in obese patients to promote general health and to reduce subsequent respiratory symptoms consistent with asthma.

Obese and overweight children should be offered weight-loss programmes to reduce the likelihood of respiratory symptoms suggestive of asthma.

Parents and parents to be should be advised of the many adverse effects which smoking has on their children including increased wheezing in infancy and increased risk of persistent asthma [53].

Allergen avoidance is recommended when there is sensitization and a clear association between allergen exposure and symptoms. Allergen testing (at all ages) to confirm the possible contribution of allergens to asthma exacerbations. Avoidance of exposure to tobacco smoke is essential for children of all ages, as well as pregnant women. A balanced diet and avoidance of obesity are favorable. Exercise should not be avoided; asthmatic children should be encouraged to participate in sports, with efficient control of asthma inflammation and symptoms "Although it hasn't been studied very much, there is no evidence that food allergy has a role in persistent wheezing unless a baby also has eczema, "We know that babies with eczema are different. They are more prone to food allergies". A practical approach for preschool wheezers was recently proposed. In a preschooler with recurrent wheezing, the possibility of an underlying allergy should be assessed (by skin prick testing or determination of specific IgE). If allergy is not present, the wheezing should be considered as nonal-

lergic (viral-induced wheezing), and usually little maintenance treatment is needed, as most of the children will grow out of it. Therefore, treatment should be focused on treating the symptoms (with beta-agonists, short coursed of prednisolone, etc). If the symptoms are frequent a leukotriene receptor antagonist might be considered in the first place, before starting ICS. In contrast, if allergy is present (positive skin prick test or positive specific IgE) there is an increased risk that the child will continue wheezing beyond preschool age. In this case ICS might be necessary to control the underlying inflammation and to prevent symptoms. [14,52,53].

Allergen avoidance to prevent the development of symptoms, in either the population as a whole or high-risk subgroups (primary prevention), is not discussed here. The rationale for using environmental control in the treatment of preschool age wheezing to reduce existing symptoms (secondary prevention) is the notion that allergen exposure contributes to the severity of symptoms [54]. There is some evidence that exposure to allergens in early life increases the risk of wheezing, but this is dependent upon the allergen, the population and other environmental factors [55].

The combination of sensitization and high exposure to sensitizing allergen in early life is associated with significantly poorer lung function at the age of 3 years [56]. Sensitization to perennial allergens during the first 3 years of life is associated with reduced lung function at school age, with concomitant high exposure to perennial allergens early in life aggravating this [57]. High allergen exposure during preschool age enhances the development of airway hyper responsiveness in sensitized children with wheeze (with later-life sensitization and exposure having much weaker effects) [57]. Moving school-age atopic asthmatic children from their homes to the low-allergen environment of high-altitude sanatoria temporarily improves levels of markers of airway inflammation and asthma severity [58]. Some studies suggest that allergen avoidance at home may also be of some benefit amongst children of this age range [59,60]. It remains unclear, however, whether the required major reduction in exposure can be achieved in normal life and whether it would be of beneficial effect in young children since no studies on the effects of allergen avoidance have been performed in preschool children with wheeze [61].

Parent and patient education on wheezing

Parent and patient education is very important part of management of wheezing child but many of the physician ignore this , so need especial care. Parental knowledge and understanding of wheezing disorders in preschool children and their treatment is often inadequate (especially with respect to medication and the preceding signs and preventive actions) [62]; however, few educational studies in wheezy children have explicitly focused on the preschool age group. Many educational studies have included children aged as young as 2 years, but the age range of the study group is frequently not described, and there is rarely an analysis of whether outcomes are different in younger children. For example, the Cochrane Review on educational interventions in children and adolescents aged 2 - 18 years with asthma included no separate analysis of outcomes in younger children [63]. Indeed, of the 32 studies included in the review, only one studied preschool children exclusively [64]; two other studies that included children aged, 2 years were excluded.

Of the few studies in preschool children, those that have utilized multiple teaching sessions have shown improvements in morbidity, with more symptom-free days and better caregiver quality of life [64,65], as well as improved knowledge and improved self-efficacy [66], and outcomes similar to those in older children. These studies all used different formats: reading of a home booklet followed by practitioner review on next consultation [66], small group teaching by nurses [64] and home-based education [65]. One other large randomized controlled trial in preschool children with acute wheeze found no effect of an education programmed upon subsequent healthcare utilization, disability score, parent's quality of life and parental knowledge of asthma [67]. This study included two structured 20-min one-to-one sessions, the first during hospital attendance and the other 1 month later.

This raises the possibility that multiple educational sessions of longer duration might be more effective in preschool children. Virtually all studies in preschool children have targeted education at parents or careers. However, young children themselves may benefit from asthma education and practical training in skills. One study found that children aged 2 - 5 years who were exposed to a developmentally appropriate educational intervention that included a picture book and video tape showed improved asthma knowledge, as well as better compliance and health, compared to controls [68]. Therefore, although educating parents of preschool children with wheeze (and perhaps also the children themselves) appears effective, and is advised, more work is needed before specific educational approaches can be recommended.

Pharmacological therapy

Short-and rapidly acting b2-agonists inhalation are the most effective bronchodilators available, and, therefore, the drugs of choice for acute symptoms of wheeze. Double-blind placebo-controlled studies have demonstrated significant bronchodilator effects [69-72] and protective effects against bronchoconstrictor agents [73,74] in infants and preschool children treated with rapidly acting inhaled b2-agonist. Thus, infants possess functional b2-receptors from birth and stimulation of these receptors can produce the same effects as in older children, although paradoxical responses to inhaled b2-agonists have been reported in infants [21,75]. Oral administration of b2- agonist is also effective but is limited by systemic side-effects [76]. Intravenous infusion of b2-agonists has only shown an advantage over hourly inhaled treatment in very severe acute wheeze in young children [77]. After inhalation, b2-agonists are usually well tolerated. Side effects, such as muscle tremor, headache, palpitations, agitation and hypokalaemia, are only seen when high doses are used [78].

Single-isomer R-albuterol is theoretically preferable (although much more expensive) to the racemic mixture of albuterol since the S-isomer is therapeutically inactive [78]. There is, however, no evidence regarding the clinical effectiveness or superiority of the use of R-albuterol compared to the racemic mixture in this age group. Long-acting inhaled b2-agonists Formoterol and salmeterol have shown long-lasting bronchodilator and bronchoprotective effects in preschool children [73,79]. There are no published double-blind randomized placebo-controlled trials in preschool children on the addition of long-acting inhaled b2-adrenergic agents to ICSs.

Inhaled corticosteroids

The approach proposed in GINA document is focused on frequency and severity of wheezing episodes in correlation with inter critical symptoms and family history of atopy in order to define the risk of children to develop asthma. A child with two or three episodes in 1 year, each lasting less than 10days without inter critical symptoms has less probability to be asthmatic and to have benefit from a regular controller therapy. On the other hand, a child with frequent, long lasting symptoms, exercise induced wheezing and a family history of atopy is more probably an asthmatic subject for whom a low regular dose of ICS therapy may be consider the most appropriate treatment [80].

Furthermore, intermitted ICS was also proposed for children with intermittent viral induced wheeze without symptoms between episodes, if short acting β2 agonist (SABA) is not sufficient.

Treatment with ICSs may be considered for the treatment of current symptoms, or possibly for the prevention of progression of symptoms (disease modification). Each is considered in turn, as follows.

Inhaled corticosteroids in treatment of multiple trigger wheeze

An international group of experts convened at the 2013 ERS Annual Congress to discuss the current state of the art of the classification and management of preschool wheeze, and to formulate a consensus statement on the current value of phenotyping preschool wheezing disorders into EVW and MTW, and the treatment approach associated with it and recommended treatment are. In children with MTW, ICS are the first choice for daily controller therapy. In children with EVW, daily therapy may be considered with either ICS or montelukast if: the attacks are severe (requiring hospital admission or systemic corticosteroids); or the attacks are frequent; or the clinician suspects that interval symptoms are being under reported Any controller therapy should be viewed as a treatment trial, with scheduled follow-up. Discontinue treatment if there has been no benefit Take favorable natural history into account: taper down to lowest effective dose and discontinue treatment if the child has been symptom-free for 3 months on low-dose therapy.

Oral corticosteroids are not indicated in preschool children with an exacerbation of viral wheeze who do not need to be admitted to Hospital Oral corticosteroids are indicated only in preschool children admitted to hospital with very severe wheeze; even in this group, evidence to support the use of prednisolone is not robust. [6] ICSs in preschool children with multiple-trigger wheeze have reported a reduction in exacerbations by, 50% [81,82]. Compared to placebo, children using 200 mg? Day-1 fluticasone exhibit a mean of 5% fewer days with symptoms [76]. The dose-response relationship of ICSs in preschool children is not entirely clear. Dose-related effects have been shown for exacerbation rate on treatment with daily ICS doses of up to 400 mg? Day-1 beclometasone equivalent (or 200 mg? day-1 fluticasone) via pressurized metered-dose inhaler (pMDI) with spacer (pMDI-S) [81], without any further benefit from higher doses. Comparison of 0.25, 0.5 and 1.0 mg nebulizer budesonide daily, however, showed similar improvement to that with placebo in one study [83], whereas another suggested a dose relation in the range 0.25-1.0 mg nebulizer budesonide bid [84]. Two recent studies using inhaled fluticasone to treat wheezy infants and preschool children failed to find any improvement in lung function [85-87]. Atopic markers, such as a history of atopic dermatitis or allergic rhinitis, did not improve the chance of responding to ICSs [85].

However, preschool children with wheeze, selected based on the asthma predictive index for the prediction of persistent wheeze (including atopic dermatitis, allergic rhinitis and eosinophilia); respond to ICSs [40,49]. Local side-effects, such as hoarseness and candidiasis, are rare in preschool children [88,89], probably because medication is usually delivered by metered-dose inhaler with spacer (MDI-S) combination. Studies on the systemic side-effects of inhaled steroids have yielded inconsistent results. In a 1-yr study of 200 mg? Day-1 fluticasone in preschool children, height growth was similar in the fluticasone-treated children to that in the cromoglycate-treated children [88]. In another study, however, height growth was reduced by 1.1 cm after 2 yrs of inhaled 200 mg? Day-1 fluticasone compared with placebo [41].

The long-term consequences of inhaled steroid therapy on growth in preschool children have not been studied. Clinically relevant effects on adrenal function have only been observed in children receiving high doses of ICSs (.400 mg? day-1 beclomethasone equivalent) [86]. The risk of cataract was not increased in a study of 358 children aged 1 - 3 years receiving daily treatment with ICSs for o1 year [88]. No other potential systemic side-effects have been studied in preschool children. Thus, ICSs are effective in preschool children with multiple trigger wheezes, but the effect is smaller than that in older children, and there is some concern about the effect on height. This justifies a more critical approach to long-term ICS use in preschool children with multiple-trigger wheeze than in older children and adults with asthma. Many clinicians tend first to give a trial of ICS for a period of, 3 months. If there is no improvement, the treatment should not be stepped up, but stopped, and further investigations should be carried out in order to identify the cause of symptoms. If preschool children with multiple-trigger wheeze respond well to ICS therapy, it is unclear whether this is due to treatment or the natural resolution of symptoms. It is recommended, therefore, that treatment be withdrawn in children who become (almost) completely free of wheeze after ICS therapy. There are also clinicians who only continue treatment with ICSs in multiple trigger wheeze if symptoms recur after withdrawal and respond to reintroduction of the medication [90].

Montelukast in multiple-trigger wheeze

In two studies, montelukast provided protection against bronchoconstriction induced by hyperventilation with cold dry air, and improved airways hyper responsiveness by one doubling dose after 4 weeks, compared to placebo [91-93]. The bronchoprotective effect was independent of concurrent steroid treatment. In a multicentre study of 689 young children with multiple-trigger wheeze, montelukast improved symptoms and achieved a 30% reduction in exacerbations [91]. One recent study showed that nebulizer budesonide was more effective at reducing exacerbation rates in 2-8-yr-old children with multiple-trigger wheeze than oral montelukast [94]. Since preschool children were not analyzed separately, it is not known whether this difference in efficacy also applies to this age range. Montelukast in episodic (viral) wheeze. Daily use of montelukast over a 1-yr period reduced the rate of wheezing episodes in 549 children with episodic (viral) wheeze by 32% compared to placebo (number needed to treat 12) [95]. A trial of intermittent montelukast, started when patients developed signs of a common cold, compared with placebo in 220 children with episodic wheeze showed a 30% reduction in unscheduled health visits (number needed to treat 11), but no effect on hospitalizations, duration of episode, and b-agonist and prednisolone use [96].

Role of Cromones, Xanthenes, Anticholinergic agents and Antihistaminess

The Cochrane Review concluded that a beneficial effect of cromolyn therapy in preschool children with multiple trigger wheeze could not be proven [97]. Most studies were of poor quality, but one well-designed randomized controlled trial found no effect on symptom scores or exacerbation frequency in children aged 1 - 4 years with multiple-trigger wheeze [98].

Xanthenes

The Cochrane Review on the effects of xanthenes (theophylline and aminophylline) in the chronic treatment of children with asthma, the effects on symptoms and exacerbations of wheeze in preschool children were small and mostly no significant [99].

Anticholinergic agents

In the Cochrane Review it was concluded that inhaled ipratropium may be beneficial in older children [100], but there is no good evidence in preschool children [101].

Antihistamines

The antihistamines ketotifen and cetirizine have been studied in preschool wheeze. In the Cochrane Review it was concluded that children treated with ketotifen were 2.4 times as likely to be able to reduce or stop bronchodilator treatment as those treated with placebo. There were also less consistent benefits with respect to asthma symptoms and exacerbations [102]. There are no good studies comparing ketotifen to other asthma medications. Cetirizine was compared to placebo in a randomized trial in infants with atopic dermatitis, with the aim of preventing the development of asthma. At the age of 3 years, there was no difference in wheeze prevalence between the two groups. In a post-hoc analysis in a subgroup of patients radioallergosorbent test-positive for cat, house dust mite or grass pollen, there appeared to be a protective effect of cetirizine [103]. This needs to be confirmed in further studies. There are no studies of cetirizine in preschool children with wheeze. No studies have been performed on the effects of immunotherapy or influenza immunization in preschool children with wheeze.

Delivery devices/Spacer

In general, inhaled drug delivery is preferable to the oral and parenteral routes, in order to provide rapid relief of symptoms and minimize systemic side-effects. Inhalation therapy in preschool children is hampered by numerous factors, including narrower airways, increased turbulence, deposition high in the respiratory tree, and lack of cooperation and coordination. Although there is anecdotal evidence suggesting that some preschool children may be able to use dry powder inhalers effectively and reliably [104], there is consensus among experts that these devices should not be used in preschool children because they lack the ability to generate sufficiently high inspiratory flows [105]. Similarly, pMDIs cannot be used by preschool children without the use of a spacer device because of difficulties in the appropriate timing of the inspiratory effort. The two inhalation systems to be considered, therefore, are pMDI-S and nebulizer. A systematic review has shown that the delivery of inhaled b2- agonists by pMDI-S in acutely wheezy infants and preschool children is more effective than by nebulizer; recovery was quicker, and the risk of hospital admission was reduced by 60% [106]. There are no studies comparing the two delivery devices for long-term management. The economic, practical and hygienic advantages of pMDI-S over nebulizers support the use of pMDI-S as the preferred means of delivery of inhaled drugs in preschool children. Although there is no formal evidence to support this, there is consensus that cooperative children should use a spacer device with a mouthpiece wherever possible [105-107]. Noncooperative children aged, 3 years should use a spacer with a face mask; a tight face mask seal is considered important for optimal drug delivery. Crying children are unlikely to receive any drug to the lower airways [107-109].

Castro-Rodriguez., *et al*. recommendation

Daily ICS remains the most effective strategy for preschoolers with recurrent wheezing, especially those with asthma. For infants and preschoolers with moderate or severe episodes of EVW, the use of high intermittent ICS doses significantly reduces the use of OCS. There is no evidence of effect of intermittent ICS at low-moderate doses in preschoolers with mild EVW episodes. In preschoolers with asthma, there were no significant differences between daily vs. intermittent ICS in terms of asthma exacerbations with insufficient evidence to conclude to equivalence; however, for other asthma control outcomes, daily ICS works significantly better than intermittent ICS for older children. In preschoolers with recurrent wheezing or asthma, daily low-dose ICS seem to be superior to montelukast in reducing symptoms and exacerbations and improving lung function. No RCTs of LABA or LTRA as adjunct to ICS have been published in preschoolers. Pre-emptive use of OCS by parents at home at the first sign of symptoms is not effective in preschoolers with EVW.

In terms of ICS safety, monitor linear growth is essential given that individual susceptibility to these drugs may vary considerably with attention given to reducing the dose to the lowest effective dose and selecting the molecule with least growth suppression [110].

Bush., *et al.* recommendation

The evidence from cross sectional physiological work and studies of end bronchial biopsies in children with severe preschool wheeze is that multiple trigger wheeze is associated with more airflow obstruction than episodic viral wheeze, and the airway pathology (eosinophilic inflammation and remodeling) is similar to childhood and adult asthma.16 By contrast, episodic viral wheeze is not associated with evidence of eosinophilic inflammation, so the use of inhaled corticosteroids in this group is questionable [111].

- No treatment has been shown to prevent progression of preschool wheeze to school age asthma, so treatment is driven solely by current symptoms
- In all but the most severe cases, episodic symptoms should be treated with episodic treatment
- If trials of prophylactic treatment are contemplated, they should be discontinued at the end of a strictly defined time period because many respiratory symptoms remit spontaneously in preschool children
- Prednisolone is not indicated in preschool children with attacks of wheeze who are well enough to remain at home and in many such children, especially those with episodic viral wheeze, who are admitted to hospital [111].

Pragmatic regimen for trial of treatment

- **Step 1:** Trial of inhaled corticosteroids or montelukast in standard dose for a defined period, usually four to eight weeks.
- **Step 2:** Stop treatment; either there has been no improvement, in which case further escalation is not valuable, or symptoms have disappeared; in the latter case, it is not possible to know if this was spontaneous or as a result of treatment. If there is no benefit and the symptoms are troublesome, referral for consideration of further investigation is recommended.
- **Step 3:** Restart treatment only if symptoms recur; then reduce treatment to the lowest level that controls symptoms [111].

Recommendations

Hussein HR., *et al*. conducted a meta-analysis and found no benefit was seen with montelukast for preschool wheeze from the limited well-conducted RCTs over at least 12 months in preschool children with recurrent wheeze [112].

The European Pediatric Asthma Group recommendation for children 0 - 2 years.

Asthma ~ > 3 episodes in the previous 6 months:

- Start with β2 agonists as first choice.
- LTRA daily controller therapy for virus induced asthma symptoms.
- Inhaled steroids for persistent wheezing, especially if severe or requiring frequent oral corticosteroid therapy.
- Oral steroids (e.g. 1 - 2 mg/kg prednisone) for 3 - 5 days during acute and frequently recurrent obstructive episodes.
- Evidence of atopy lowers the threshold for use of ICS and they may be used as first-line treatment in such cases [52].

No justification for the administration of prednisolone to preschoolers without atopy who have episodic (viral) wheezing in either a community or hospital setting unless a severe clinical course is anticipated [113].

What treatment can be recommended for acute episodic wheezing in preschool children?

B2-Agonists that are inhaled through an appropriate spacer, with a mask if age appropriate, should be given. Intermittent use of leukotriene receptor antagonists may be beneficial, but comparisons with intermittent inhaled corticosteroids are needed. Prednisolone should be administered to preschoolers only when they are severely ill in the hospital. Intermittent, high-dose inhaled corticosteroids should not be used [114].

The recommended ICS in children aged less than five years is fluticasone 50 - 100 micrograms, twice daily, via a spacer and mask device, for up to three months.

If required, oral prednisolone can be given at 1 - 2 mg/kg per day, up to maximum of 40 mg, for three days. Where required, bronchodilator treatment should be with a short-acting beta-agonist (SABA). ERS J3Salbutamol, 100 micrograms, as required, to a maximum of 800 micrograms per day, is recommended for children [115].

Dutch Pediatric Respiratory Society recently recommended using ICS as the first choice of maintenance treatment in all preschool children, irrespective of phenotype [116]. A similar recommendation was issued by GINA (Global Initiative for Asthma) [117]. The British Thoracic Society guideline also does not provide a phenotype-directed treatment recommendation for preschool children with recurrent wheeze [118].

Any preschool child with troublesome recurrent wheeze could be started on either ICS or montelukast. The most consensus group agrees that all children using controller therapy must be reviewed regularly to evaluate the response to treatment and any changes in symptom pattern. Atopy does not predict the response to controller therapy. Oral prednisolone is not required in the large majority of preschool children with an acute wheeze exacerbation and should be reserved for those with most severe symptoms. The evidence base for understanding the pathophysiology and treatment of preschool wheezing is still limited.

The "Ten Commandments" of treating preschool children who wheeze [119]:

1. Wheezing that has a very early age of onset (< 1 year) is likely to be viral in origin.
2. All preschool children who wheeze must undergo an allergy test, preferably a skin-prick test (SPT).
3. A family history of asthma suggests that the child has asthma.
4. The presence of a cough is important in the diagnosis of asthma.
5. Use the term "asthma" if it fits.
6. Environmental control, and patient and parent education are necessary for all asthmatics, and controller medication may be required [inhaled corticosteroids (ICS) or montelukast].
7. Treat virus-induced wheezing with montelukast for 14 days.
8. Avoid the use of oral corticosteroids when treating virus- induced wheezing exacerbations.

Asthma in preschoolers: diagnosis and treatment GINA Guidelines

The 2016 GINA guidelines [80] acknowledged that asthma may be clinically evident in children below the age of 5 years. Given that a definite diagnosis of asthma in preschool children may be complicated by such confounding factors as recurrent respiratory tract infections and given the paucity of tests available for this age group, the GINA expert panel devised a tentative risk characterization for a diagnosis of asthma in children focused on symptom severity and frequency, personal and family characteristics suggestive of atopy, and response to trial treatment with inhaled corticosteroids.

According to the GINA guidelines [80] while short-acting beta 2 agonists are recommended for all asthma patients when needed, therapeutic strategies in preschool children with recurrent wheezing should be frequently reviewed and be tailored to the characteristics of each child because he/she may be affected by early asthma as opposed to transient viral wheezing. Regular therapy with inhaled corticosteroids is the first option in preschool children presenting with recurrent wheezing if episodes are frequent and/or severe, or if interval symptoms are report. Therefore, while inhaled corticosteroids were previously administered only in young children who presented with early signs of asthma, the most recent position documents recommend inhaled corticosteroids also in viral wheezes, either with low-dose regular treatment or with a high-dose intermittent strategy. The GINA document confirms the use of Systemic Corticosteroids in the treatment of severe exacerbations in children aged 5 years or younger. In preschool children, treatment with oral corticosteroids may be beneficial in those with frequent severe exacerbations, mostly those with an atopy background, and in those requiring emergency department or hospital admission and are closely monitored [80].

Recommendation from this review

Most preschool wheeze is not same as asthma and should be considered as a separate entity, diagnosis is clinical and is achieved by exclusion of other serious pathologies, and it is primarily a neutrophilic disease while asthma is an eosinophilic disease.

Inhaled Corticoid steroid (ICS), the first-choice maintenance therapy for MTW. In EVW, either ICS or montelukast may be prescribed. Any treatment given should be viewed as a therapeutic trial; regular scheduled follow-up is essential to review the response to treatment. If there is no benefit of the controller therapy started after 2-3 months, it should be discontinued, and the child investigated further. If symptoms resolve during controller therapy, this may be due either to an effect of treatment or to the favorable natural history of preschool wheezing. Preschool children with an acute exacerbation of wheeze can be treated with only inhaled bronchodilators. It is also recommended not to treat children who do not require hospitalization with systemic corticosteroids, and to Limit the use of prednisolone in hospitalized patients to those with very severe wheeze and dyspnea, requiring frequent inhalations and supplemental oxygen or respiratory support.

1. A diagnosis of asthma in children 5 years and younger may be difficult - label as wheezing.
2. Ban maternal and environmental smoking.
3. It can be based on symptom patterns and on a careful clinical assessment of family history and physical findings.
4. Asthma education should be provided to parents and patients..
5. For patients with asthma, the goal of treatment is to control the clinical manifestations of the disease for prolonged periods.
6. The prolonged use of high doses of inhaled or systemic glucocorticosteroids must be avoided.
7. Use a pressurized MDI with a valved spacer.
8. Inhaled steroids in children 5 years and younger are effective.
9. Rapid-acting inhaled β2-agonists are the preferred reliever treatment.
10. A low-dose inhaled glucocorticosteroid is recommended as the preferred initial treatment to control asthma.
11. If it does not control symptoms (check technique & adherence!), double the initial dose of glucocorticosteroid.

Ethics Approval and Consent to Participate

Since it is a review paper, the study did not need ethical committee approval.

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