Review Article

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An update on management of recurrent wheezing disorders in Hong Kong preschool children

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Abstract

Recurrent wheezing disorder is a common problem in preschool children. It can be classified by its temporal pattern into episodic (viral) wheeze and multiple-trigger wheeze. A detailed history is important in clarifying the pattern of wheeze and quantifying the risk factors such as household smoking and family history of atopy. Allergen testing is useful in guiding subsequent management. Inhaled short-acting beta-2 agonist remains the first-line treatment for acute wheeze while ipratropium bromide and oral corticosteroids may be added in severe cases. For recurrent wheeze (3 times/year or more), maintenance therapy with inhaled corticosteroids for multiple-trigger wheeze, or montelukast for episodic (viral) wheeze should be initiated. Treatment response as documented in a diary must be assessed after 3 months and a decision as to whether to stop the medication and observe or to start another add-on medication, or to refer to specialist for further investigation must be made.

Keywords: Asthma, children, preschool, wheeze

Introduction

Recurrent wheezing disorder is commonly found in preschool children. It is a problem encountered frequently by medical practitioners throughout the world. Recently, guidelines have been published by the European Respiratory Society Task Force[1] and the PRACTALL consensus report.[2] We aim to review and summarise the literature on management of recurrent wheezing disorder in preschool children aged below 6 years, and to produce a practical recommendation to medical practitioners in Hong Kong.

Epidemiology

Population studies showed that about 1 in 3 children had at least one wheezing episode before 3 years of age, with the cumulative prevalence about 50% by 6 years of age.[3,4] Concerning the long-term outcome, studies showed that for children with persistent asthma, 25% started to wheeze by 6 months of age, and 75% by 3 years of age.[3,5-7] For those having more severe early wheeze, 50% became symptom-free by 5 years of age, 70% by 10 years, but only 57% by 20 years. This signified a tendency for relapse during adolescence.[8-10] Airway hyperresponsiveness is known to be associated with prematurity,[11] and it was reported that airway hyperresponsiveness might occur in 50-60% of adolescents born prematurely with bronchopulmonary dysplasia.[12-14] Risk factors for symptoms continuing into early adulthood include female sex, passive smoking during infancy, and early sensitisation to allergens.

Classification

According to the Global Initiative for Asthma (GINA) guidelines, asthma is a syndrome with highly variable clinical spectrum, characterised by airway

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inflammation.[15] However, the airway inflammation has been poorly studied in preschool children, and may be absent in very young children with wheeze.[16] It is also important to realise that causative factors for recurrent wheeze vary from child to child and within a child over time. Both genetic and environmental factors determine an individual's phenotype. Hence, a symptom-only descriptive approach might be the best approach (Table 1), in which recurrent wheeze can be classified either by its temporal pattern, i.e. episodic (viral) wheeze and multiple-trigger wheeze;[1,17,18] or by its duration, i.e. transient, late-onset and persistent wheeze.[1,3,5,6] For clinical purposes, it is recommended to describe wheeze in terms of its temporal pattern, classifying as episodic (viral) wheeze or multiple-trigger wheeze as the duration-based classification i.e. transient, late-onset & persistent wheeze could only be made retrospectively.

For episodic (viral) wheeze, it occurs in discrete episodes, with the child being well between episodes. It usually declines over time, disappearing by the age of 6 years. It is most common in preschool children, usually associated with viral upper respiratory infection such as rhinovirus, RSV, parainfluenza virus and adenovirus.[19] Factors affecting the frequency and severity of wheeze include atopy, prematurity, tobacco smoke, severity and the causative agent of the first wheezing episode.[20-26]

For multiple-trigger wheeze, the child wheezes in response to triggers other than viral upper respiratory infection, including tobacco smoke, allergen exposure, mist, crying, laughter and exercise.[17] It is believed that multiple-trigger wheeze in preschool children reflects chronic allergic airway inflammation.

Assessment

A detailed history should be taken to clarify the presence of wheeze, the pattern and triggers of wheeze, the frequency and severity of acute exacerbations, and the frequency of using rescue medication. Personal and family history of atopy, and household smoking should be assessed.

Physical examination should include assessment of the child's growth parameters and the degree of airway narrowing, which can be estimated indirectly by assessing the work of breathing (chest retractions, nasal flaring, and use of accessory respiratory muscles) and the expiration to inspiration ratio.

Allergen testing such as skin-prick test can be done to confirm any allergen sensitisation. One study showed that 32% of preschool wheezers had positive skin-prick test results to aeroallergens, compared to 11% of healthy children (likelihood ratio 2.9).[27] Aeroallergen sensitisation in preschool children

Table 1. Classification of wheeze

Temporal pattern of wheeze

- Episodic (viral) wheeze: Wheezing during discrete time periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes
- Multiple-trigger wheeze: Wheezing that shows discrete exacerbations, but also symptoms of troubling cough and/or shortness of breath between episodes

Duration of wheeze

- Transient wheeze: Symptoms that commenced before the age of 3 years and are found (retrospectively) to have disappeared by the age of 6 years
- Persistent wheeze: Symptoms that are found (retrospectively) to have continued until the age of >6 years
- Late-onset wheeze: Symptoms that start after the age of 3 years

increases the likelihood of asthma at 6 years of age by a factor of 2.[28] Elevated eosinophil level in preschool wheezers was associated with symptom persistence.[29] However, serum IgE was not predictive of the outcome.[30] Allergen testing by either skin prick test or specific IgE is advised for patients requiring long-term treatment and follow-up.

Studies showed that reduced forced expiratory flows were associated with wheeze.[31-34] However, spirometry may not be possible in preschool children due to the difficulties in cooperating during the test. To document airway hyperresponsiveness, 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. In addition, significantly higher exhaled nitric oxide fractions (FeNO) have been found in preschool wheezers, as compared to the healthy subjects. The exhaled air samples, at least 5 breaths collected in an inert bag with a face mask tightly fitted infants' nose and mouth during tidal breathing under sedation, were analysed by a fast response NO analyzer within 1 hour. Elevated FeNO is associated with atopy with its implication of higher risk for developing asthma.[35,36] Detecting elevated FeNO can help evaluating airway inflammation and hence guide the optimisation of ICS therapy. However, there are no reference values available for children aged below 4 years.[37]

Few studies were published for bronchoalveolar lavage (BAL) or bronchial biopsy in preschool wheezers, with limited generalisability of findings. Variable degree of inflammation and infiltrate composition was found, with neutrophils dominating in some studies while eosinophils dominating in others.[38] BAL and bronchial biopsy should be therefore reserved for unusual cases.

Although gastro-esophageal reflux was reported to be found in recurrent wheezers, no beneficial effect of treating gastro-oesophageal reflux were shown on recurrent wheezing.[39]

Management

The management of recurrent wheezing disorder consists of three parts, including general measures, the treatment for acute wheezing episodes, and the maintenance therapy (Figure 1).

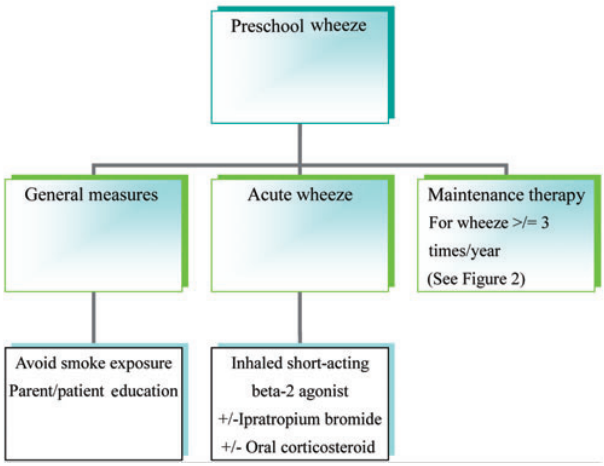

Figure 1. Management of recurrent wheeze in preschool children.

A) General measures

1) Environmental manipulation

There is strong evidence that passive smoking is deleterious to preschool wheezers in both induction and exacerbation of wheeze and therefore should be firmly discouraged.[40] There is evidence that high allergen exposure in early life is associated with poorer lung function at 3 years of age, measured by specific airway resistance with body plethysmograph.[41] High allergen exposure in preschool age was associated with increased airway hyper-responsiveness, defined as the histamine concentration causing 20% decrease in FEV1 of less than 0.85 mg/ml in bronchial histamine challenge test.[42] Some studies suggested that allergen avoidance at home was beneficial for school-age asthmatic children,[43,44] but there are no studies for allergen avoidance performed in preschool children.

2) Parent and patient education

Educational studies in preschool children showed that those with multiple teaching sessions to parents had more symptom-free days, better caregiver quality of life and improved knowledge.[45-47] One study found that preschool children with appropriate education themselves, including picture book and video tape, showed better compliance and health.[48] Therefore, effective educational program for both parents and children is beneficial.

B) Acute wheezing episode

Inhaled short-acting β2-agonist is the most effective bronchodilator for acute wheeze. RCTs have demonstrated its bronchodilatory effect in preschool children.[49-52] Side-effects, such as muscle tremor and hypokalaemia, are only seen when high doses are used. Oral β2-agonist is limited by its systemic side-effects.[53] Addition of ipratropium bromide to short-acting β2-agonists may be considered in patients with severe wheeze.

Oral corticosteroid should also be considered for severe wheezing attack in preschool children. Data for preschool children are currently lacking although a systematic review of systemic corticosteroids in hospitalised children with acute asthma found that corticosteroid-treated school-age children were 7 times more likely to be discharged early than placebo, and 5 times less likely to relapse in 1-3 months.[54]

C) Maintenance therapy

Maintenance therapy should be initiated for children with recurrent wheezing episodes for at least 3 times per year (Figure 2).

1) Multiple-trigger wheeze

Inhaled corticosteroid (ICS) is recommended as maintenance therapy for preschool children with multiple-trigger wheeze. A systematic review of RCTs of inhaled corticosteroids in preschool children with multiple-trigger wheeze showed significant improvement in symptoms, exacerbation rates, lung

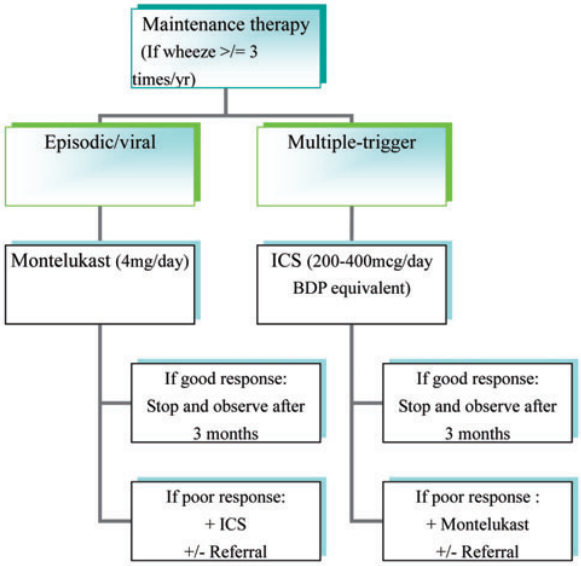

Figure 2. Maintenance therapy to preschool wheeze.

function and airway hyper-responsiveness.[55] In a *post hoc* analysis of 2 RCTs, better response to fluticasone was shown in those with family history of asthma, compared to those without family history of asthma.[56] Studies on systemic side-effects of ICS yielded inconsistent results. A study of fluticasone (200 mcg/day) in preschool showed similar height growth after 1 year compared with cromoglycate group.[57] In another study of fluticasone (200 mcg/day), height growth was reduced by 1.1 cm after 2 years compared with placebo.[58] A meta-analysis suggested that moderate doses of inhaled beclomethasone dipropionate (BDP) and fluticasone caused a decrease in linear growth velocity of 1.51 cm/year and 0.43 cm/year respectively.[59]

Although ICS is effective in preschool children with multiple-trigger wheeze, its effect is smaller than in older children. Therefore a more critical approach to long-term ICS in preschool children is advised. It is recommended to start with initial maintenance of 200 mcg/day BDP equivalent. The ICS equivalent table is shown in Table 2.[15] ICS should be withdrawn if the response is good after giving ICS for 3 months,

Table 2. Estimated equipotent daily doses of inhaled corticosteroids

Drug	Daily dose (microgram)	Relative potency
Beclomethasone dipropionate	200-500	1
Budesonide*	200-400	1
Mometasone furoate*	200-400	1
Fluticasone	100-250	2
Ciclesonide*	80-160	2.5

* Approved for once-daily dosing in mild patients.

to judge whether symptoms resolve or continuous treatment is needed. ICS may be resumed if symptoms recur after withdrawal. If no improvement is seen after giving low dose ICS for 3 months, risk factors for poor control such as poor drug compliance, inappropriate inhalation technique, smokers at home, etc. should be evaluated before stepping up to 400 mcg/day BDP or equivalent. An option would be to add leucotriene modifier such as montelukast, a useful add-on therapy with a different and complimentary mechanism of action from ICS.[60] Two studies showed that montelukast provided protection against bronchoconstriction caused by cold air in multiple-trigger wheeze.[61,62] One study showed that montelukast improved symptoms and reduced exacerbations by 30%.[63]

For long-acting beta-2 agonist, such as salmeterol, its efficacy is not well documented in children. Safety concerns have been raised recently, suggesting the use to be restricted to add-on therapy to ICS when indicated.[64] Due to the lack of supporting evidence, other alternatives including cromones, ketotifen, xanthines and immunotherapy are not recommended for preschool children with wheeze. For treatment resistant cases, referral to specialist for further investigation should be considered.

2) Episodic (viral) wheeze

Montelukast is recommended as maintenance therapy for preschool children with episodic (viral) wheeze, with a daily dose of 2-5 mg, depending on age. It has been shown to provide bronchoprotection and reduce airway inflammation.[61,63,65,66] Daily use for 1 year was shown to reduce the rate of episodic (viral) wheeze by 32% compared to placebo.[67] A trial of intermittent montelukast for episodic wheeze, given for a minimum of 7 days or until symptoms resolved for 2 days, showed 30% reduction in health visits.[68] However, in another RCT, montelukast given for 24 weeks did not improve post-RSV bronchiolitic respiratory symptoms.[69]

After giving montelukast for 3 months for those with good response, it is recommended to stop the medication to judge whether symptoms have resolved or continuous treatment is needed. If the response is poor after 3 months, add-on therapy with ICS should be considered especially for those with personal or family history of atopy. Systematic reviews concluded that intermittent high-dose ICS (1.6-3.2 mg/day budesonide) provided some benefit, with 50% reduction in requirement for oral steroids in episodic wheeze.[55,70] A recent study on intermittent fluticasone (1.5 mg/day) for less than ten days for episodic wheeze has shown a reduced severity and duration of symptoms.[71] For treatment resistant cases, referral to specialist for further investigation should be considered.

Treatment devices

Dry powder inhalers should not be used in preschool children because they cannot generate sufficiently high inspiratory flows. Meter dose inhaler (MDI)-spacer combination or nebuliser can be considered. A systematic review has shown that the delivery of inhaled β2-agonists by MDI-spacer in acutely wheezing preschool children is more effective than nebuliser, with quicker recovery and reduced risk of hospital admission by 60%.[72] Therefore, an MDI-spacer combination is recommended to deliver inhalation therapy in preschool children. For preschool children, a small volume spacer with the least dead space from the mask, e.g. aerochamber, should be used. One should choose the smallest mask that fits

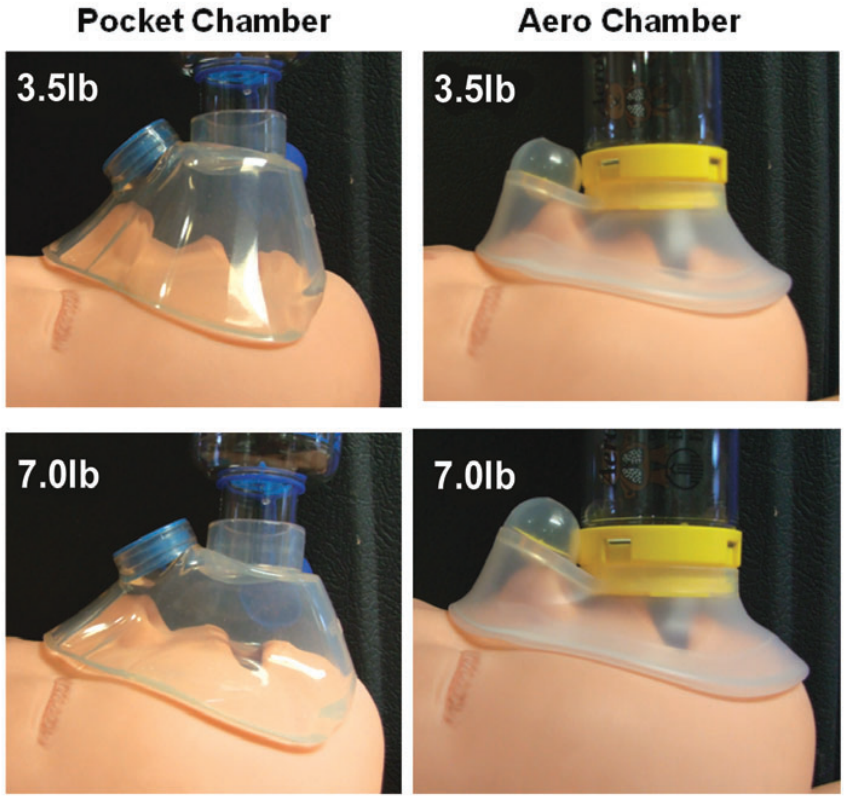

Figure 3. Effect of different pressure levels on different masks (Note the difference of mask rigidity and pressure impacting on mask volume or dead space).

the face and can be readily compressed to minimise the dead space in the mask as shown in Figure 3. There is consensus that cooperative children should use spacers with mouthpiece, while uncooperative children should use spacers with tight-fitting face mask. Plastic spacers should be treated and cleansed with detergent followed by drip-dry before use to reduce their electrostatic charge.

Monitoring

Monitoring the signs and symptoms of wheezing disorders involves parents, children and physicians. Symptoms diary like asthma diary should be given to parents for better documentation of the frequency and severity of respiratory symptoms. Drug compliance as well as inhaler technique should be checked, especially if symptom control is poor.

Conclusion

Recurrent wheezing disorder is commonly found in preschool children. A systematic outcome-based approach supported by current evidence would help optimise management in this common disorder.

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