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CME article

The Management of Pre-School Wheeze

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EDUCATIONAL AIMS THE READER WILL:

- Become familiar with diagnostic and labelling difficulties in pre-school children with wheeze
- Be able to discuss the management of preschool wheeze
- Be aware of the current evidence regarding different treatment strategies for pre-school wheeze.

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SUMMARY

Wheeze, a common symptom in pre-school children, is a continuous high-pitched sound, with a musical quality, emitting from the chest during expiration. A pragmatic clinical classification is episodic (viral) wheeze and multiple-trigger wheeze. Diagnostic difficulties include other conditions that give rise to noisy breathing which could be misinterpreted as wheeze. Most preschool children with wheeze do not need rigorous investigations. Primary prevention is not possible but avoidance of environmental tobacco smoke exposure should be strongly encouraged. Bronchodilators provide symptomatic relief in acute wheezy episodes but the evidence for using oral steroids is conflicting for children presenting to the Emergency Department [ED]. Parent initiated oral steroid courses cannot be recommended. High dose inhaled corticosteroids [ICS] used intermittently are effective in children with frequent episodes of moderately severe episodic (viral) wheeze or multiple-trigger wheeze, but this associated with short term effects on growth and cannot be recommended as a routine. Maintenance treatment with low to moderate continuous ICS in pure episodic (viral) wheeze is ineffective. Whilst low to moderate dose regular ICS work in multi-trigger wheeze, the medication does not modify the natural history of the condition. Even if there is a successful trial of treatment with ICS, a break in treatment should be given to see if the symptoms have resolved or continuous therapy is still required. Maintenance as well as intermittent Montelukast has a role in both episodic and multi trigger wheeze. Good multidisciplinary support and education is essential in managing this common condition.

DEFINITIONS

Wheeze has been defined as a continuous high-pitched sound, with musical quality, emitting from the chest during expiration.[1] Wheezing is a common symptom in pre-school children, with almost half of children having a least one episode of wheeze by the age of 6 years.[2] Much progress has been made in classifying wheezing illness in older children and categorising it in terms of stepwise management, based on several national[3] and international[4] guidelines. Pre-school wheeze has been defined in epidemiological studies, according to its natural history.[2] Symptoms with onset before 3 years may be termed transient (resolved by 6 years) or persistent (continuing after 6 years). Late onset wheeze refers to symptoms which commence after 3 years and persist. Whilst this classification may help with understanding the mechanisms and natural history of wheezing illness in young children, it does not help with clinical management. A pragmatic clinical classification has therefore been proposed[1] which divides wheezing illness in pre-school children into episodic (viral) wheeze and multiple-trigger wheeze and we will use these terms in this review. Children with episodic (viral) wheeze are well between episodes. The most common viral triggers include rhinovirus, respiratory syncytial virus (RSV), coronavirus, human metapneumovirus, parainfluenza virus and adenovirus,[5] though in

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Abbreviations: BAL, Bronchoalveolar lavage; ED, Emergency department; ICS, Inhaled corticosteroids; LTRA, Leukotriene receptor antagonist; Mcg, micrograms; Mg, milligrammes; RCT, Randomised controlled trial.

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routine clinical practice microbiological diagnostic studies are rarely performed.

Young infants, with episodic (viral) wheeze may be difficult to distinguish from those with acute bronchiolitis, not least because the definition used for the clinical syndrome of bronchiolitis varies in different parts of the world. In the UK, Australia and parts of Europe bronchiolitis is defined as the presence of upper respiratory tract symptoms with coryza and cough preceding the abrupt onset of lower respiratory symptoms, with a variable degree of respiratory distress, feeding difficulties and hypoxia. On auscultation there are widespread crepitations. Wheeze may or may not be present. In most of North America and parts of Europe the term bronchiolitis is generally applied to all conditions involving expiratory wheeze and evidence of a respiratory viral infection such as rhinorrhoea and cough.[6] Whether or not the initial episode is classified as bronchiolitis is irrelevant but recurrent wheezing is common following initial infection with RSV and other viruses.[7,8] In the case of RSV, most studies show that this has disappeared by the age of 11 yrs, and is not associated with an increased risk of atopy.[9] For rhinovirus, such long-term data are lacking. Episodic (viral) wheeze most commonly declines over time, disappearing by the age of 6 yrs, but can continue as episodic (viral) wheeze into school age, change into multiple-trigger wheeze or disappear at an older age. Other factors that influence the frequency and severity of episodes include the severity of the first episode, atopy, prematurity and exposure to tobacco smoke.[1]

Viral infections are also one of the most important precipitants of multiple-trigger wheeze but factors such as passive smoking exposure, allergens and exercise are also important.[1] Children with multiple-trigger wheeze may therefore have symptoms which are not confined to discrete episodes (interval symptoms) such as nocturnal cough and exercise induced dyspnoea. The phenotypes defined in the task force report[1] are not exhaustive, and individual patients may not fit into the categories described. Also there can be an overlap between phenotypes and patients can move from one phenotype to the other.[10]

WHEN IS A WHEEZE NOT A WHEEZE?

Parents may ascribe a different meaning to the word "wheeze" to that understood by health professionals – leading to over-diagnosis of wheezing illness. Parents' understanding of wheeze is often different from the definition used in epidemiological studies[11] and many parents are better at locating sounds rather than labelling them.[12] In a series of interviews,[13] parents were first asked an open question, asking how they would describe their child's noisy breathing, followed by specific questions asking them to select the medical terminology which they thought was the best description. Finally they were asked to select the sound closest to the noise made by their child, from a number of options. Over half of parents used the word wheeze initially but only one third were still using the term at the end of the interview - whereas the use of the word "ruttle" doubled. Ruttle (also known as "rattle") is lower in pitch with a rattling quality and lacking any musical features. Parents may be able to feel this noise as a vibration over the baby's back. Ruttle may be related to excessive secretions or to abnormal tone in the larger airways.[13] Wheeze and ruttle have quite distinct acoustic patterns when assessed objectively using acoustic analysis.[14] There is also a different response to ipratropium when assessed by computerised breath sounds analysis with a clear reduction in breath sounds intensity evident at 5 minutes in infants with ruttles but not until 20 minutes in those with wheeze, suggesting a different pathophysiology.[15] Even amongst health professionals there are inter observer variations in assessing wheeze using a stethoscope.[16] Furthermore, lung function[17] and bronchoscopic findings[18] are different in preschool children with parent reported wheeze as compared to doctor confirmed wheeze. Risk factors and outcomes for different respiratory sounds are also different when children are followed up to school age.[19] In view of these difficulties clinicians should undertake a detailed clinical assessment of each child, which does not place undue weight on any one symptom.[20]

PREVALENCE

The prevalence of wheezing illness in pre-school children in the UK seems to be increasing. Silverman *et al.*[21] conducted a repeated parent-completed postal questionnaire survey of the prevalence of respiratory symptoms in 1990 and 1998. The number of pre-school children reported to have one or more episodes of wheeze increased from 16% to 29%. This is less than the prevalence of 48% reported from the US.[2] The difference may be accounted for by the use of a different methodology in the two studies. Silverman *et al.*[21] showed that the prevalence of episodic (viral) wheeze increased from 9% to 19% and multiple-trigger wheeze from 6% to 10%. The associated healthcare costs of caring for pre-school children with wheezing illness in the UK has been estimated at £53 million *per annum*.[22]

DIFFERENTIAL DIAGNOSIS

Airway resistance is inversely proportional to the fourth power of the radius of the airway (Poiseuille's Law). It follows therefore that young children, who have smaller airways are much more likely to wheeze and that the prevalence of wheeze will fall off steeply as children get older and their airways radius increases. In young children, any inflammatory process, causing airway oedema, may narrow the airway, leading to wheeze. Children who have smaller airways, to start off with (for example infants of smoking mothers) are more vulnerable.[2] It follows that wheezing is a common symptom in young children and has a wide differential diagnosis. Table 1 lists a number of differential diagnoses and the appropriate investigations. Most children with a characteristic history and examination findings in keeping with episodic (viral) wheeze or multiple-trigger wheeze do not need further investigations. Skin prick testing may identify triggers in multiple-trigger wheeze and help with allergen avoidance. Children should be investigated further if there are features in the history suggestive of other pathology, some of which have been listed in Table 1.

Saglani *et al.*[28] reported a study of children with severe recurrent wheeze who were rigorously investigated, including bronchoscopy with bronchoalveolar lavage (BAL) and endobronchial biopsy. BAL fluid was analysed for eosinophils and lipid laden macrophages and subjected to bacterial culture. In this series of 47 children, "asthma" (based on histological appearances or BAL eosinophils) was diagnosed in 21%, gastro-oesophageal reflux in 27% and predominant infection in 50%. Such intensive investigations are only justified in severe, debilitating disease. The findings on biopsy and BAL analysis do not differ between atopic and non-atopic children with multiple-trigger wheeze.[29]

MANAGEMENT

Primary prevention

Primary prevention of asthma is a highly desirable objective but, for practical reasons, can only be attempted in families where there is a strong history of atopy and the intervention may need to be commenced prenatally. Most interventions, assessed in randomised controlled trials, have assessed allergen avoidance – most commonly reducing exposure to house dust mite.[30–33] These interventions achieve a reduction in house dust mite allergens in the child's immediate environment, but not a reduction in symptoms of wheeze. A Cochrane review has concluded that

Table 1
Differential diagnosis of wheezing illness in pre-school children and suggested investigations

Diagnosis	Key clinical features	Diagnostic and supportive tests
Episodic (viral) wheeze	Clear history of viral trigger	Thorough history and examination. Exclusion of other likely diagnoses (see below).
Multiple-trigger wheeze	Strong family history of atopy.	Thorough history and examination. Skin prick testing may be useful in multiple-trigger wheeze
Viral infection	Features of bronchiolitis – corryza, hyperinflation and basal crackles.	Nasopharyngeal aspirate for immunofluoresence, PCR or viral culture.
Gastro-oesophageal reflux[23]	Vomiting or poor weight gain.	pH study. Contrast swallow. Bronchoscopy for lipid laden macrophages
Inhaled foreign body	Prior episode of coughing or choking (not always present[24]). Chronic cough.	Chest radiograph. Rigid bronchoscopy.
Immune deficiency	Wheeze with infections which are Severe, Persistent, Unusual or Recurrent (SPUR).	Initially, immunoglobulins, functional antibodies and T & B cells.
Cystic fibrosis	Cough in the first weeks of life. Poor weight gain (in the pancreatic insufficient).	Sweat test (most cases identified by newborn screening)
Primary ciliary dyskinesia	Chronically discharging ears and persisting coloured nasal secretions or a history of rhinorrhoea in the first weeks of life[25].	Chest radiograph to look for dextrocardia (present in 50%)[25]. Ciliary studies.
Bronchomalacia	Harsh, monophonic expiratory noise[26].	Flexible bronchoscopy
Cardiac abnormality (particularly those causing left to right shunt)	May be evidence of biventricular failure (tachycardia, hepatomegaly and pulmonary crackles).	Chest radiograph, ECG and echocardiogram
Post infectious Obliterative bronchiolitis	History of previous viral especially adenovirus infection	Mosaic perfusion on expiratory films on High-resolution CT chest scan[27].

reduction of exposure to single allergens, such as house dust mite, does not reduce the prevalence of physician diagnosed "asthma" in the under fives.[34] However, reduction of exposure to multiple allergens in early life, including dietary and inhaled allergens, leads to a reduction in the prevalence of doctor diagnosed asthma in the under fives of around 30%.[34] Environmental allergen reduction (e.g. occlusive bedding and mattresses) is expensive and dietary exclusion is inconvenient and intrusive. Therefore these interventions are only justified young infants at very high risk of asthma and with highly motivated parents (number needed to treat 17 per case prevented).[34] Amongst the many reasons for encouraging women contemplating pregnancy to quit smoking, the strong association between pre-school wheeze and maternal smoking[2] is one of the most compelling.

TREATING ACUTE WHEEZY EPISODES

Bronchodilators

When an infant presents with an acute episode of wheezing, it is important to distinguish episodic (viral) wheeze from bronchiolitis. A diagnostic approach is suggested in Table 1. It is important to make the distinction because bronchodilators produce at best a small and short lived benefit when given to infants with bronchiolitis.[35] There are few randomised controlled trials of inhaled bronchodilators in pre-school children with wheeze. Conner randomised 29 children under 3 years to receive albuterol (salbutamol) or placebo for one week periods, during episodes of episodic (viral) wheeze, and showed an improvement in parent rated symptom score in the active group.[36] Kraemer[37] studied 36 wheezy infants, randomised to inhaled albuterol (salbutamol) or placebo and measured pulmonary function before and after the intervention. Significantly more infants in the active group showed improvement (as measured by thoracic gas volume and airway conductance). In contrast Chavasse *et al.* using a cross over design, randomised 80 wheezy infants under one year to salbutamol or placebo each administered three times daily for a period of 4 weeks.[38] They found that salbutamol was not superior to placebo in terms of symptom control or lung function. However, the trial had a high attrition rate (48 infants completed the study) and employed a regimen of regular bronchodilator use for prolonged periods, which is now rarely used in clinical practice.

Different regimens of bronchodilator administration have been compared in acutely wheezy children. A Cochrane review by Camargo *et al.*[39] included 8 studies of intermittent *vs.* continuous (back to back) nebulisers but only one of these was restricted to children and this study enrolled children aged 2-18 years.[40] The review finds benefit from continuous nebulisation, compared to intermittent nebulisers, but wisely advises caution in extrapolating the results to children – especially the very young. In contrast, the Cochrane review of bronchodilator administration by spacer *vs.* nebuliser includes 27 trials involving 2295 children – many more children than adults are included.[41] Five of the trials were in pre-school children. In children, the use of a spacer (rather than a nebuliser) to administer a beta 2 agonist does not significantly reduce the risk of admission but does reduce the length of stay in the emergency department. With a spacer there were significantly fewer adverse effects, such as tachycardia.

The effects of adding an anticholinergic bronchodilator in children have been studied in a Cochrane review which included 13 trials (6 including children in the pre-school age group).[42] Multiple doses of anticholinergic bronchodilators, such as ipratropium bromide, in addition to beta 2 agonists reduce admissions by 25% (number needed to treat = 12). In a further Cochrane review, Everard *et al.*[43] studied the effects of adding an anticholinergic to a beta 2 agonist in wheezy children under two years and found that the combined group had improved symptom scores after 24 hours, compared to beta 2 agonist alone.

ORAL CORTICOSTEROIDS

Short courses (3-5 days) of oral corticosteroids are commonly administered to wheezy pre-school children both for episodic (viral) wheeze and multiple-trigger wheeze. However the evidence for this approach is conflicting. In a Cochrane review, which included children of all ages, Smith et al. studied randomised controlled trials of systemic steroids for hospitalised children with asthma.[44] Four of seven eligible studies of oral steroids included some children in the pre-school age group.[45–48] The review concludes that the use of oral steroids may allow more children to be discharged early (around 4 hours) and may lead to a shorter length of stay. The randomized controlled trials which have been restricted to the pre-school age group are summarized in Table 2. A randomised controlled trial by Csonka *et al.*, published after the Cochrane review, studied children aged 6-35 months, with wheeze or breathing difficulty and symptoms of a viral infection. They randomised 230 children to

Table 2
Summary of double blind, placebo controlled, randomised controlled trials of oral steroids for preschool wheeze

	Study	N	Study population	Design	Age	Intervention	Duration	Findings
ED all pre-school age range	Csonka 2003	230	ED Exclusion = 2 or more previous episodes of wheezing	Parallel - 2 arm	6-35 mo	Prednisolone 2 mg/kg/day	3 days	Significantly fewer prednisolone patients needed additional asthma medication. Significantly shorter hospital stay. No reduction in hospitalisation.
	Panickar 2009	687	Hospitalised children	Parallel - 2 arm	10 mo - 6 y	Prednisolone 20 mg/day (10 mg for <2 years)	5 days	No reduction in time to discharge.
ED< 2 years	Daugbjerg 1993	123	Hospitalised children	Parallel - 4 arm	1.5-18 mo	1. Prednisolone & Terbutaline 2. Budesonide & Terbutaline 3. Terbutaline alone 4. Placebo alone Prednisolone D1 4-6 mg/kg D2&3 2 mg/kg	3 days	Children from each of the prednisolone & bud groups discharged significantly earlier
	Fox 1996	59	Hospitalised children Inclusion = 1 or more previous episodes wheezing	Parallel - 3 arm	3-14 mo	Salbutamol plus prednisolone (2 mg/kg) or placebo or double placebo	5 days	No difference in treatment failures between prednisolone & placebo
Parent initiated	Grant 1995	86	ED / primary care Inclusion = 2 or more visits with wheezing in last year	Crossover - 2 arm	2-14 y	Prednisolone 2 mg/kg	1 dose	No reduction in outpatient visits or hospitalisation
	Oommen 2003	233	Previously hospitalised children	Parallel - 2 arm	1-5 y	Prednisolone 20 mg/day	5 days	No difference in symptom score or hospital admissions

receive prednisolone (2 mg/kg/day for 3 days) or placebo. In the prednisolone group there was a shorter hospital stay (one day shorter), a shorter duration of symptoms and fewer children needing additional medication.[49] Panickar et al., studied almost 700 preschool children randomised to prednisolone or placebo on admission to hospital.[50] In contrast to the earlier studies, they found no significant difference between groups in the time until children were considered fit for discharge or in the time until actual discharge. The differences seen between the two recent, large trials are difficult to explain. In the Panickar study, children were enrolled only after they had failed to respond to an initial dose of salbutamol and so may have been a more severe group than the patients studied by Csonka (half of whom were discharged from the emergency department). The dose of prednisolone used by Csonka was higher than that used in the Panickar study, although in the latter study the per kilo dose varied with age.

In studies which have been restricted to children under 2 years the findings have also been conflicting. Daugbjerg *et al.*, in a four arm study of children aged up to 18 months, reported significantly earlier discharge in the group receiving prednisolone *vs.* terbutaline alone.[51] In contrast, Fox et al. studied children aged 3-14 months in a randomised trial and found that prednisolone, given with oral salbutamol, produced no difference in treatment failures compared to placebo plus salbutamol.[52]

Parents of children who suffer from episodic (viral) wheeze are frequently given oral prednisolone, to keep at home, and administer at the first sign of symptoms in an effort to truncate the attack. Is there any evidence to support this practice? Here the evidence is consistently negative. The effects of a single dose of oral prednisolone (2 mg/kg), administered by the parents of children aged 2-14 years at the first sign of wheezing, were studied by Grant *et al.* in a double blind, placebo controlled, crossover study.[53] Follow up was for 12 months - 6months of prednisolone *vs.* 6months placebo. There was no benefit from prednisolone, in terms of number of outpatient visits, number of attacks or hospitalisations. In a large randomised controlled trial, Oommen and colleagues enrolled over 200 children aged 1-5 years during an episode of viral wheeze and advised the parents to administer study medication (prednisolone or placebo) during the next episode.[54] Study medication was administered for 5 days and the outcome was the mean 7 day symptom score (day and night time symptoms). The children were stratified for eosinophil priming. There was no difference between steroid and placebo groups and no effect seen of eosinophil priming. The practice of giving parents a supply of oral prednisolone to administer to their children at the first sign of a wheezing episode cannot therefore be justified. A recent survey of physicians and parents suggested that such advice is still commonly given by doctors (though not always recalled by parents).[55]

INHALED CORTICOSTEROIDS

Episodic (viral) wheeze is characterised by intermittent symptoms and many parents would prefer it if inhaled corticosteroids (ICS) could be given intermittently rather than continuously, as is recommended for the treatment of asthma in older individuals. A Cochrane review of ICS for the treatment of episodic (viral) wheeze was published some years ago and further studies have since been conducted.[56] Table 3 summarises the five high quality randomised controlled trials of the use of ICS (often in high doses) for the acute management of episodic (viral) wheeze in preschool children. The studies are listed in order of increasing total daily dose (given as beclomethasone equivalent). The studies which used less rigorous outcome measures (such as symptom score) were more likely to show benefit than those which used outcomes such as symptom free days. Older studies were less likely

Table 3
Randomised controlled trials of inhaled corticosteroids used acutely for the management of episodic (viral wheeze)

Study	Inhaled corticosteroid	Duration (days)	Total daily dose (mcg)	Beclomethasone equivalent	Benefit	Harm
Bisgaard 2006[58]	Budesonide	14	400	400	No difference in symptom free days	No effect on height
Svedmyr 1999[59]	Budesonide	3[1]	1600	1600	Reduced symptom score	No effect on morning cortisol
Wilson 1990[60]	Beclomethasone	5	2250	2250	Reduced symptom score	Not reported
Ducharme 2009[57]	Fluticasone	</= 10	1500	3000	50% reduction in oral steroid use	Reduced height & weight velocity
Connett 1993[61]	Budesonide	</= 14	3200[2]	3200	Reduced symptom score	Not reported

1. Then budesonide 800 mcg daily for a further 7 days.
2. Children who were able to use the spacer device without a face mask were given 1600 mcg / day.

to measure and report adverse effects such as effects on height and early morning cortisol. When ICS are used in doses sufficient to reduce oral steroid use as in the study of Ducharme *et al.* (1500 mcg / day of fluticasone)[57] then adverse effects on growth are clearly demonstrated. The authors advised against the use of this regimen in clinical practice. Based on the current evidence, it appears that intermittent high dose ICS are effective in children with frequent episodes of moderately severe episodic (viral) wheeze or multiple-trigger wheeze, but this associated with short term effects on growth and cannot be recommended as a routine.

MAINTENANCE TREATMENT

Maintenance treatment with low to moderate continuous ICS in pure episodic (viral) wheeze is ineffective as shown by Wilson *et al.*[62] They compared Budesonide 400 mcg/day with placebo in preschool children given for a four month period and showed no significant difference in overall scores or number of symptom free days, acute episodes, or symptoms between episodes between the groups.[62]

The situation for multiple-trigger wheeze is different and maintenance ICS have a role. Chavasse *et al.* showed improved mean daily symptom score and symptom free days in infants under 1 year, with recurrent wheeze, when treated with Fluticasone 150 mcg twice daily via spacer (compared to placebo) for 12 weeks.[63] All infants had a personal or family history of atopy. Pao *et al.* showed that airway resistance measured by interrupter resistance (R_{int}) improves by 16% and bronchodilator responsiveness is reduced in pre school children who are skin prick test positive to one or more inhaled allergens when treated with inhaled Fluticasone 100 mcg twice daily via spacer for 6 weeks as compared to a placebo.[64]

Maintenance treatment is effective while it is being used but not once it is discontinued. The episode-free days, number of exacerbations, or lung function are not significantly different in patients who have previously been randomised to fluticasone or placebo but have stopped treatment.[64] Fluticasone (around 200 mcg/day), increases symptom free days, whilst reducing exacerbations and use of reliever medication, when commenced in children with a high asthma predicative index at around 1 year of age.[65] However, in the same study, fluticasone did not prevent lung function decline or reduce airway reactivity at age 5 years. Furthermore fluticasone had a significant negative effect on the increase in height achieved by treated children (around 1 cm less than the placebo group at 2 years).

A trial of standard dose ICS trial is therefore a reasonable strategy in children with multiple-trigger wheeze but therapy is only effective while being taken and cannot alter the natural history of the disease. Treatment should only be continued after a successful trial and a break in treatment should be given to see if the symptoms have resolved or continuous therapy is still required.[1]

MONTELUKAST

Continuous use

Montelukast is an anti-inflammatory medication – a leukotriene receptor antagonist (LTRA) - which is licensed for use in children from 6 months upwards with mild persistent asthma or exercise induced symptoms. Suitable formulations (granules) are available for pre-school children. The summary of product characteristics lists sleep disturbance, headache, abdominal pain and diarrhoea as adverse effects. However, the drug is generally well tolerated and long term treatment is an option, in contrast to oral steroid therapy.

In a 12 month multicenter, double-blind, parallel-group study of 2 to 5 year old children with episodic "asthma" exacerbations, associated with respiratory infections and minimal symptoms between episodes, oral montelukast, once daily for 12 months, was compared to placebo. Montelukast reduced the number of exacerbations by approximately 32% compared with placebo and the median time to first exacerbation was reduced by around 2 months.[66]

Even when used for a shorter duration of 12 weeks, montelukast 4 mg once daily compared with placebo produces clinical benefit within 1 day of starting therapy in children aged 2 to 5 years. There is significant improvement in daytime and night-time symptoms, the percentage of days with and without symptoms, the need for bronchodilators or oral corticosteroids and peripheral blood eosinophils.[67]

INTERMITTENT

Montelukast has a rapid onset of action. Recently parent or caregiver initiated intermittent use of Montelukast therapy for 7 days or until symptoms had resolved for 48 hours in children aged 2 -14 years resulted in clinically significant reductions in symptoms, primary care visits, emergency department attendances, number of days off from school or childcare (for the child) and days lost from work (for the parent or caregiver). However there was no significant effect on bronchodilator or oral prednisolone use.[68]

Intermittent use of ICS and montelukast have shown some benefits, a recent randomised trial looked at head to head comparison of intermittent ICS, montelukast and placebo in children aged 12-59 months. The investigators randomised 238 children who had experienced at least two episodes of viral wheezing within the past year to receive either inhaled budesonide 1 mg twice daily; montelukast 4 mg once daily; placebo ICS; or placebo LTRA for 7 days. There was no significant effect of these therapies on episode free days over a one year period, but there was a statistically significant, albeit modest, reduction in symptom burden during respiratory tract illnesses. Also those children with a positive asthma predictive index or a greater illness severity (i.e. use of oral corticosteroids in the preceding year) had a greater

likelihood of experiencing a clinical benefit with these treatment strategies during episodic wheezing and both high dose ICS and Montelukast provided very similar effects.[69]

NONPHARMACOLOGIC MANAGEMENT

Environmental tobacco smoke exposure: As well as having a role in primary prevention,[2] tobacco smoke exposure increases the risk of lower respiratory illness in young children (by 70% in the case of maternal smoking).[70] Smoking amongst parents of young children should be firmly discouraged and smoking cessation interventions offered.

Education: An uncontrolled study has shown that parents of pre-school children who take part in an educational programme have improved asthma knowledge and self efficacy.[71] In an RCT, using multiple teaching sessions led to an improvement in symptom free days for the child, less parental sleep disturbance and more accurate administration of asthma treatment by parents.[72] One RCT has suggested that multi-session education sessions show greater benefit when the intervention is used with the parents of younger (1-3 years) rather than older pre-school children (4-6 years).[73] In a randomised study, developmentally appropriate education targeted at pre school children themselves (rather than their parents) led to better knowledge, compliance and health.[74] However another large RCT in preschool children with acute wheeze compared an education programme comprising two face to face sessions, written information and a written asthma action plan with usual care.[75] There was no difference between groups in subsequent healthcare utilisation, disability score, parent's quality of life and parental knowledge of asthma when assessed at 12 months. The more effective interventions appear to be those which are prolonged and intensive and this approach may be impractical in routine clinical care.

CONCLUSIONS

Effective management of pre-school children with episodic (viral) wheeze or multiple-trigger wheeze requires careful clinical assessment to rule out alternative diagnosis and a clear discussion with the child's parents about the likely prognosis and the limitations of current treatment. Regular, careful re-evaluation of children's symptoms is essential as the wheeze phenotype can change over time in pre-school children. Both high dose intermittent inhaled corticosteroids (1500 mcg/day of fluticasone for up to 10 days) and low dose long term maintenance (200 mcg/day of fluticasone) are associated with reduced linear growth. Where inhaled steroids are used, they should be stopped if symptoms do not improve and treatment breaks should be employed. Montelukast offers some benefit in both episodic (viral) wheeze and multiple-trigger wheeze. Parent initiated courses of oral steroids are ineffective. Whatever treatment strategy is chosen, good multidisciplinary support and education is essential.

Directions for future research in the management of pre-school children with wheeze

Ongoing epidemiological studies to determine trends in the incidence of wheezing in pre-school children, risk factors and economic cost.

Studies to identify markers or steroid response – genotype, phenotype or biomarkers.

An RCT of intermittent montelukast, enrolling entirely from the pre-school age group

Development and evaluation of improved drug delivery systems for young children – small particle aerosols and the next generation of nebulisers and spacer devices.

Evaluation of improved support to avoid admission – telephone advice, community nurse support, educational materials, treatment action plans, home-administered montelukast.

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Educational questions

Please answer as true or false

1. Wheeze is a continuous high-pitched sound, without any musical quality, emitting from the chest during expiration.
2. The categories of pre-school wheeze according to its natural history as defined in epidemiological studies are: transient early; persistent; late onset.
3. The most common viral triggers for wheezing in children include: Rhinovirus, respiratory syncytial virus (RSV), rotavirus, human metapneumovirus, parainfluenza virus and adenovirus.

4. Parents may ascribe a different meaning to the word ‘‘wheeze’’ to that understood by health professionals.
5. Many parents are better at locating sounds rather than labelling them.
6. Ruttle / ‘‘rattle’’ is a low pitch sound with a rattling quality and lacking any musical features.
7. As required bronchodilator treatment of acute wheezy episodes does not improve parent rated symptom score and some measures of lung function.
8. Adding an anticholinergic bronchodilator to a beta 2 agonist in wheezy children under two years is beneficial.
9. Oral prednisolone administered by the parents at the first sign of wheezing reduces number of outpatient visits, number of attacks and hospitalisations.
10. Oral prednisolone administered by parents improves symptom score in children who are eosinophil primed.
11. There is incontrovertible evidence that oral steroids in preschool wheezing children are ineffective.
12. Ruttles have distinct acoustic patterns as compared to wheeze when assessed objectively using acoustic analysis and are related to excessive secretions or to abnormal tone in the larger airways.
13. Atopic and non-atopic children with multiple-trigger wheeze have different findings on bronchoalveolar lavage and bronchial biopsy.
14. Inhaled corticosteroids for preschool wheeze affect growth when used in high doses intermittently.
15. High dose intermittent inhaled corticosteroids reduce oral steroid use in pre-school wheeze.
16. Maintenance treatment with low to moderate continuous ICS improve symptoms and reduce exacerbations in multi-trigger wheeze.
17. Maintenance inhaled corticosteroids modifies the natural history of pre school wheeze.
18. A successful treatment trial with inhaled corticosteroids justifies continuous therapy in multi-trigger wheeze.
19. Long term regular use of Montelukast reduces the number of exacerbations and prolongs the time to next exacerbation in episodic wheeze.
20. The clinical benefit with Montelukast is seen within a day of starting treatment.
21. Parent initiated intermittent use of Montelukast therapy for 7 days is an effective treatment option for preschool wheeze.
22. Intermittent Montelukast is better than high dose inhaled corticosteroids at reducing symptom burden during episodic wheezing.
23. Tobacco smoke exposure is important in both primary and secondary prevention of preschool wheeze.
24. Developmentally appropriate education targeted at pre school children themselves can improve outcomes and knowledge in these children.
25. Regular, careful re-evaluation of children’s symptoms is essential as the wheeze phenotype can change over time in pre-school children.