Recent advances in the management of pre-school wheeze

A Bush

Abstract

Pre-school wheeze is very common and often difficult to treat. Most children do not require any investigations, only a detailed history and physical examination to ensure an alternative diagnosis is not being missed; the differential diagnosis, and hence investigation protocols for the child in whom a major illness is suspected, shows geographical variation. The pattern of symptoms should be divided into episodic viral and multiple trigger to guide treatment, and the pattern of symptoms re-assessed regularly. Attention to the proper use of spacers, and adverse environmental exposures such as tobacco smoke exposure, is essential. There are no disease-modifying therapies, so therapy is symptomatic. This paper reviews recent advances in treatment, specifically new data on the place of leukotriene receptor antagonists, prednisolone for acute attacks of wheeze and antibiotics, and proposes treatment protocols for the two types of wheeze.

Introduction

In some parts of the world, more than 30% of infants are reported to wheeze before age three years.[1] and many are very difficult therapeutic problems. This paper proposes a framework for management of these infants, based on modern insights into pathophysiology. It should be stressed it is written from a European perspective; the reader should evaluate critically the extent to which it applies to Africa, especially in a low- and middle-income setting.

Initial approach: am I missing a diagnosis?

Especially in the very young, specific diagnoses should be considered; there will be marked geographical variation in the differential, for example airway compression by tuberculous lymph nodes is common in parts of Africa, but very rare in the United Kingdom. The first step is as always to take a good history and perform a detailed physical examination. This should determine whether the sound heard is really wheezing (I am always sceptical until a reliable paediatrician has actually heard a wheeze), whether they get breathless, and if in fact what was complained of is an isolated dry cough, which in a community context in a well child is unlikely to betoken significant disease.[2] The pattern of symptoms should be determined because this will determine treatment (below). Red flags that more detailed assessments are needed are given in Table 1.

Coughs and wheezes can be divided into five categories (Table 2).[3] In my practice, 'Nursery School syndrome' is commonest. This afflicts children placed early into a child care facility, often first-time parents; the child gets a succession of viral colds (ten/year, with two weeks of symptoms with each cold being well within the normal range) with very few healthy days in between each cold. Of course, symptoms do not respond to inhalers or antibiotics; reassurance is what is needed. The most important lesson is that, before abnormality can be diagnosed, the paediatrician must be fully familiar with the limits of normality.[4]

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AB was supported by the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London.

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Planning treatment: how?

If on the basis of history and examination it is decided to treat the child for an asthma syndrome, the first step is to determine if the child only has symptoms at the time of viral colds (episodic viral wheeze, EVW) or in addition has symptoms between viral colds triggered by, for example, excited behaviour, allergen exposure (multiple trigger wheeze, MTW).[5] These clinical phenotypes may change over time, and detailed re-assessment at regular intervals is essential. This distinction is not merely of academic interest; preschool children with MTW, but not EVW have eosinophilic airway inflammation,[6] and this has implications for treatment: the use of inhaled corticosteroids (ICS) is only likely to be successful in eosinophilic airway disease, a point which is discussed further below. The many brilliant epidemiological studies that classify wheeze phenotypes can only be applied retrospectively, and currently are not useful in planning treatment.[1,7,8]

In theory, treatment of the pre-school child with wheeze could aim to prevent the transition to established asthma, or treat symptoms. We have no medications that can prevent progression to asthma; three excellent studies have shown that ICS given early as preventive therapy do not work,[9–11] and the pathological correlate of this is the complete absence of inflammation in very early wheeze.[12] Hence symptomatic treatment is appropriate, including intermittent therapy for intermittent symptoms.

Treatment options: what?

Before escalating pharmacotherapy, it is important to ensure the environment is optimal, especially that tobacco smoke exposure is eliminated, and any inhaled medications

Red flags on the history	Red flags on the physical examination
Prominent upper airway symptoms Symptoms from first day of life Sudden-onset symptoms, which always suggests a foreign body Chronic moist cough/sputum >8 weeks duration every day Worse after meals, irritable feeder, arches back, vomits, suggests gastro-oesophageal reflux Systemic illness or immunodeficiency Continuous, unremitting symptoms	Clubbing, weight loss, failure to thrive Upper airway disease – tonsillar hypertrophy, rhinitis, nasal polyps which last mandates consideration of cystic fibrosis Unusually severe chest deformity Fixed monophonic wheeze, stridor, asymmetrical signs Signs of cardiac or systemic disease

Table 1: Red flags on history and physical examination, which should prompt consideration of more detailed investigations

Diagnostic category	Examples
Normal child (the hardest diagnosis!)	Recurrent viral colds Pertussis
Serious illness	Will show regional variation; likely includes TB and bronchiectasis in Africa
An 'asthma syndrome'	Episodic viral wheeze Multiple trigger wheeze
Minor mimics or exacerbators of symptoms	Allergic or infective rhinitis Gastro-oesophageal reflux
Over-anxious parents	Often first-time parents who do not appreciate the range of normality Find out if they have some concealed fear, e.g. a friend's child died of TB having had a non-specific presentation

Table 2: A pre-school child with cough or wheeze will fall into one of these five categories

are properly administered. It is also important to consider whether treatment is needed at all; if the child merely has noisy breathing but remains well otherwise, then doing nothing is almost certainly appropriate. The simplest therapies are intermittent bronchodilators – either anticholinergics or short-acting β-2 agonists – via a mask and spacer. There is no way of predicting responses in an individual child, and a therapeutic trial is indicated. The next series of options are oral leukotriene receptor antagonists, ICS, and, controversially, antibiotics. Each will be considered in turn.

Leukotriene receptor antagonists

Respiratory viral infections have long been known to be associated with an elevation in cysteinyl leukotrienes,[13] and intermittent and continuous montelukast has been suggested as a treatment strategy. However, recent trials[14–17] have not been encouraging (Table 3). In summary, the two largest recent trials, recruiting over 3000 children, have failed to show benefit for montelukast. Hence although anecdotally a few individuals may respond to montelukast, most will not. There is no way we can determine which rare individuals will respond, except by a therapeutic trial. It should be noted that the behavioural side-effects of montelukast are not trivial. In summary, for the vast majority of pre-school wheezers, therapy with montelukast has no place.

ICS

Relevant studies using ICS are summarised in Table 4.[15,18–20] The very high dose intermittent ICS regime showed benefit, but at a cost of growth suppression;[10] and considering how many viral colds a child may have, this high dose cannot be recommended. We know that continuous inhaled or nebulised steroids are ineffective in preventing EVW. If the attacks are really so severe that it is felt that something must be done then a trial of ICS for a defined and well-monitored period (Dutch regime) may be indicated,[21] but they should be discontinued if there is no benefit (the likely scenario). There is limited evidence for acute benefit of ICS, and the risks are not small if high doses are used; I would not use doses above 200 µg beclomethasone equivalent as acute intermittent therapy. Atopy is not helpful in predicting ICS response in preschool wheeze.

The A-word: what is the role of antibiotics?

The role of bacteria in exacerbations of airway disease has increasingly come to prominence. In a study of adults with viral colds, co-amoxyclav significantly shortened the duration of symptoms, but only in those with a positive upper airway bacterial culture.[22] In a recent study, bacteria and viruses were equally likely to be cultured from the upper airway.[23] However, the mere presence of bacteria does not mean they are of pathophysiological significance; it might merely be that viral infection causes a transient local immune paresis leading to secondary bacterial colonization. A recent highly controversial study from Denmark[24] randomised 72 children aged 1–3 years with 158 asthma-like episodes lasting at least three days to azithromycin or placebo for 3 days. Symptoms were shortened, especially if azithromycin was started early (less than six days after the onset of symptoms). For the majority of children, no

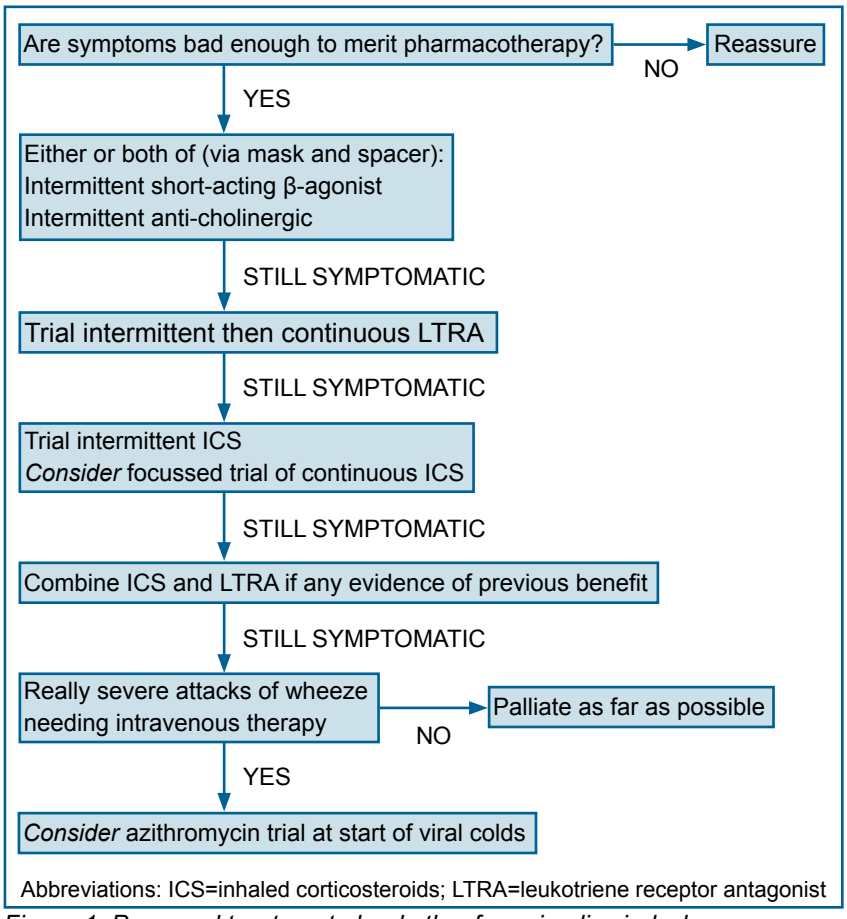

Figure 1: Proposed treatment algorhythm for episodic viral wheeze.

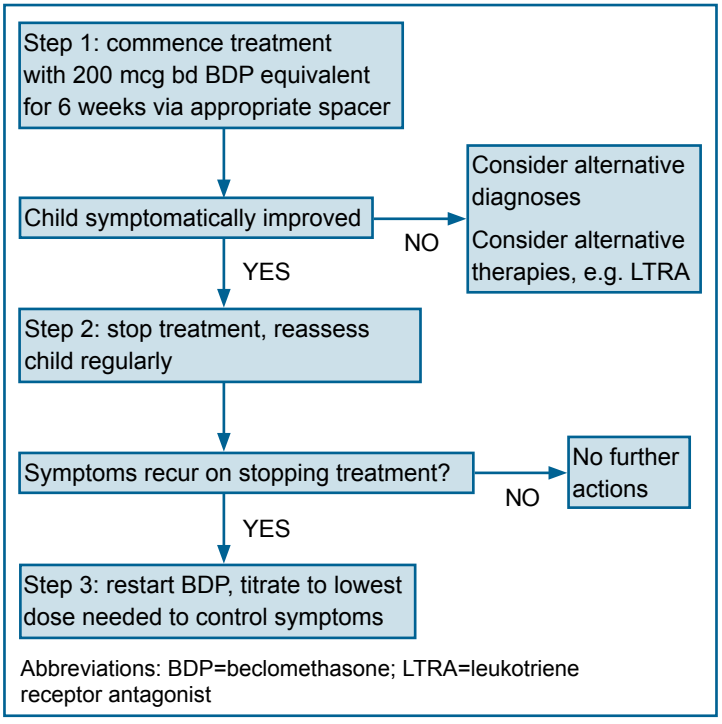

Figure 2: Proposed treatment algorhythm for multiple trigger wheeze.

bacterial cultures results were reported. It is of course unclear whether the effects of azithromycin were mediated by antibacterial or any of the many different immunological effects of the medication.[25] This could have been resolved if there had been a third limb to the trial, using (for example) co-amoxyclav.

What then is the role of azithromycin in pre-school wheeze? Clearly if every child with a cold is prescribed azithromycin, azithromycin resistance in the community will rise dramatically and azithromycin will cease to be useful. There can be no justification for the routine prescription of antibiotics to children with viral colds, irrespective of whether a positive bacterial upper airway culture is found. Azithromycin can only be justified as a trial in pre-school children with wheeze so severe that they require at least intravenous treatment and oxygen, and should only be continued if it prevents hospital admission.

Prednisolone in pre-school wheeze

Two recent studies[26,27] involving nearly 1000 children have clarified the role of prednisolone in pre-school children. It is clear that if the child is well enough to be looked after in the community, then prednisolone does not need to be prescribed. Furthermore, most children admitted to hospital will not need prednisolone. Oral steroids are only needed in really severe pre-school wheeze, for example if the child is oxygen dependent and intravenous treatment is being contemplated.

Treatment protocols: EVW and MTW

EVW

A proposed treatment flow chart is given in Figure 1. The evidence base is scanty and the diagram reflects personal practice. In all cases, if a treatment approach is not working, it should be discontinued without hesitation.

MTW

Preventive treatment is recommended in the following situations: if the child has symptoms which respond to short-acting β-2 agonists at least three days a week in between viral colds; if attacks of viral wheeze are very severe (although this is not likely to be a good strategy, and should certainly be discontinued if there is no evidence of benefit); and if symptom under-reporting by the parents is suspected. A three-stage flow chart is given in Figure 2. It is essential to have a trial of stopping an apparently successful treatment, because many children improve spontaneously, and without this step, unnecessary treatment will be prolonged

Summary and conclusions

The vast majority of pre-school children who wheeze do not need any investigations, but only a careful history and physical examination to ensure there are no features

suspicious of an alternative diagnosis. The key is to be sure that the noises the family describe are really wheeze, and keep an open mind until a physician has actually heard the noises. For the purposes of treatment, classify pre-school wheeze as 'episodic (viral)' and 'multi-trigger', but keep re-assessing the child, because these phenotypes may change over time, and hence treatment may need to change. Since there are no disease-modifying therapies, treatment is symptomatic, and episodic symptoms can be treated episodically, assuming they are severe enough to merit treatment. If preventive therapy is being trialled, a three-step protocol is mandatory to avoid over-treating the child. There is no justification for the routine use of oral antibiotics with viral colds, despite recent data. Finally, oral corticosteroids have been over-prescribed in the past for acute attacks of pre-school wheeze and should be reserved for very severe attacks.

Reference	Intervention	Numbers	Result
Robertson et al[14]	Intermittent ML vs placebo	220	Intermittent ML superior to placebo
Bacharier et al[15]	Intermittent ML vs intermittent nebulised BUD vs placebo	238	Intermittent ML and nebulised BUD equivalent and better than placebo
Valovirta et al[16]	Intermittent ML vs continuous ML vs placebo	1771	No benefit of either ML regime
Nwokoro et al[17]	Intermittent ML vs placebo Sub analysis by ALOX5 promoter polymorphisms	1346	No benefit of ML Possible benefit of ALOX5 promoter genotyping
Abbreviations: BUD, budesonide; ML, montelukast			

Table 3: Recent large trials of montelukast in episodic wheeze

Author	Intervention	Numbers	Result
Wilson et al[18]	Regular inhaled BUD 200 µg bd vs placebo	40	No effect of BUD on episodes of wheeze
Bacharier et al[15]	Intermittent ML vs intermittent nebulised BUD vs placebo	238	Intermittent ML and nebulised BUD equivalent and better than placebo
Ducharme et al[19]	Intermittent FP 1.5 mg/day vs placebo	129	Less use of prednisolone in FP group
Zeiger et al[20]	Intermittent nebulised BUD vs continuous nebulised BUD (no placebo)	278	No difference between the regimes
Abbreviations: BUD, budesonide; FP, fluticasone propionate; ICS, inhaled corticosteroids			

Table 4: Relevant studies of ICS in episodic wheeze in pre-school children

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