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REVIEW ARTICLE

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Basic clinical management of preschool wheeze

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Abstract

Preschool 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; and the differential diagnosis, and hence investigation protocols for the child in whom a major illness is suspected, shows geographical variation. The pattern of symptoms may be divided into episodic viral and multiple trigger to guide treatment, but the pattern of symptoms must be re-assessed regularly. However, symptom patterns are a poor guide to underlying pathology. 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, including new data on the place of leukotriene receptor antagonists, prednisolone for acute attacks of wheeze, and antibiotics, based on new attempts to understand the underlying pathology in a way that is clinically practical.

KEYWORDS
atopy, azithromycin, leukotriene receptor antagonist, prednisolone, tiotropium

1 | INTRODUCTION

The epidemiology of preschool wheeze is covered in detail elsewhere in this series. In brief, this is a common problem with few solutions. In the UK, the greatest burden of hospitalizations for wheeze is on children age <5 years old.[1,2] Most suffer from recurrent episodic, commonly viral-induced attacks (EVW). Most remit over time.[3] Worldwide, preschool wheeze is a problem in all environments,[4] which makes it all the more disappointing that we have so few evidence-based, personalized treatments.

The treatment of preschool wheeze, especially the role of inhaled corticosteroids (ICS), has been be-devilled by the mindless "at what age can asthma be diagnosed?" Clearly, the answer depends on the definition of asthma.[5] The *Lancet* Asthma Commission cut through this by defining asthma purely clinically, wheeze, chest tightness, breathlessness, and sometimes excessive cough.[6] This is because asthma is considered an umbrella term like anemia (low hemoglobin) and arthritis (hot, painful joints). As with anemia and arthritis, so with asthma, the next question is, "what sort of asthma has this child got?" with a specific focus on treatable traits[7] (Table 1). Notably, the treatable trait approach should be extended beyond pulmonary disease; the description of the detailed management of extrapulmonary and social/environmental treatable traits is out with the scope of this review. However consideration of these traits is necessary for the holistic management of the child Thus, asthma can be diagnosed at any age if a good history is taken, but the underlying endotype will vary across the life course. In preschool wheeze, the key treatable traits are the presence or otherwise of eosinophilic airway inflammation, bronchodilator responsiveness, and bacterial airway infection. Thus the management approach set out in this review draws on this paradigm to determine treatment options. Preschool is defined as age 1–5 years inclusive. Very little is known about the pathophysiology

and management of wheeze in the first year of life.[8] We do know that there is no evidence of airway inflammation in these very young children, even if they are really severely affected, atopic, and with documented acute bronchodilator reversibility[9]; it is thus very difficult to justify any prescription of ICS in wheezing babies.

Key Message

Management includes getting the basics right and moving to personalized medicine for preschool children with severe symptoms.

2 | CLINICAL APPROACH TO THE PRESCHOOL CHILD REFERRED WITH WHEEZE AND COUGH

The first step is to determine what respiratory noises are being described by the parents. The word "wheeze" is used by parents in the UK at least to describe many different sounds, including the true musical polyphonic noise of diffuse airway narrowing, upper and lower airway crackling noises, and even stridor. The use of a video questionnaire may help determine this.[10,11] Asking the parent to record what they hear on their mobile phone may be useful. Many medical professionals cannot be relied on to diagnose wheeze,[12] and a healthy skepticism is indicated until the noise has been assessed by a really experienced professional. In future, hand-held detectors with the data downloaded to a smartphone given to the family may be helpful in resolving this conundrum. If in fact the child has a chronic wet cough, then investigations need to be directed to confirming or otherwise persistent bacterial bronchitis[13] and bronchiectasis,[14,15] both themselves umbrella terms,[16] and the underlying cause thereof, which is beyond the scope of this review.

There are five main groups of causes of chronic respiratory symptoms in preschool children (Table 2).[17] It is important to appreciate the extent of respiratory symptomatology in normal children.[18] Isolated dry cough in an otherwise well child rarely betokens a significant diagnosis. Asthma should not be diagnosed if cough is the sole symptom, with no breathlessness, chest tightness, or wheeze; neglect of this rule has led to over-diagnosis and over-treatment of "cough variant asthma." All normal children cough; intermittent wet cough in association with viral colds, with complete recovery between colds, is normal; and a normal preschool child may have more than 10 colds/year with symptoms lasting 2–3 weeks each time.[18] In my practice, this "Nursery School syndrome" is very common; the child is placed early into a childcare facility, by often first-time parents. As a result, the child (and the parents!) gets a succession of viral colds with very few healthy days in between each cold. These do not respond to inhalers or antibiotics; reassurance is what is needed. A prolonged but gradually clearing postbronchiolitic syndrome of cough and wheeze is also commonly seen in an otherwise normal child. Red flags are progressive symptoms with no symptom-free intervals and a chronic wet cough with no periods of remission.

Although most preschool children with cough and wheeze are normal or have preschool asthma, in a few these symptoms betoken a serious disease. The differential diagnosis shows geographical differences, for example, compression of the large airways by tuberculous lymph nodes is common in endemic areas. Clues on history and physical examination are shown in Table 3. Most preschool children with wheeze are managed just on the basis of history and physical

TABLE 1 Examples of treatable traits in preschool wheeze (based on reference [7]).

	Treatable trait	Treatment	What treatment success looks like
Airway	Eosinophilic airway inflammation Reversible airflow obstruction due to smooth muscle constriction Airway bacterial infection	ICS Salbutamol Ipratropium Tiotropium Antibiotics	Fewer and less severe wheeze attacks Improved quality of life Less severe wheeze attacks Improved quality of life Eradication of infection Fewer and less severe wheeze attacks Improved quality of life
Extrapulmonary	Obesity Gastroesophageal reflux Unsafe swallow Rhinitis Eczema Food allergy	Weight reduction May be coincidental PPI Thicken feeds Antihistamine Nasal steroids Emollients Topical steroids Avoidance	Restore normal BMI Fewer wheeze attacks and better quality of life Fewer wheeze attacks and better quality of life Improved symptoms Rash and itching resolved No allergic reactions
Social/environmental	Nicotine exposure (tobacco or vapes) Exposure to allergens to which child sensitized	Refer to smoking cessation clinic Allergen avoidance, including pet removal	Exposure ceases, fewer attacks, and better quality of life Exposure ceases, fewer attacks, and better quality of life

Abbreviations: BMI, body mass index; ICS, inhaled corticosteroids; PPI, proton pump inhibitors.

TABLE 2 A preschool child with cough or wheeze will fall into one of these five categories.[17]

Diagnostic category	Examples
Normal child (the hardest diagnosis!)	Recurrent viral colds Pertussis "Nursery School Syndrome" (see text)
Serious illness	Will show regional variation; includes cystic fibrosis, bronchiectasis, interstitial lung disease, tuberculosis
An "asthma syndrome"	Episodic viral wheeze Multiple trigger wheeze
Minor mimics or exacerbators of symptoms	Allergic or infective rhinitis Gastroesophageal reflux
Over-anxious parents	Often first-time parents who do not appreciate the range of normality Find out if they have some concealed fear, for example, a friend's child died of leukemia having had a nonspecific presentation

TABLE 3 Red flags on history and physical examination, which should prompt consideration of more detailed investigations.[17]

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

examination. If investigations are performed, they should be focused and address two questions, "can I confirm or exclude an underlying diagnosis?" and "what sort of asthma does this child have?" (This last is addressed later in the review) There is no place for doing many investigations in the hope that something will turn up.

3 | WHAT ARE THE GOALS OF TREATMENT?

3.1 | General measures

Assuming that an underlying diagnosis has been excluded as far as possible, and the child is thought to have asthma, the next question is what treatment should be instituted. Before any pharmacotherapy is contemplated, attention should be turned to the environment. Smoking and vaping should be strictly avoided. Where possible, exposure to indoor and outdoor pollution should be minimized. If the child is sensitized to any aeroallergens, exposure should be minimized.

3.2 | Pharmacotherapy: General principles

Reasons for initiation of pharmacotherapy therapy could be the treatment of present symptoms, or prevention of progression to school-age, atopic asthma. It was initially thought that since ICS are excellent in treating the symptoms of school-age asthma, starting them very early would prevent atopic, allergic asthma from developing at school age. However, three excellent randomized controlled trials (two of early initiation of continuous ICS,[19,20] one of intermittent ICS just at the time of viral wheeze[21]) have shown that there is no effect on long-term asthma outcomes. So unlike in school-age asthma, where failure to institute ICS therapy in children having multiple asthma attacks is associated with a less favorable pattern of growth in spirometry,[22] there is no need to institute preventive therapy unless it is needed to control present symptoms. Indeed, inappropriate use of ICS may actually worsen airflow obstruction.[20]

3.3 | Pharmacotherapy: Bronchodilators

In clinical practice, lung function tests are infrequently used to guide treatment response, and the pediatrician has to rely on auscultation or changes in oxygen saturation. First-line therapy is with either or both short-acting β-2 agonists and anticholinergics (Ipratropium) administered via a large-volume spacer and mask (or a mouthpiece in those aged 3 years and over). Experience is that response is variable to both these agents, and empirical trials are the best that can be offered. However, before prescribing any inhaled medications it is important to be sure that treatment is actually indicated—administering inhaled medications to a fractious and vigorous toddler is not easy,

and if the child is only making a noise when breathing, with no respiratory distress or increased work of breathing, then the question arises, are we trying to treat the child or the parents?

A recent small study explored the use of the anti-muscarinic agent tiotropium in preschool wheeze.[23] This was a 48-weeks, open-label parallel-group randomized controlled trial in children aged between 6 and 35 months, who had suffered at least two episodes of doctor-confirmed wheeze with or without dyspnea. Children were randomized during a respiratory tract infection to either tiotropium 5 μg once daily for 7–14 days ($n=27$), or as-needed short-acting β-2 agonists ($n=28$) or twice daily fluticasone propionate 125 μg and as-needed short-acting β-2 agonists ($n=25$) for the same time period. The primary outcome was the proportion of episode-free days. The tiotropium regime was significantly better than either of the others, with more symptom-free days, and patients less likely to discontinue treatment. However, it is a relatively small study, requires confirmation and tiotropium needs to be licensed before it can be widely recommended for this indication.

Clearly, if a spacer is to be used, correct technique and education are essential; and most children aged 3 years and older can use a mouthpiece. Medication must be administered during quiet breathing—a crying infant guarantees that no medication will be deposited in the lower airway. Unsurprisingly, adherence is often poor.[24]

3.4 | Pharmacotherapy: Leukotriene receptor antagonists

Montelukast is popular and widely prescribed, but the evidence base is weak and the side-effect profile unfavorable. The theoretical basis is sound, cysteinyl leukotrienes are released during viral infections and are proinflammatory, but they just do not work for the majority. Respiratory viral infections cause elevations in cysteinyl leukotrienes,[25] and treatment with intermittent or continuous montelukast has been suggested. However, recent trials[26–29] are discouraging (Table 4). The two largest recent trials,[28,29] recruiting over 3000 children, have failed to show benefit for either intermittent or continuous montelukast. Anecdotally a few preschool wheezers respond to montelukast, but most do not. A therapeutic trial may be considered, but unless there is clear benefit it should be discontinued. Parents should be warned about the behavioral side-effects of montelukast, which have a prevalence of around 20% and can be very distressing.[30] Hence, for most preschool wheezers, montelukast is not useful.

3.5 | Pharmacotherapy: Macrolide antibiotics

Azithromycin has been most studied in this context; it has a complex portfolio of antibiotic and anti-inflammatory properties.[31] Although it was once thought that exacerbations of wheeze were driven solely by respiratory viruses, the role of bacteria has attracted increasing attention. Adults with viral colds and a positive upper airway bacterial culture treated with co-amoxyclav had a significantly shorter duration of symptoms.[32] In a study of acute wheeze in children and adults, bacteria and viruses were equally likely to be cultured from the upper airway.[33] However, because bacteria are present 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. In this setting, three studies attempted to determine whether azithromycin was a useful treatment in preschool wheeze. A Danish study[34] recruited 72 children aged 1–3 years who had a total of 158 of what were termed "asthma-like episodes" lasting at least 3 days. They were randomized to a 3-day course of either azithromycin or placebo. Symptom duration was less in the azithromycin group, especially if treatment was started <6 days after the onset of symptoms. No bacterial culture results were reported in most children. In a larger study, 607 children (12–71 months) who had been acutely ill enough to have previously been prescribed at least one prednisolone burst and had no interval symptoms were randomized to azithromycin or placebo, and fewer further prednisolone bursts were given in the azithromycin group.[35] A third large study was completely negative; 300 children aged 1–5 years were randomized to azithromycin or placebo in the emergency room, and there was no effect of active treatment.[36]

Is there then a role for azithromycin in preschool wheeze? If azithromycin is prescribed indiscriminately to children with trivial symptoms, macrolide resistance in the community will rise dramatically.[37] Perhaps a trial of azithromycin is warranted in preschool children with wheeze so severe that they require at least intravenous treatment and oxygen, and only continued if it prevents hospital admission. It is unclear whether any effects of azithromycin are immunomodulatory or antibacterial.[31]

TABLE 4 Recent large trials of montelukast in episodic wheeze.

Author	Intervention	Numbers	Result
Robertson et al[26]	Intermittent ML versus placebo	220	Intermittent ML superior to placebo
Bacharier et al[27]	Intermittent ML versus intermittent nebulized BUD versus placebo	238	Intermittent ML and nebulized BUD equivalent and better than placebo
Valovirta et al[28]	Intermittent ML versus continuous ML versus placebo	1771	No benefit of either ML regime
Nwokoro et al[29]	Intermittent ML versus placebo Subanalysis by *ALOX5* promoter polymorphisms	1346	No benefit of ML Possible benefit of ALOX5 promoter genotyping

Abbreviations: ALOX, arachidonate 5-lipoxygenase; BUD, budesonide; ML, montelukast.

TABLE 5 Relevant studies of ICS in episodic wheeze in preschool children.

Author	Intervention	Numbers	Result
Wilson et al[38]	Regular inhaled BUD 200 mcg bd versus placebo	40	No effect of BUD on episodes of wheeze
Bacharier et al[27]	Intermittent ML versus intermittent nebulized BUD versus placebo	238	Intermittent ML and nebulized BUD equivalent and better than placebo
Ducharme et al[39]	Intermittent FP 1.5 mg/day versus placebo	129	Less use of prednisolone in FP group
Zeiger et al[40]	Intermittent nebulized BUD versus continuous nebulized BUD (no placebo)	278	No difference between the regimes

Abbreviations: BUD, budesonide; FP, fluticasone propionate; ICS, inhaled corticosteroids.

3.6 | Pharmacotherapy: ICS

The major relevant studies are summarized in Table 5.[27,38–40] ICS may be prescribed either as intermittent or continuous therapy. A very high dose intermittent strategy reduced the use of prednisolone, but at a cost of growth suppression[39]; the efficacy of lower doses (e.g., beclomethasone equivalent 400 mcg/day) is less clear. Neither continuously inhaled nor nebulized steroids prevent EVW. If attacks are really so severe that it is felt that something must be done then a trial ICS for a defined and well-monitored period (Dutch regime) may be indicated,[41] especially if parental under-reporting of interval symptoms is suspected. However, they should be discontinued if as is likely, there is no benefit. The indications for targeted ICS therapy are discussed in more detail below.

3.7 | Pharmacotherapy: Oral corticosteroids

The use of oral corticosteroids for acute wheeze in school-age children is not controversial. A large study randomized preschool children who had been admitted to hospital to placebo or prednisolone to be given by the parents at the next wheeze attack; no benefit was seen.[42] From this study, it is clear that preschool children with acute wheeze, which is insufficiently severe to merit admission to hospital do not need to be prescribed oral corticosteroids. A subsequent study in children with acute preschool wheeze who were admitted to hospital showed that the duration of admission was not significantly shortened by administering oral prednisolone.[43] A subsequent meta-analysis of 1773 children in 11 studies confirmed that in most contexts oral prednisolone was not useful in acute preschool wheeze.[44] Surprisingly, a subsequent study of 624 patients randomized to placebo or prednisolone in the emergency department and[45] the prednisolone group had a shorter admission time (170 min, $p = .0227$—exactly the same time shortening as in the previous study, which was not statistically significant!). The design of this latter study was severely criticized.[46] In terms of parental preference, I suspect most families would think an extra time period of less than 3 h in hospital a small price to pay for the avoidance of a course of prednisolone.

Which preschool child with acute wheeze who is admitted to hospital should be prescribed oral prednisolone? I suggest that most do not, but systemic steroids are only indicated in really severe preschool wheeze requiring treatment in a High Dependency Unit. There is no doubt they have been over-prescribed in the past (and this still continues).

4 | TREATMENT APPROACHES: SYMPTOM-BASED TREATMENT

The 2008 European Respiratory Society Task Force proposed dividing preschool wheezers into EVW and "multiple trigger (MTW)" wheeze.[3] Both EVW and MTW were characterized by symptoms present only with a (usually clinically) diagnosed viral respiratory tract infection, but in MTW, there were also symptoms between viral infections, triggered by, for example, exposure to allergens to which the child was sensitized, and excitement. It was made clear that EVW was not the same as transient wheeze and could persist beyond school age, and MTW was not the same as persistent wheeze and could be transient. Furthermore, it was clear that the pattern of wheeze could change spontaneously over time, and with treatment (MTW treated with ICS could present as EVW). MTW was often but not exclusively associated with atopic disease and allergen sensitization, whereas EVW was usually not. Intermittent therapy was the recommendation for EVW, whereas children with MTW were considered for continuous ICS therapy. However, the obvious weaknesses of this approach are that there is heavy reliance on parental reporting of symptoms, and the underlying endotype was not even considered, let alone measured. The 2012 update[41] recognized the reliance on parental reporting and recommended that an N-of-1 trial of ICS was reasonable in EVW if symptoms were very severe or parental under-reporting of symptoms was suspected but discontinuing if there was no benefit. However, there was still no attempt to tailor treatment to underlying pathology, and it should also be said that just because symptoms are severe is not a reason to try a treatment, which does not work! Proposed treatment algo rhythms have been published, but these remain symptom-based.[47]

However, when symptom pattern is compared with pathology, it was very clear that both EVW and MTW could have BAL eosinophilia or a normal BAL, and atopy was also not predictive of BAL findings.[48] This may reflect the difficulties of symptom perception and recall by parents. Whatever the reason, it became increasingly clear that history-taking is an inadequate guide to treatment.

5 | TREATMENT APPROACHES: PERSONALIZING THERAPY USING BIOMARKERS

The first serious attempt to personalize therapy was the INFANT study, using peripheral blood eosinophil count and aeroallergen sensitization, both readily available in the clinic.[49] Three hundred children aged between 12 and 59 months prescribed step two treatment were recruited from 18 sites in the USA. They received in a blinded, three-way crossover trial in random order either daily ICS, daily montelukast, or as-needed ICS and short-acting β-2 agonist. Each treatment period was 4 months, with the first 2 weeks of data in each treatment arm being discarded in lieu of a washout period, which was thought to be unethical. The primary endpoint was a composite outcome of asthma control days and time to attack requiring oral corticosteroids. They prespecified that aeroallergen sensitization, gender, and wheeze attacks would predict a differential treatment response; the use of blood eosinophil count was a post-hoc analysis. Sixty of 300 improved spontaneously, and unsurprisingly there was no differential response to treatment; whatever they received they did well. One hundred seventy children showed a differential response, and in this group as a whole, regular ICS was the best option, and montelukast the least good. When they divided the group by aeroallergen sensitization, the nonsensitized patients ($n = 130$) did equally well (or badly) irrespective of treatment, whereas those allergen-sensitized ($n = 100$) did best in the regular ICS arm. They then carried out a post-hoc analysis, dividing the groups at the semi-arbitrary cut point of a blood eosinophil count of 300 cells/μλ. Below this level, the treatment results were the same in all three arms ($n = 82$). Those with a count of 300 and above ($n = 71$) were the group that did best on regular ICS. Those who were both aeroallergen-sensitized and with a blood eosinophil count of at least 300 ($n = 64$) were the group who did best when prescribed regular ICS; in all others, treatment effects were the same.

This study has opened the door to personalizing treatment using two simple biomarkers, but a note of caution must be sounded. The blood eosinophil analyses were post-hoc, and thus hypothesis generating and requiring confirmation in a second study. The stability of blood eosinophil count was not measured; at least in school-age children with asthma, sputum inflammatory biomarkers are not stable.[50] The cut-off level of blood eosinophils needs to be thought; 300 cells/μλ is the upper limit of normal for adults and used as an indicator for Type 2 biologics,[51] but the upper limit of normal in children is much higher.[52] Furthermore, elevated blood eosinophil count may be caused by eczema or other atopic disease, or parasitic infections. There are limited pediatric data showing bronchoalveolar lavage and peripheral blood eosinophil counts correlate,[48] but probably, the safest interpretation is that if blood eosinophil count is normal, airway eosinophilia is unlikely; if high, then one possible explanation is that the treatable trait of airway eosinophilia may be present.

The use of biomarkers was further explored in a meta-analysis[53] of three previously reported randomized controlled trials in 1074 children aged 12–71 months (Table 6).[27,35,40] Blood eosinophil count and aeroallergen sensitization were determined at the start of the trial. The investigators determined the predictive value of different blood eosinophil counts from ≥150 to 350 cells/μλ. Unsurprisingly, patients with eczema had higher blood eosinophil counts. The risk of an exacerbation increased with increasing blood eosinophil count, but the predictive value of a blood eosinophil count was low. Prediction was improved if allergen sensitization was added to the model, such that at any level of eosinophil count, allergen sensitization was present. In children prescribed ICS, the predictive effect of the two biomarkers was not clinically significant. Perhaps it is unsurprising that these three studies did not give clear-cut answers; the treatments were randomized, not clinically prescribed, and this may well have affected the findings.

Future work, in addition to validating the original INFANT observations, will include optimizing the eosinophil cut-off, including in areas of high parasite burden, and exploring whether the addition of exhaled nitric oxide (FeNO), as in adults,[54] will improve risk assessment and personalizing medicine. At the present time, it seems reasonable at least in secondary care to measure both biomarkers and use them to guide whether ICS are indicated—specifically, if neither blood eosinophilia nor aeroallergen sensitization is present, it is probably right to withhold ICS.

Whatever the biomarker status, if an N-of-1 trial of ICS is contemplated, a three-step protocol is advocated, to prevent transient symptoms from being interpreted as chronic. The steps are:

TABLE 6 Trials re-analyzed to study the effect of biomarker-driven treatments in preschool wheeze.

	Bacharier et al[27]	Zieger et al[40]	Bacharier et al[35]
Number enrolled	238	278	607
Age (months)	12–59	12–53	12–71
Entry criteria	≥2 clinically significant wheeze attacks	≥1 clinically significant wheeze attacks Positive API	≥2 clinically significant wheeze attacks
Duration (weeks)	52	52	52–78
Intervention	Intermittent ICS, or intermittent LTRA, versus placebo during respiratory illnesses	Daily ICS versus ICS only during respiratory illnesses	Azithromycin versus placebo during respiratory illnesses

Abbreviations: API, asthma predictive index; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist.

1. Commence ICS through an age-appropriate spacer; dose is arbitrary, but I would use a relatively high dose, beclomethasone 200 mcg twice daily on the basis that if the child does not respond, then a steroid-sensitive airway disease is unlikely. The family is told that the treatment will be reviewed and discontinued after 6 weeks (again, an arbitrary time period). Ideally adherence should be monitored electronically
2. Review the child at 6 weeks. If there has been no response, then the treatable trait of airway eosinophilia is not present, and alternative diagnoses and management strategies should be sought. If the child is symptomatically improved, it is not clear whether this was spontaneous or treatment-related. This is resolved by a period off treatment.
3. Review again after 6–8 weeks. If the child is asymptomatic, no further action is needed. If symptoms have recurred, then ICS are re-started and titrated down to the lowest dose needed to control symptoms

6 | FUTURISTIC TREATMENT APPROACHES: BEYOND ALLERGY AND THE EOSINOPHIL

Increasingly, attention is turning to the role of chronic bacterial and viral infection in preschool wheeze. In a study of 35 severe preschool wheezers who underwent bronchoscopy and bronchoalveolar lavage (BAL) at a time of clinical stability,[55] 60% had a positive bacterial culture or viral detection, and 26% had both. Unsupervised analysis revealed two subgroups. One was positive for *Moraxella catarrhalis* with marked BAL neutrophilia, the second was a mixed microbiota picture. Although there was a tendency for EVW patients to be in the *Moraxella* group, in general, there was very poor agreement between symptom patterns and BAL findings.

We also performed a larger analysis of 136 children aged 1–5 years, of whom 105 had recurrent severe wheeze-RSW and 31 had nonwheeze respiratory disorders the best control group we could find since normal children cannot ethically undergo bronchoscopy.[56] We measured peripheral blood leukocyte counts and specific IgE to common inhalant and food allergens. We defined allergic sensitization as allergen-specific IgE ≥ 0.35 kUA/L to at least one allergen tested. All children underwent a clinically indicated bronchoscopy, BAL, and endobronchial biopsy. Bacterial culture, multiplex PCR to 20 viruses, and *Mycoplasma* were performed on BAL. Data were analyzed by the Partition Around Medoids algorithm coupled with Gower's distance for mixed data. Clinically, 30/105 of the severe wheeze patients had EVW and 44/105 as MTW; 28 patients could not be classified as either, again underscoring the weakness of clinical phenotyping. Eight variables were used to determine the clusters, namely blood and BAL neutrophil and eosinophil counts, atopy, whether viral PCR and bacterial culture were positive, and whether ICS had been prescribed (it was considered unethical to stop treatment in these very fragile patients). We identified four clusters on 134/136 children, which are no relationship to symptom pattern. All patients in cluster 1 were sensitized; they had the highest blood eosinophils (mean = 5.54%, SD = 2.86%), the highest rate of ICS use (91.7%), and moderate rates of bacterial culture positivity (69.5%, especially *Moraxella*) and viral detection (56.5%). Cluster 2 was characterized by low BAL neutrophils (mean = 9.44%, SD = 13.89%), and a low rate of positive bacteriology (17.1%) ad viral detection (15.0%). All were prescribed ICS. In cluster 3 there was the highest rate of positive bacterial cultures (*Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*) ad viral infection (96.8% and 86.7%, respectively), and the highest level of BAL neutrophils (mean = 31.7%, SD = 25.11%); 67.7% were prescribed ICS. Finally, no 1 in cluster 4 was prescribed ICS, and most were nonatopic with persistent cough not wheeze.

A number of things need to be considered when interpreting this first preschool wheeze cluster analysis. This is a highly selected group of children with really severe wheeze who have failed to respond to therapy. There needs to be another validation cohort. We could not ethically stop treatment. We do not know how well the families were adherent to treatment or how much of the prescribed dose was actually deposited in the lower airway. Hence the effect of any prior ICS prescription on pathology, especially airway eosinophilia, cannot be determined. We also do not know the stability of phenotypes over time. However, what this study does do is to turn the spotlight firmly on infection, in at least some children. The relationship between disease and infection is unclear. One hypothesis is that chronic infection causes wheeze; another is that infection is merely a marker of underlying topical immunosuppression, which is the underlying cause of wheeze. It is also possible to hypothesize that ICS may be causing topical immunosuppression and thus allowing infection to become chronic.

This study points to possible cluster-based treatments (Table 7). It must be stressed that this is speculative, and the approach needs to be subjected to testing with randomized controlled trials before it can be recommended. However, it is hoped that considering this will broaden the reader's perspective on the etiology of preschool wheeze.

7 | IS PHENOTYPE-BASED TREATMENT PRACTICAL?

This was studied in a proof-of-concept, randomized trial.[24] Sixty children aged 1–5 years with at least two wheeze attacks in the previous year were categorized on history as EVW or MTW. The intervention group was prescribed ICS if blood eosinophils ≥3%, or targeted antibiotics if there was a positive culture on induced sputum or cough swab, compared with a control group receiving standard care. The primary outcome was unscheduled healthcare visits over 4 months. There was no relationship between EVW, MTW, and either blood eosinophils, atopic status, or infection. Median blood eosinophils were 5.2 (range 0–21)%, 27 of 60 (45%) children were atopic, and 8 (13%) had airway bacterial infection. 67% in each group were prescribed ICS. There was no difference

TABLE 7 Hypothetical cluster-based treatments for preschool wheeze. Note that this is a speculative analysis, and needs testing in prospective randomized controlled trials.[56]

	Nature of cluster	Possible treatment
Cluster 1	Highly atopic and eosinophilic	ICS Type 2 biologics or omalizumab?
Cluster 2	Low BAL neutrophils, no infection	LAMA
Cluster 3	No atopy, infection common	Targeted antibiotics
Cluster 4	No sensitization, infection, or inflammation	LAMA

Abbreviations: BAL, bronchoalveolar lavage; ICS, inhaled corticosteroids; LAMA, long-acting muscarinic agents.

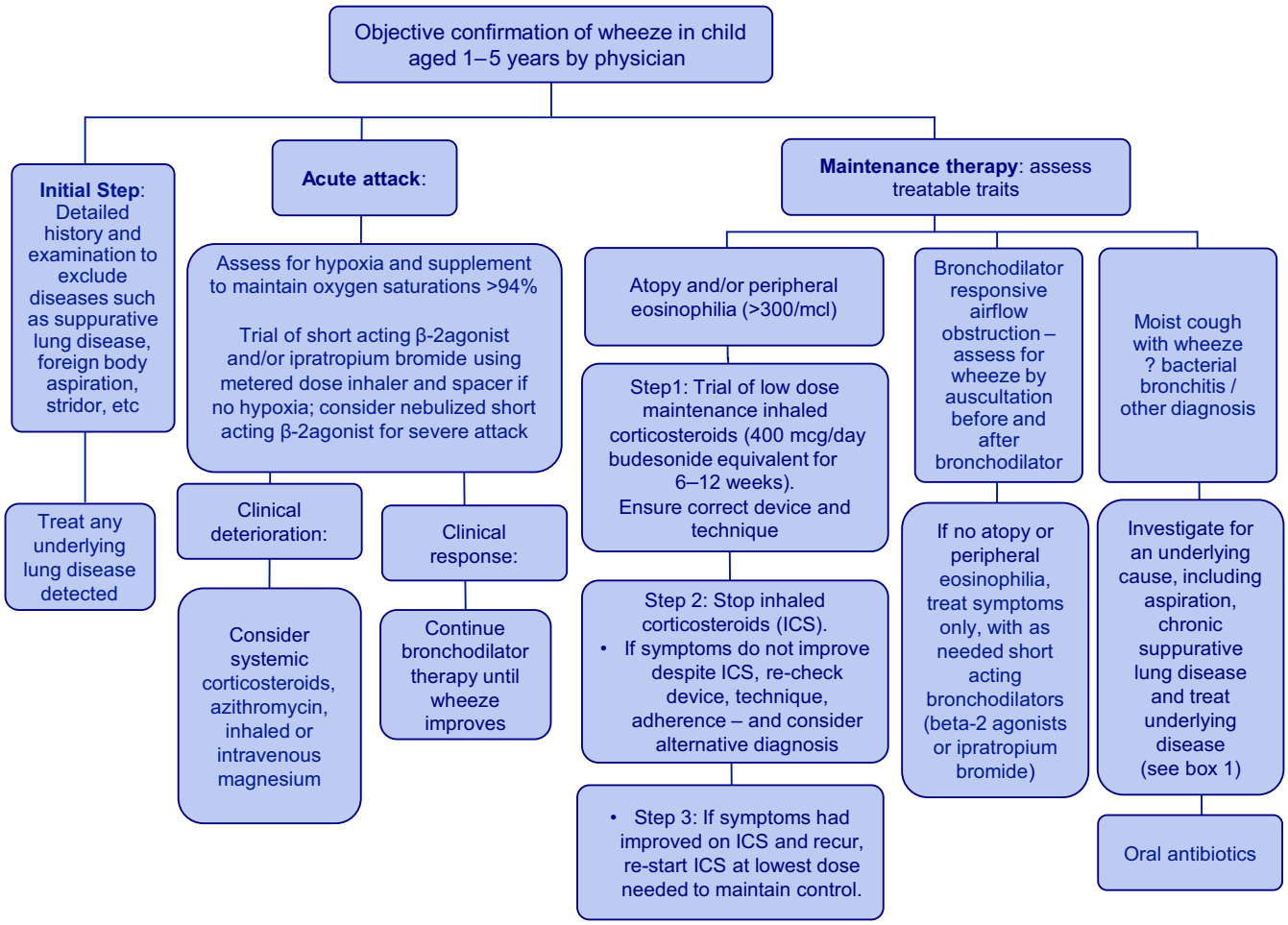

FIGURE 1 Proposed treatment algorithm for the treatment of preschool wheeze. Adapted from Bush A, Saglani S. Medical Algorithm: Diagnosis and Treatment of Pre-school Asthma.[47]

in the primary end point between groups. Median ICS adherence was 67% in the 50% of patients who returned adherence monitors. Also, parents were reluctant to change treatment during the winter viral season, when these patients were recruited; reluctance to change is also a feature of adult studies[57] and is a factor that needs to be overcome. In summary, the clinical phenotype was unrelated to allergen sensitization or blood eosinophils. ICS treatment determined by blood eosinophils did not impact outcomes, but ICS adherence was poor.

8 | HOW DO WE MEASURE SUCCESS OF TREATMENT?

Patient-reported outcomes (PROMs) highlight what is important to the patient ("can I get upstairs?") rather than what is conventionally measured by physicians, for example, changes in spirometry, and are increasingly used in clinical practice and research.[58] They need to be co-designed with families. Unfortunately, currently none such exist for preschool wheeze. Disease control can be assessed by the

Test for Respiratory and Asthma Control[59] and the Pediatric Asthma Quality of Life questionnaire in children age over 2 years. There are versions designed for parents to answer,[60,61] and instruments assessing the severity of attacks and parental feelings during the episode.[62,63] Developing PROMs for preschool wheeze is an important research priority.

9 | SUMMARY AND CONCLUSIONS

Basic management requires the pediatrician to determine that wheeze is really present and that an underlying diagnosis is not being missed. Symptom-based assessments bear little relationship to the presence or otherwise of the treatable trait of airway eosinophilia. We are beginning to appreciate that chronic bacterial infection may also be important, and perhaps some patients will benefit from targeted antibiotics. A proposed treatment algorithm is shown in the Figure 1.[47] The future must be phenotype not history-based treatment, but it will be essential to convince parents of the merits of this approach.

AUTHOR CONTRIBUTIONS

Andrew Bush: Investigation; writing – original draft; writing – review and editing; supervision; conceptualization; visualization; methodology; validation; project administration.

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