Blood eosinophils as a marker of likely corticosteroid response in children with preschool wheeze: time for an eosinophil guided clinical trial?

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Summary

Childhood wheezing is common particularly in children under the age of 6 years and in this age group is generally referred to as preschool wheezing. Particular diagnostic and treatment uncertainties exist in these young children due to the difficulty in obtaining objective evidence of reversible airways narrowing and inflammation. A diagnosis of asthma depends on the presence of relevant clinical signs and symptoms and the demonstration of reversible airways narrowing on lung function testing, which is difficult to perform in young children. Few treatments are available and inhaled corticosteroids are the recommended preventer treatment in most international asthma guidelines. There is, however, considerable controversy about its effectiveness in children with preschool wheeze and a corticosteroid responder phenotype has not been established. These diagnostic and treatment uncertainties in conjunction with the knowledge of corticosteroid side effects, in particular the reduction of growth velocity, have resulted in a variable approach to inhaled corticosteroid prescribing by medical practitioners and a reluctance in carers to regularly administer the treatment. Identifying children who are likely responders to corticosteroid therapy would be a major benefit in the management of this condition. Eosinophils have emerged as a promising biomarker of corticosteroid responsive airways disease, and evaluation of this biomarker in sputum has successfully been employed to direct management in adults with asthma. Obtaining sputum from young children is time consuming and difficult, and it is hard to justify more invasive procedures such as a bronchoscopy in young children routinely. Recently, in children, interest has shifted to assessing the value of less invasive biomarkers of likely corticosteroid response and the biomarker ‘blood eosinophils’ has emerged as an attractive candidate. The aim of this review was to summarize the evidence for blood eosinophils as a predictive biomarker for corticosteroid responsive disease with a particular focus on the difficult area of preschool wheeze.

The preschool wheeze epidemic

It is estimated that 1.1 million children in the UK have asthma, which is considered severe in over 10% of children using data from the International Study of Asthma and Allergies in Childhood [1]. Wheezing in young children aged 6 months to 5 years is particularly common and affects approximately one in three children growing up in the UK [2, 3]. Exacerbations, unscheduled healthcare visits and hospital admissions in this age band are the highest for any age group [4, 5] and result in considerable family stress [6] and a significant healthcare burden.

The vast majority of acute exacerbations in young children with recurrent wheezing are associated with viral respiratory tract infections, particularly the human rhinovirus [7, 8]. Children with human rhinovirus-induced wheeze are also more likely to have allergic sensitization [9]. In addition, recent studies have suggested that acute rhinovirus bronchiolitis in infancy is linked with genetic variation at the asthma susceptibility 17q21 locus [10] and to be a strong predictor of
later asthma [11, 12]. Absolute blood eosinophil counts are higher in young children with human rhinovirus associated bronchiolitis compared to bronchiolitis caused by other respiratory viruses [8, 12] and a recent study of infants hospitalized with bronchiolitis found that absolute blood eosinophil counts > 0.4 x 10^9/L in conjunction with human rhinovirus infection are highly predictive of recurrent wheezing 3 years later [12].

For the medical professional faced with a child with preschool wheezing, two broad patterns of presentation are recognized: 'episodic viral wheeze', comprising children who experience exacerbations with colds but are asymptomatic between episodes; and 'multiple trigger wheeze' where children have interval symptoms including daytime and night-time wheezing and wheezing with exercise as well as viral triggered episodes [13, 14]. It is widely thought that the latter group is more likely to respond to regular treatment with inhaled corticosteroids (ICS) although only few studies have specifically recruited from a clinical preschool wheeze phenotype. Moreover, several problems exist with these phenotypes including phenotype switching [15] which means that the clinical pattern of preschool wheeze is more easily recognized retrospectively than prospectively. In addition, 'episodic viral wheeze' and 'multiple trigger wheeze' may represent a marker of disease severity rather than pathophysiologically different disease entities [16]. Moreover, severity and frequency of acute wheezing episodes are not taken into account when assigning the clinical phenotype.

One other difficulty in practice is to predict which children with preschool wheeze will continue to have persistent asthma as older children or teenagers. Children with 'multiple trigger wheezing' are more likely to have persistent asthma at school age [2] and several asthma predictive tools and indices have been described based on data obtained from prospective cohort studies [17, 18]. The key characteristic features associated with persistence of wheezing in young children have been recently reviewed [19]. This is important because medical practitioners are more likely to prescribe regular preventer medication to children they believe will continue to wheeze into older childhood.

In summary, despite the common nature of preschool wheezing there is uncertainty and controversy about which children should be treated with regular preventer medication and we do not know which children will respond to regular ICS treatment, currently the most effective medication available to treat preschool wheezing with an estimated 40% responders based on available pooled data [4, 20]. The validation of phenotypic and biological markers capable of identifying children with preschool wheeze who respond to treatment with corticosteroids would be an important advance.

**Current treatment recommendations particularly for preschool wheeze are controversial**

Treatment algorithms for preschool wheeze are based on existing treatment strategies largely derived from data obtained in adults with asthma. These recommendations do not distinguish between clinical preschool wheeze patterns despite some limited evidence suggesting differences in treatment responses between the clinical phenotypes [21]. Inhaled corticosteroids are recommended as first-line controller treatment by the British Thoracic Society (BTS) asthma guideline [22] and the European Preschool Wheeze Task Force [13]. The BTS asthma guideline states that: 'In children aged 0-4 years with a high probability of asthma: start a trial of treatment'. It goes on to say that: 'the choice of treatment (e.g. example, inhaled short acting bronchodilators or corticosteroids) depends on the severity and frequency of symptoms'. There is no test for asthma in preschool children who generally cannot perform lung function testing and the decision to start treatment and to measure improvements is therefore subjective based upon an assessment of perceived severity of symptoms and number of exacerbations. If ICS fail to control the symptoms, an oral leukotriene receptor antagonist can be prescribed as add-on treatment (Table 1).

Previous research in preschool children has shown that oral corticosteroids have no benefit over placebo when given during an acute exacerbation [23, 24] and only modest efficacy in school-age children. Vuillermin et al. [25] reported a recent randomized controlled trial and calculated that 20 children aged 5–12 years with acute asthma needed to be treated with oral corticosteroids for benefit in one.

There are more than 20 published randomized controlled trials involving regular ICS in children with preschool wheeze. A frequently quoted systematic review and meta-analysis found moderate benefit of regular ICS treatment on daytime and night-time symptoms and the reduction of acute exacerbations requiring unscheduled healthcare visits when pooling all the data [20]. These findings have been confirmed again by a more recent study [26]. Patient numbers recruited have frequently been relatively small and selection criteria have varied from study to study but they all included some degree of symptomatic or troublesome wheezing with frequent short acting bronchodilator use and usually a history of exacerbations requiring unscheduled healthcare visits. None of the studies stratified on the basis of one or more biomarkers and a corticosteroid responsive phenotype has not been identified. What the pooled data shows is that patient stratification based on clinical criteria alone is inadequate to identify those children that are likely corticosteroid responders.
Identifying responders, however, is important because children on regular long-term ICS experience a significant reduction in growth velocity [27, 28]. Moreover, it has been shown that regular use of ICS in children with preschool wheeze does not alter the natural history of asthma or persistent wheeze in later childhood [27, 28]. Both studies with long-term follow-up found similar numbers of children with persistent older childhood wheeze irrespective as to whether they were prescribed regular long-term ICS in the preschool period or not. Both studies selected patients on the basis of current wheeze and a history of exacerbations requiring unscheduled healthcare visits and a history of atopic disease in either parent. Patient selection in the large RCT reported by Guilbert et al. [28] was based on the well-described ‘Asthma Predictive Index’ (API). The API has been derived from epidemiological studies and takes into consideration wheeze frequency, parental history of asthma and physician diagnosed atopic dermatitis as major criteria and wheezing away from colds, allergic sensitization to milk, egg or peanuts and blood eosinophils above 4% as minor criteria [17]. The hypothesis in the development of the API was that the index would identify preschool children with early onset atopic asthma and that these children were more likely to respond to corticosteroid therapy. However, the proportion of subjects with a positive index who develop the outcome, defined as physician diagnosed asthma or more than three wheezing episodes during the year prior to age 6 years, is less than 50% [29]. Moreover, when children with a positive API were randomized to either long-term ICS or placebo, there was...
no significant difference in unscheduled healthcare visits for wheeze exacerbations between the groups during the treatment period suggesting that a positive API does not predict a corticosteroid response. Therefore, whilst an estimated 40% of children with troublesome preschool wheeze may benefit from regular ICS treatment, the lack of a responder phenotype paired with the knowledge of known side effects on growth velocity have resulted in hesitant medical prescribing, poor parental adherence and unabated high rates of exacerbations in these children. We urgently need to assess simple and currently widely available biological markers for their ability to predict treatment responses, particularly to ICS, as validated personalized treatments are likely to be the approach that is most likely to succeed. Recently, blood eosinophils have emerged as a potentially promising biomarker of corticosteroid sensitive asthma [30].

Eosinophils and asthma

Allergic asthma in adults and older children is characterized by increased numbers of circulating eosinophils [31, 32] thought to be the result of an inappropriate immune response to common aero-allergens in genetically susceptible individuals [33]. In animal models of asthma, aerosol challenge with ovalbumin induces an influx of eosinophils into the blood and the lung [34]. Eosinophils are bone marrow-derived inflammatory effector cells that differentiate from myeloid precursor cells in response to interleukin (IL)-3 and granulocyte-macrophage colony-stimulating factor [33]. Mediators such as IL-4, IL-5 and IL-13 released by CD4 positive T-helper (Th) 2 cells are central to the pathogenesis of asthma, orchestrating the recruitment and activation of mast cells and eosinophils, the principal effector cells of allergic asthma [33]. IL-5 is the key mediator necessary for the development, differentiation, recruitment, activation and survival of circulating eosinophils [35, 36]. Blood and sputum IL-5, eosinophil numbers and their secreted products correlate with the severity and frequency of asthma exacerbations [34, 37–39]. Moreover, in a prospective study involving more than 1000 subjects with asthma, an absolute peripheral blood eosinophil count >0.45 × 10^9/L was associated with a more than 7-fold increase in the relative risk of asthma-related death [40].

Blood eosinophils

Blood eosinophils rise during the late allergic response occurring 24 h after inhalation allergen challenge [41] and peripheral blood eosinophilia has long been known to be a characteristic feature of asthma and is considered an indirect marker of airway eosinophilic inflammation [31, 42]. Teenage children with symptomatic, but not acute asthma have significantly greater numbers of activated blood eosinophils but not elevated concentrations of the eosinophil mediator eosinophil cationic protein (ECP) in serum compared to children with well-controlled asthma [43]. Geometric mean blood eosinophils >0.40 × 10^9/L were reported in children with uncontrolled asthma in that study.

Peripheral blood eosinophil numbers correlate with the severity of symptoms [44, 45], the degree of airflow limitation [31, 42] and airways responsiveness to direct [46] and indirect bronchial challenge testing [47]. In a study of young adults with doctor-diagnosed asthma, the presence of an absolute blood eosinophil count >0.35 × 10^9/L was the best predictor of significant exercise induced bronchoconstriction (≥15% reduction in FEV1) [47]. Ulrik et al [31] studying school-age children with allergic and non-allergic asthma found that numbers of blood eosinophils correlated with the asthma symptom score, diurnal peak expiratory flow variation and airway histamine responsiveness. An inverse correlation was reported with FEV1.

Moreover, two recent, large cross-sectional studies link peripheral blood eosinophils with asthma exacerbations. Malinovschi et al [48] reviewing the laboratory markers of more than 12 000 individuals with asthma aged 6–80 years found that peripheral blood eosinophils of more than 3% are independently associated with emergency healthcare visits due to exacerbations. This finding has since been confirmed by a separate study [49]. Reviewing data from 3162 subjects with asthma from the National Health and Nutrition Examination Survey, an annual cross-sectional survey of the United States general population, the authors found that the presence of absolute blood eosinophil counts ≥0.3 × 10^9/L was associated with an increased frequency of acute asthma attacks in respondents, particularly in children.

In preschool children, systemic eosinophil activation is present in those experiencing an acute exacerbation [50] and in several longitudinal epidemiological studies the presence of elevated blood eosinophils in children with preschool wheeze was associated with the persistence of asthma at school-age [51–53] which was independent of allergic sensitization [54].

Values for blood eosinophils in young children need to be interpreted in the context of clinical presentation. The blood eosinophil range in children 5 years and younger is wide and has been reported between 0.04–1.28 × 10^9/L in a study of >1200 apparently healthy children aged 0–16 years [55]. Increased numbers of blood eosinophils are present in individuals with atopic diseases such as rhinitis [56] and eczema [57, 58].

Recent data presented as part of a small study in preschool children showed that absolute blood eosinophil
counts $>0.5 \times 10^9$/L are present in about half the children with preschool wheeze [59] and levels of blood eosinophils correlated with airway eosinophils obtained at bronchoscopv.

There is a lack of longitudinal blood eosinophil data reported in the literature in adults and children. We are not aware of any studies reporting serially measured blood eosinophils in children or adults with asthma to study fluctuation. It is also not known if the numbers of blood eosinophils are higher during exacerbations. In children, particularly there are important ethical issues with repeat blood taking that is an important limitation to perform such studies.

**Sputum eosinophils**

Following early observations of peripheral blood eosinophilia in subjects with asthma further studies established the presence of eosinophils in the sputum and airways as a characteristic, albeit not universal, feature of asthma in adults [60–63] and older children [64–67]. Elevated sputum eosinophils are also an important feature in subjects with poorly controlled asthma [68] and children experiencing an exacerbation [66, 67]. Treatment strategies in adults with asthma, based on regular monitoring and titrating of corticosteroid medication based on sputum eosinophils have been shown to reduce exacerbations and lower sputum eosinophils [68–70].

There are relatively few studies with often small numbers that have investigated airway inflammation in young children with mild, moderate and severe wheezing. Most studies in preschool children suggest that eosinophilic airway inflammation is detectable in bronchoalveolar lavage fluid [71] and in subepithelial bronchial biopsy tissue [72–75] obtained from children with recurrent wheezing with greater numbers of eosinophils present in children with concomitant atopic diseases. Overall however, the level of eosinophilic airway inflammation particularly in children 3 years and younger is low [75, 76], compared to that found in older children [64, 77, 78] and adults [68].

One large study in young children with virus associated wheeze, with and without coexisting atopic disease, reported airway eosinophils well below 2.5%, a frequently quoted cut-off point for a diagnosis of eosinophilic asthma in children [71]. The median percentage of airway eosinophils in this study was 0.8%, well below the threshold for eosinophilic asthma. It is of note that the study was not limited to preschool children and that more than half of the recruits were prescribed regular ICS. Age stratification suggested that more eosinophils were present in children older than 5 years. Similar findings have been reported by two other studies [77, 78].

In young children with wheezing, in particular those under 6 years old, the sampling of sputum usually involve a bronchoscopy and a general anaesthetic. Such techniques are invasive and cannot repeatedly be performed in the same patient. Sputum induction in young children is possible and has been employed in infants to obtain sputum samples in the investigation of tuberculosis [79]. The procedure is time consuming and requires specialist laboratory staff trained to work with children, and this test is unlikely to be performed in large numbers to guide treatment [80].

**Eosinophil cationic protein**

Activated eosinophils release mediators that induce changes in the airways and produce the symptoms of the disease. Eosinophil granules contain four major cationic proteins released upon activation. Eosinophil cationic protein (ECP), eosinophil protein X (EPX), eosinophil peroxidase (EPO) and major basic protein (MBP) are capable of causing bronchial epithelial tissue damage [81–83] and dysfunction resulting in airways hyperresponsiveness [84, 85].

ECP is the most widely studied biomarker of eosinophil activity in asthma, and it has been suggested that serum ECP may be a useful indirect and more accurate marker of airway inflammation in asthma [86]. ECP is synthesized in eosinophil progenitors in human bone marrow and stored in specific granules in mature peripheral blood eosinophils [87]. Serum ECP levels are increased in adults and older children with asthma and correlate with disease activity and adherence with inhaled corticosteroid therapy [88–90]. Serum ECP levels are significantly raised in children during an asthma exacerbation [91]. In infants (all $<12$ months old) with wheezing but free from other allergic disease, serum ECP concentrations were found to be significantly higher when compared to infants with respiratory tract infection without wheezing or healthy controls. Infants with levels $>20$ μg/L were more likely to still wheeze 1 year later [92].

However, the relationship between bronchial hyperresponsiveness and serum ECP is less clear [93]. In a study by Rao et al. [94] involving 48 children with asthma aged 5–10 years, serum markers of eosinophil activation were negatively correlated with FEV$_1$, FEF$_{25–75}$ and the PC20 for histamine. This was not confirmed by a separate study involving nearly 200 children with asthma [95]. Here, the authors also reported higher levels of serum ECP in children with asthma and the highest levels in children with severe asthma; however, serum ECP was not associated with the response to direct bronchial challenge testing. Similarly, a large study in children aged 12–30 months found no
association between airway hyperresponsiveness to
direct challenge and serum ECP concentration [96].

The measurement of mediators such as ECP may add
little to the simple cell counts [97]. Moreover, there are
important limitations in the use of eosinophil markers
such as the need to collect and process blood under
tightly controlled and standardized conditions. Immediately
after collection, the blood needs to be clotted in a
water bath at 24°C for exactly 90 min followed by cen-
trifugation at 1300 g for 10 min at room temperature
making this test impractical for widespread clinical use.

Exhaled nitric oxide

Several inflammatory cells in the lung produce and
secrete nitric oxide (NO) including eosinophils. How-
ever, the inflamed airway epithelium, not confined to
eosinophilic inflammation, contributes to the amount
of exhaled NO measured [98]. There is a moderate cor-
relation only between eosinophil percentages in sput-
um and the level of exhaled NO in adults [99, 100]
and children [64] with asthma. A link between blood
eosinophils and eNO has also been reported [101, 102].
It has been suggested that eNO and blood eosinophils relate
to different inflammatory pathways. Whilst eNO
is considered a marker of corticosteroid responsive
asthma [103], the tailoring of the dose of ICS pre-
scribed to the value of eNO is controversial. A Cochr-
ane systematic review of studies concluded that this
approach resulted in only small reductions of acute
exacerbations and children in the eNO study arms
tended to be on higher doses of ICS by the end of the
study compared to controls [104].

Relationship between blood and sputum eosinophils

Only a small number of studies systematically studied
the association between sputum and blood eosinophils.
Pizzichini et al. [105] compared blood and sputum eos-
inophils and eosinophil markers obtained at the same
visit from 19 adults with symptomatic asthma. The
median sputum eosinophils were 5.2% and the median
absolute blood eosinophil count $0.35 \times 10^9$/L. When
analysing the data using the area under receiver–oper-
tor curves (ROC), the authors found that sputum eosin-
ophils were more sensitive and specific (0.9) compared
to blood eosinophils (0.72) at distinguishing patients
with asthma from controls, however, both, sputum and
blood eosinophils showed a good correlation with clini-
cal and physiological markers of asthma severity. Blood
eosinophils were a better marker that serum ECP. The
usefulness of blood eosinophils as a surrogate marker
of airway eosinophilia has been confirmed by two
recent studies [106, 107]. Wagener et al. [106] prospec-
tively studied over 100 patients with mild to moderate
asthma and found that an absolute blood eosinophil cut
point of $0.27 \times 10^9$/L had a sensitivity of 78% and
specificity of 91% in distinguishing between airway
eosinophilic (defined as 3% or more sputum eosinoph-
ils) and non-eosinophilic airway inflammation. The
addition of eNO into the ROC analysis did not improve
the prediction model. The findings were replicated in a
separate cohort of patients with moderate to severe
asthma, and similar results have been reported in a
large but retrospective study of over 500 patients with
asthma [107].

This association has also been found in preschool
children with viral-induced wheeze and allergic asthma
where a close relationship between blood and sputum
eosinophilic inflammation has been reported [71].
Further support is provided by a bronchial biopsy study
reporting that numbers of blood eosinophils mirrored
eosinophilic inflammation in bronchial biopsies of
young children with recurrent wheeze. In particular, of
all children considered non-eosinophilic based on bron-
chial tissue analysis, none had peripheral blood eosino-
philia and nearly half the children considered
eosinophilic by tissue analysis, had peripheral blood
eosinophilia greater than $0.45 \times 10^9$/L [72].

Overall, the evidence suggests that sputum eosinoph-
ils are more closely and accurately associated with
asthma symptoms and severity than blood eosinophils.
However, although an asthma management and treat-
ment strategy for adults with asthma based upon num-
bers of sputum eosinophils is feasible and potentially
cost effective in specialist secondary and tertiary care
settings, it has proved difficult to implement nationally
even in this setting [68]. It is therefore unrealistic to
expect that a strategy based on sputum eosinophils
would be suitable for young children and that this
could be implemented routinely in primary or second-
ary care. Blood eosinophils in contrast are a relatively
easy biomarker to measure in children that has been
shown to be highly predictive of sputum eosinophilia in
patients with asthma.

Eosinophils and eosinophil products as markers of
corticosteroid responsive asthma

Treatment with oral corticosteroids results in a decrease
in sputum and blood eosinophils and a drop in the
blood ECP concentration in adults with asthma [108].
Moreover, the reduction in the numbers of blood and
sputum eosinophils is mirrored by the clinical and lung
function improvement following an acute exacerbation
of asthma in response to treatment with corticosteroids
as shown by serial testing [109–111]. Following oral
corticosteroids, absolute blood eosinophil counts reach
their lowest reading after 3 days of treatment and spu-
tum eosinophils after 7 days [111].
Blood eosinophils

There is less reported data of associations between asthma severity, the response to corticosteroids and blood eosinophils. There is, however, good evidence that blood eosinophils are associated with corticosteroid responsive asthma [30]. In an early study, Horn et al. [42] reported absolute blood eosinophil counts of $>0.35 \times 10^9/L$ in a group of adult patients with poorly controlled asthma. Blood eosinophils dropped significantly after adjusting corticosteroid treatment doses and asthma control improved. In a separate adult study, lung function was significantly negatively correlated to both blood eosinophil counts and serum ECP. Blood eosinophil numbers were more closely associated with respiratory function than eosinophil markers [110].

In children, there is a reluctance to perform blood tests; hence, few data exist describing the relationship between blood eosinophilia and corticosteroid responsive asthma. Nonetheless, in a corticosteroid reduction study conducted in children, blood eosinophils increased significantly in the withdrawal group but not in the continuous treatment group [112].

Sputum eosinophils

The presence of airway eosinophils predicts a response to corticosteroid therapy in adult patients with asthma [113, 114]. In adult subjects with eosinophilic asthma, defined as sputum eosinophils $\geq 3\%$, ICS treatment leads to a reduction in airway eosinophils [115, 116] and a reduction in airway hyperresponsiveness [116]. Several studies also reported a rise in sputum eosinophils that were associated with a loss of asthma control following the withdrawal of ICS [117, 118]. In support of these findings, several other studies have shown that non-eosinophilic asthma responds poorly to ICS therapy [119–121]. In a rare paediatric study, the absence of sputum eosinophils has been shown to be a predictor for successful ICS dose reduction in children with asthma [122].

Some of the best evidence for corticosteroid responsiveness of eosinophilic asthma comes from randomized controlled trials. In a landmark study involving adults with moderate to severe asthma adjustments of the corticosteroid dose based on sputum eosinophil counts resulted not only in a significant reduction in sputum eosinophils in the sputum management group over a 12-month period compared to patients where treatment was based on symptoms and lung function alone, but the reduction in sputum eosinophils was associated with a significant reduction in severe asthma exacerbations requiring unscheduled healthcare visits or admission to hospital [68]. The findings from this study suggest that eosinophils are an indicator of corticosteroid responsive asthma in adults and anti-inflammatory treatments directed at reducing elevated numbers result in better asthma control. Blood eosinophils were not reported. The findings from this study have been replicated in two other studies involving adult patients [69, 70].

The effectiveness of a management strategy based on sputum eosinophils has not been confirmed in children. One small study in older children with severe asthma found little benefit in titrating corticosteroid dose in accordance with the sputum eosinophil count [123] at 3 monthly reviews. The annual rate of exacerbations was similar between the clinical and the sputum management group, but significantly fewer subjects in the sputum management group experienced an exacerbation within 28 days of a study visit, perhaps suggesting that more frequent measures would be needed for a clinically useful effect. Also there was no run-in period; therefore, the results could be confounded by improved adherence in the clinical group as described previously in a study involving children with severe asthma [124]. However, it is of note that the sputum management group was on lower doses of ICS at the end of the study compared to the clinical group and in both groups of children, the median percentage sputum eosinophils fell to below 2.5%, a level considered within normal limits.

Serum and sputum ECP

The investigators of a 12-month prospective intervention pilot study in school-age children monitoring and adapting corticosteroid dose according to the serum ECP concentration found that raised levels of serum ECP denoted active disease better than lung function parameters [125]. The blood ECP concentration fell after initiation of ICS treatment and the authors suggested that ECP may be a useful marker of adherence to corticosteroid treatment [125]. However, a study by Wolthers et al. [126] showed that blood ECP is not sensitive to ICS dose changes and in a study involving adults with chronic persistent asthma ICS caused a significant reduction in sputum and blood eosinophils but not sputum or blood ECP [127]. Review of the evidence suggests that sputum and blood ECP concentrations are not a sensitive or reliable means of evaluating airway inflammation.

Interleukin-5

This mediator has a critical role in the expansion of the eosinophil pool in the bone marrow and in the induction of blood eosinophilia in response to allergic stimulation [128]. Two recent randomized, double-blind and placebo-controlled clinical trials using a monoclonal anti-IL-5 antibody (mepolizumab) showed a significant reduction in the exacerbation frequency in a group of
patients with refractory eosinophilic asthma. Mepolizumab treatment also led to a significant reduction in blood and sputum eosinophil counts [129, 130]. These findings have been confirmed by two further large multicentre clinical trials each involving more than 500 patients. The MENSA study enrolled patients with exacerbation prone asthma on high-dose corticosteroid maintenance treatment who had evidence of blood eosinophilic inflammation defined as an absolute blood eosinophil count of $0.15 \times 10^6$/L or more [131]. The exacerbation frequency in the mepolizumab group was approximately halved at the end of the study. In the DREAM study, higher blood eosinophil counts were associated with a greater treatment response to mepolizumab [132]. There are no reported data in children <12 years old.

Towards a personalized approach to treatment of preschool and childhood wheeze

Current treatment algorithms based on clinical predictive indices are not working in young children with troublesome wheeze. They have not led to reduced morbidity or indeed a reduction in severe exacerbations. Furthermore, expert reports agree that the benefit of ICS in an unselected cohort of children with troublesome preschool wheeze is modest and recommend more research into identifying corticosteroid responsive disease [13, 14]. The controversy surrounding the efficacy of anti-inflammatory treatments particularly but not exclusively in preschool wheeze combined with the concerns about side effects of corticosteroids has resulted in inconsistent medical prescribing and parental adherence [4].

There is an urgent clinical need to identify a reliable and widely available biomarker with the ability to predict which children are likely to have corticosteroid responsive disease. Eosinophils are strongly associated with corticosteroid responsive allergic asthma and exacerbations in older children and adults. Blood eosinophils are an easily measurable and widely available indirect marker of eosinophilic airway inflammation and blood testing is more likely to succeed in young children. This biomarker merits further study and the best way to answer the question as to whether blood eosinophils predict a corticosteroid response in children with troublesome preschool wheeze is to conduct a blood eosinophil stratified randomized controlled trial.

Identifying those children who are corticosteroid responsive would allow promotion of this treatment in this group to reduce exacerbations, improve quality of life and reduce healthcare costs whilst avoiding unnecessary side effects in those likely to be unresponsive.

Conflict of interest

The authors declare no conflict of interest.

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