Role of corticosteroids in preschool wheeze: going, going, but not gone

Inhaled and oral steroids are widely and beneficially used in older children and adults, but their place in preschool and episodic (viral) wheeze is less clear. This paper reviews recommendations in the light of new clinical trials evidence. Inhaled corticosteroids do not prevent the progression from episodic wheeze to multitrigger wheeze and asthma later in childhood. They may be beneficial to treat current symptoms in a small minority of atopic preschool children with multitrigger wheeze, especially those over 3 years old. Some in this group may benefit from regular treatment; for the majority, there will be no benefit. If a therapeutic trial is contemplated, then a three-stage protocol is advised, with a trial of discontinuing the medication. Oral steroids have been shown not to be useful for home or hospital treatment of episodic wheeze, but may be useful in very severe episodes needing high dependency care. There are safety issues with the use of steroids, including a possible effect on the developing alveoli. In summary, any form of steroid therapy should be used sparingly and on an individualized basis in preschool and episodic viral wheeze.

KEYWORDS: airway inflammation, asthma, bronchial biopsy, bronchoalveolar lavage, corticosteroid, eosinophil, lung growth

Andrew Bush
Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK
Tel.: +44 207 351 8232
Fax: +44 207 351 8763
a.bush@rbh.nthames.nhs.uk

The advent of inhaled corticosteroids for adults and older children heralded a new age when control of asthma symptoms was to be expected, and the use of oral corticosteroids in acute severe asthma undoubtedly slashed mortality. Investigation of the pathophysiology of asthma, initially in adults [1–3] and then in children [4–8], demonstrated the reasons; airway eosinophilic inflammation is the hallmark, and numerous beneficial actions of steroids on eosinophilic chemoattractants and cell survival have been delineated. Thus, there is a sound scientific basis for steroid therapy, and this is matched by a solid evidence base for clinical benefit.

However, perhaps not all in the garden is lovely. The undoubted benefits of steroids in older children have been anticipated in preschool wheeze, but not delivered. The weight of evidence is increasingly that steroids are overprescribed; in particular, in children under 2 years of age. The purpose of this article is to review the proper role of these powerful medications in young children, especially in the light of new evidence from clinical trials.

The following are some definitions used in this manuscript. 'Episodic viral wheeze' is characterized by discrete bouts of wheeze and respiratory distress in association with coryzal symptoms; there are no symptoms between viral colds. 'Multi-trigger wheeze' is also usually characterized by wheezing with coryzal symptoms, but in addition, there is episodic or chronic wheeze and respiratory distress between viral colds, triggered, for example, by exercise, cold air, smoke and allergen exposure.

The problem of viral colds

Firstly, it is necessary to review the context. The most common trigger for wheezing in the preschool years is a viral cold, and between colds, the children are usually well (episodic viral wheeze). A large community-based study documented that the median number of viral colds was five per year in childhood, but more than 10% of children have ten or more colds per year [9,10]. A viral cold is usually a trivial illness, but although the mean duration of symptoms is around 8 days, the normal range extends beyond 2 weeks [10]. Symptoms are nasal congestion, rhinorrhea, cough, sore throat and fever, and do not require treatment. Thus, a normal child may have symptoms of the common cold for nearly 6 months in the year. Common rhinitic and other symptoms are often misinterpreted as 'wheeze' [11–13] and may lead to an incorrect diagnosis of asthma or an inappropriate prescription of medication. Not unexpectedly, early life attendance in child day-care facilities increases the risks of viral colds [14]. In particular, the frequency and duration of colds may come as a surprise to first-time parents, and misconceptions regarding the need for treatment are common [15]. Therefore,

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it should be noted that a treatment that may be low-risk as a 'one-off', such as oral or very high dose inhaled corticosteroids, may be prescribed more than ten times a year in an otherwise normal infant, leading to a very high burden of therapy indeed.

Does asthma cause isolated cough?

The next important issue is the significance of cough as a symptom of asthma. Critical is the context, but in primary care, isolated dry cough is rarely, if ever, a symptom of asthma [16]. Even in tertiary care, bronchoscopic studies on chronic coughers rarely show any evidence of the airway eosinophilia, which would be expected in asthmatics and might respond to steroid therapy [17]. Thus, cough without significant breathlessness and respiratory distress should not be treated as asthma with inhaled corticosteroids. Guidelines for the management of cough have recently been published [18].

Baseline control & exacerbations

The final background consideration is not to confuse good background control and prevention of exacerbations. Loss of baseline control, and exacerbation of asthma, is not the same thing [19]. These authors defined exacerbations as a linear decline and then a linear recovery in consecutive peak flow values, with no significant increase in diurnal variability. This pattern was strikingly different from that seen during the initial period of poor asthma control, when peak flow charts were characterized by morning dipping, wide diurnal variability and by postbronchodilator peak flow values approximately 30% higher than prebronchodilator values. In preschool children, symptom pattern will have to substitute for peak flow measurements. It should be pointed out that there is some interaction, but it is perfectly possible to have no chronic airway inflammation or interval symptoms, and yet have bad viral-induced exacerbations, not prevented by increasing prophylactic medications between viral colds. It is perfectly true that in older children and adults, studies have shown that admission to hospital with exacerbations of asthma are most likely if there is evidence of all three symptoms; acute viral infection, sensitization to an aeroallergen and high levels of exposure to that allergen in the home, and the prescription of inhaled corticosteroid is protective to some extent [20]. In addition, studies in which the dose of prophylactic medication is titrated to reduce airway eosinophilia, irrespective of symptoms, leads to a reduction in numbers of acute exacerbations [21]. However, it is a common clinical observation that children of all ages, even on high doses of systemic steroids with documented adherence, may still suffer severe viral-induced exacerbations of asthma. Thus, it is important not to slavishly increase prophylactic medication in a child who is experienced viral exacerbations of asthma.

What is the pathology of preschool wheeze?

As discussed previously, the pathophysiology of school age and adult asthma is very similar [1–8], with good evidence of a TH2-lymphocyte-driven, eosinophil-mediated airway inflammation amenable to therapy with inhaled corticosteroids. This is not the case in young preschool children or in older children with pure episodic (viral) wheeze, where antenatal factors may be much more important [22]. A bronchoalveolar lavage (BAL) study showed, as expected, that asthmatic children, presumably with a multitrigger pattern of wheeze who were predominantly of school age, had an eosinophilic lavage, but that infant wheezers with presumably episodic (viral) wheeze, had a neutrophilic BAL, similar in severity to that seen in cystic fibrosis children [23]. Also of note, children with chronic isolated cough had a normal BAL [23]. In a study using nonbronchoscopic BAL in children anaesthetized for routine surgery, children with asthma, also presumably with a multitrigger pattern of wheeze, had an eosinophilic lavage, whereas those with isolated episodic wheeze did not [24], underscoring the differences in pathophysiology. The view that the neutrophil is the key cell in preschool episodic wheeze is also borne out by studies demonstrating neutrophil and not eosinophil activation at the time of wheeze [25,26].

Two cross-sectional studies in different populations have shed further light on the timescale of the development of eosinophilic airway inflammation. In the first, three groups of infants, with a median age of approximately 1 year, were compared [27]. Their symptoms were of sufficient severity to merit referral to a specialist children's hospital. The groups were made up of children with airflow obstruction responsive to acute inhalation of bronchodilators, many of whom were atopic; children with airflow obstruction that was nonresponsive; and children with normal lung function. There was no evidence of airway inflammation or remodeling in any group; specifically, even the atopic children with reversible airflow obstruction, the group most closely resembling asthmatics in later life, had normal airway

wall structure. In a second study, the presence of wheeze was confirmed using a video questionnaire [13]. Children with really severe confirmed wheeze were compared with a group referred with wheeze, but whose parents identified different sounds on the video questionnaire, and a group of controls, largely infants with stridor being investigated by bronchoscopy [28]. The children with confirmed wheeze and a mean age around 3 months had eosinophilic inflammation and reticular basement membrane thickening when compared with the normal controls. Reticular basement membrane thickening was not as marked as in older children and adults with asthma. These biopsy studies would suggest that there is a time window between the onset of symptoms and the development of the pathological changes of asthma, which offers an opportunity for disease modification. However, it is important to note that:

- We do not know how to modify this disease, but we do know that steroids will not do it (see below and [29–33]).
- The time window may be different for children with different levels of severity of wheeze.

The hypothesis does, however, find support in other studies; persistent wheezers are born with normal airway function, but develop airflow obstruction by the first 3–6 years of age [34,35]; aeroallergen sensitization in the first 3 years of life is strongly predictive of persistent wheeze [36]; and immigration studies show that if you move to a new environment with a different asthma prevalence after the age of 4 years, you retain the prevalence of your country of origin, whereas if you move before 4 years, the risk is that of the country into which you immigrated [37].

What is the role of steroids in any type of preschool wheeze?

Assuming that the nonasthmatic coughers and those who make noises that are not wheezing with colds are excluded, why would one want to use steroids in preschool wheezing children? Three possible reasons are: to prevent acute attacks; to treat acute attacks; and to prevent the progression of episodic wheeze to multitrigger wheeze. The latter is the easiest indication to dismiss. If the child has multitrigger wheeze, then a fourth reason is to prevent day-to-day symptoms.

Are steroids 'disease-modifying' in preschool wheeze?

Four good studies have addressed the question of whether inhaled corticosteroids are disease-modifying [29–33]. In the first of two recent studies of long-term inhaled corticosteroids (peak study) [29], 285 participants 2 or 3 years of age with a modified positive asthma predictive index (i.e., at high risk for developing asthma in childhood, based on a scoring system [38]) were randomly allotted treatment with fluticasone propionate (88 µg twice-daily) or placebo for 2 years, followed by a 1-year period observation without study medication. The primary difference between groups was the proportion of episode-free days during the observation year. During the observation year, there were no differences in the proportion of episode-free days, the number of exacerbations or lung function. During the treatment period, fluticasone treatment was associated with a greater proportion of episode-free days ($p = 0.006$), a lower exacerbation rate ($p < 0.001$) and less use of controller medication ($p < 0.001$). In the fluticasone group, the mean increase in height was 1.1 cm less at 24 months ($p < 0.001$), but by the end of the trial, the height increase was 0.7 cm less ($p = 0.008$). Thus, during treatment, fluticasone reduced symptoms and exacerbations to a modest extent, but slowed growth, albeit temporarily and not progressively. The minor systemic effects at least confirmed that the children were being given a reasonable amount of the prescribed medication.

The second study was of a more complex design [30]. It was a randomized, double-blind, placebo-controlled study of the same dose of inhaled fluticasone propionate in young children who were followed prospectively and randomized after either one prolonged (>1 month) or two medically confirmed but briefer wheezy episodes. The dose of study drug was reduced every 3 months to the minimum needed. If the symptoms were not under control by 3 months, open-label fluticasone propionate 100 µg twice-daily was added to the treatment. Children were followed-up to 5 years of age, at which point, their parents or guardians were given questionnaires, and the children's lung function and airway reactivity was measured. A total of 173 (85 treatment, 88 placebo) of the 200 randomized children completed the follow-up at age 5 years. There was no treatment effect at age 5 years for the proportion of children with current wheeze, physician-diagnosed asthma or use of asthma medication; lung function; or airway reactivity. There were no differences in the results after adjustment for open-label fluticasone propionate, nor between the two groups in the time before the open-label drug was added, nor in the proportion needing the open-label drug. Interestingly, the groups that received fluticasone were reported to have a higher airway resistance

(i.e., worse lung function) at follow-up, but this did not reach statistical significance; whether there is any true clinical significance remains an open question.

These two studies are confirmatory of an older study using inhaled budesonide, which was shown to reduce airway reactivity compared with regular inhaled salbutamol in school-age children with asthma. However, a plateau was never reached: many children on salbutamol did very well and when budesonide was stopped, airway reactivity reverted to prestudy levels [31,32].

In a study testing an alternative strategy, namely the use of intermittent inhaled steroids, 411 1-month-old infants were randomly assigned to treatment with 2-week courses of inhaled budesonide (400 µg per day, n = 294) or placebo, initiated after a 3-day episode of wheezing, in a single-center, randomized, double-blind, prospective study lasting 3 years [33]. The primary outcome was the number of symptom-free days. Key secondary outcomes were the time to discontinuation due to persistent wheezing and safety, as evaluated by height and bone mineral density at the end of the study. There was no effect of treatment on symptom-free days, nor in the proportion of infants who went on to persistent wheezing. This latter finding was unaffected by the presence or absence of atopic dermatitis. There were no safety issues.

In summary, neither continuous nor intermittent inhaled steroids modified the course of asthma, even in infants who were in a high-risk group for disease progression. Although there is some evidence in adults and older children that early use of inhaled corticosteroids may be beneficial in terms of long-term lung function [39,40], this evidence does not exist in children, and, even in adult patients, physicians are moving away from dogmatically insisting on continuous and regular inhaled corticosteroids in mild asthmatics [41]. It could be argued that higher doses might have been more beneficial, but in the Prevention of Early Asthma in Kids (PEAK) study, there were systemic side-effects of fluticasone, and in a larger study of very-high-dose-inhaled fluticasone as an intermittent treatment (below), published only in abstract, systemic side-effects were also noted [42,43].

Should continuous inhaled corticosteroids be prescribed for wheeze in young children?

There is little doubt that prophylactic inhaled corticosteroids in this age group are very ineffective at preventing exacerbations of wheeze induced by viral infections [44]. In the PEAK study, in which the entry criteria meant the children were at high risk of subsequent asthma, and thus, most likely to benefit from inhaled corticosteroids, at the end of the 2-year treatment period, the mean benefit in the fluticasone group was an extra 2–3 symptom-free days a month, together with fewer exacerbations, prescribed oral corticosteroids (one per 3-child-years of treatment) and less supplementary use of medications. Thus, for the group as a whole, the benefits were not striking. However, given the confidence intervals of the data, it is likely that there were individuals within the group who benefited considerably, and conversely, those for whom the therapy was not worthwhile. It seems likely that any benefits in nonatopic children will be substantially less [45].

Despite these caveats, it would not seem unreasonable to trial prophylactic inhaled corticosteroids; in particular, in preschool children who are at least 3 years old, who are atopic or at least have a family background that makes atopy likely and who have multitrigger wheeze. However, there should be no hesitation in discontinuing the medication if there is no benefit. We recommend a formal therapeutic trial, in which a reasonably high dose of inhaled corticosteroid (e.g., budesonide 400 µg twice daily or equivalent) is given for 6–8 weeks. If there is no symptom response, then the medication is stopped. If symptoms disappear, the medication is also stopped, to see if in fact, this represents spontaneous resolution of the problem. If symptoms recur and respond to restarting inhaled corticosteroids, then therapy is continued at the lowest dose to control the problem. This three-stage trial is designed to prevent a child being unnecessarily treated in the long term because onset of therapy coincided with spontaneous resolution of symptoms.

In conclusion, there is only a limited role for prophylactic-inhaled corticosteroids in a highly selected group of preschool wheezy children; the majority will derive no benefit from this therapy.

Should oral corticosteroids be prescribed for acute wheeze in young children?

Oral corticosteroids are the bedrock of the management of acute asthma in older children and adults, and failure to prescribe them early and in adequate doses have been blamed as contributory to asthma deaths [46]. The evidence in preschool children is far less compelling. A large study stratified preschool children with

acute wheeze by levels of serum eosinophil cationic protein (ECP) and eosinophil protein X (EPX) [47]. They were then randomized to have a parent-initiated course of treatment to be given at the onset of the next episode of (presumptively viral) wheeze, either placebo (n = 108) or 20 mg prednisolone (n = 109) for 5 days. Outcome data were available for 120 (78%) of 153 children who had a further episode of viral wheeze. A total of 51 children received prednisolone and 69 placebo. There was no clear benefit of treatment, irrespective of stratification by previous eosinophil activation.

It could be argued that these children were mildly affected, and there was no chance of benefit, although it must be said that the entry requirement mandated a previous admission to hospital. The next study, to date only published in abstract, extended the findings to children brought to hospital with an acute exacerbation of episodic wheeze [48]. Hospitalized children (1–5 years) with clinical viral-triggered wheeze, and no evidence of multitrigger wheeze, who remained symptomatic after one nebulized dose of salbutamol, were recruited. Children were randomly assigned to receive either oral prednisolone for 5 days or placebo (20 mg and 10 mg for 2–5 years and 1–2 years age groups, respectively). The joint primary outcomes were the time at which children were 'fit for discharge' from hospital and time to 'actual discharge'. Secondary outcomes included a validated respiratory symptom score and time to the complete resolution of symptoms. A total of 1180 children were assessed for eligibility and 699 were randomized. There was no difference between placebo and oral steroids for the time fit for discharge (median 12 vs 10 h; p = 0.17) or duration to actual discharge (median 13 vs 11 h; p = 0.22). There were no differences between placebo and prednisolone for any secondary outcome variables.

In both of these studies, together involving several hundred children, viral studies were not carried out, and the diagnosis of episodic (viral) wheeze was made clinically, as is almost invariably the case. In a much smaller study, oral prednisolone (2 mg/kg/day in three divided doses for 3 days) was compared with placebo in hospitalized wheezing children in whom a positive virological diagnosis was made. A total of 661 patients were hospitalized, 293 randomized and 58 out of 661 (i.e., <10%) were finally analyzed and contributed to the conclusions [49]. The mean age was 2.6 (standard deviation: 1.3) years. The time to discharge was the same irrespective of treatment in all patients (prednisolone vs placebo; median 18 vs 24 h, p = 0.11). However, prednisolone decreased the time until fit for discharge in children with picornavirus infection (12 vs 24 h, respectively; p = 0.0022) and more specifically, in children with enterovirus infection (6 vs 35 h, p = 0.0007). Prednisolone decreased the duration of cough and dyspnoea in rhinovirus-affected children (p = 0.033 for both). These subgroup analyses were based on small numbers (rhinoviruses: seven given prednisolone vs 13 given placebo; enteroviruses: nine given prednisolone vs 12 placebo), and can at best be considered preliminary, underpowered and hypothesis generating. Thus, it is possible that there may be effects of oral prednisolone with specific viruses, but this hypothesis needs further testing in a much larger population.

This does not mean that prednisolone should never be prescribed for acute exacerbations of viral preschool wheeze. In particular, two large trials recruited children with moderate symptomatology, and it is possible that very severely affected preschool children may benefit. First-line treatment should be high-dose-inhaled salbutamol only. However, the only logical conclusion that can be drawn from present evidence is that prednisolone therapy is only warranted in those in whom a prolonged hospital stay is likely needed, and probably also with the need for high dependency unit care. There seems little justification for the prescription of oral corticosteroids in preschool children with episodic wheeze managed in the community. It is also possible that young children with multitrigger wheeze may benefit from prednisolone at a lower level of severity of acute exacerbation, but it is essential to be sure that this is true wheeze (see above). In conclusion, unlike older children and adults, in whom the default position for acute exacerbations of asthma is the prescription of systemic corticosteroids, it should be suggested that, in preschool children, especially those with presumptive episodic wheeze, the default position should be not to prescribe prednisolone.

Should high-dose, intermittent inhaled corticosteroids be prescribed for acute wheeze in young children?

If oral corticosteroids are of dubious benefit, what about very high dose (e.g., 1–3 mg/day beclomethasone equivalent) inhaled steroids for acute use? In older children, although the acute use of inhaled corticosteroids has some action in acute asthma, the benefit is clearly inferior to systemic prednisolone [50,51]. In

episodic wheeze in preschool children, there is some evidence of benefit [52]. It might seem paradoxical that high-dose inhaled corticosteroids may be beneficial whereas systemic are not, but the effect might be mediated by the topical, vasoconstrictor action of steroids, rather than an anti-inflammatory effect. However, it is by no means clear that high-dose inhaled corticosteroids are necessarily beneficial, and one study, again published only in abstract [42,43], suggested that there may be systemic side effects with this approach. For certain, more data are needed before this approach can be widely recommended.

Are steroids safe?

The problem of profound hypoglycemia due to adrenal failure with high-dose, inhaled steroid therapy has been highlighted [53,54]. In particular, other side effects such as growth suppression [55] and effects of oral steroid bursts [56] are well known. However, one unknown possible effect is on the developing alveoli. It is known that the first 18–20 months of life are when alveolar numbers are laid down [54]. There is evidence in animals that parenteral and nebulized steroids can adversely affect the growing lung [57–59]. There are no safety data from this perspective in humans, but the possibility of toxicity to alveoli needs to be born in mind. This is not to say that steroids should never be used in the first 2 years of life, only that extra caution and thought is necessary before using them.

Conclusions: where to go from here?

This review has been somewhat negative regarding the role of steroids in preschool wheeze. The negativity has been buttressed with positive evidence, rather than making recommendations in the absence of evidence. The intention is not to discourage the appropriate use of steroids in this age group, but merely to urge their cautious and rational use. Furthermore, whereas low-dose inhaled steroids and infrequent-rescue bursts of oral corticosteroids are the answer to asthma in many older children and adults, we are very far from solutions in preschool wheezers, especially those with an episodic (viral) pattern. In terms of those with multitrigger wheeze, clearly at 1 year of age, the pathological evidence is that steroids are highly unlikely to be useful, by 3 years there is at least the pathological substrate for their use, but for any individual, it may be difficult to determine at what point airway eosinophilia becomes significant. Children are not small adults, and preschoolers are more than small children!

Future perspective

The immediate future will hopefully see better education regarding the nature of preschool wheeze, and a reduction in the use of steroids in these children. Speculatively, the future will bring a better understanding of the mechanisms of episodic viral wheeze, and with it inflammatory pathway-specific treatments. The second area will be interventions to prevent progression to multitrigger wheeze. These may be primary, for example dietary manipulations, but more likely, interventions that will be applied after the first episode of viral wheeze. This will require the developments of better biomarkers of progression, to target a high-risk group. The nature of the intervention is still unclear, but perhaps macrolides, with their multiple anti-inflammatory and antiremodeling actions [60], might be good

Executive summary

What is the pathology of preschool wheeze?

- Preschool wheeze is a neutrophil-, not eosinophil-, dominated disease; therefore, benefit with inhaled corticosteroids is not likely.

Are steroids 'disease-modifying' in preschool wheeze?

- Inhaled corticosteroids do not prevent the evolution of intermittent (viral) wheeze into persistent, multitrigger wheeze.

Should continuous inhaled corticosteroids be prescribed for wheeze in young children?

- Inhaled corticosteroids are beneficial in only a small minority of preschool wheezers, largely those who are atopic with multitrigger wheeze and are at least 3-years old.
- If a therapeutic trial of inhaled corticosteroids is contemplated, a three-stage protocol with a trial of discontinuation is mandated.

Should oral corticosteroids be prescribed for acute wheeze in young children?

- Oral steroids should only be used in preschool children with episodic (viral) wheeze if they are so ill that a prolonged hospital course or high dependency unit care seems likely. They are not an out-patient therapy in this group.

Are steroids safe?

- High-dose inhaled corticosteroids may cause hypoglycemia due to adrenal failure and affect linear growth.
- Reduced bone-mineral density is a risk, especially if multiple steroid bursts are given.
- There are animal data suggesting steroids may adversely impact alveolar development.

candidates. Once we know the molecular and cellular pathways that lead to progression, a targeted therapy becomes more likely.

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