

Current drug therapies: relievers and preventers

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OUR ABILITY TO DEFINE the optimal treatment for infants and preschool children with recurrent or persistent wheeze is restricted by a number of factors, including

- The heterogeneity of wheezing phenotypes, which include transient infant wheezers, non-atopic virally induced wheezers and persistent, generally atopic, wheezers.¹
- The lack of objective markers to help predict the wheezing phenotype at the time of onset of symptoms, which would, in turn, help determine the need for and likely response to therapy.¹
- The influence of age and wheezing phenotype on response to treatment: for example, the increase in bronchodilator responsiveness with age,² and the lack of efficacy of inhaled corticosteroids in children with predominantly episodic viral wheeze.³
- The lack of data supporting the benefit of early use of anti-inflammatory agents in preventing long-term, irreversible impairment of lung function.¹

Furthermore, there remain many unresolved issues regarding the use of reliever and preventer medication to treat asthma in early childhood.

Reliever medication

Beta-agonists

β -Agonists are still the first-line reliever medication for managing acute asthma. A Cochrane review comparing the use of holding chambers (spacers) and nebulisers for β -agonist treatment of acute asthma has confirmed that β -agonists are effective using either mode of delivery in children as young as two years of age presenting to emergency departments.⁴ A recent randomised trial of salbutamol, again comparing spacer versus nebuliser delivery, in children less than two years of age presenting to the emergency department with "moderate to severe" wheezing also confirmed the benefit of β -agonists in this age group.⁵ Thus, despite the apparent age effect on bronchodilator responsiveness,² β -agonists appear to be effective even in infancy.

One issue that needs to be resolved is whether all wheezy infants will respond to bronchodilators. For example: (a)

ABSTRACT

What we know

- The different wheezing phenotypes in early childhood may influence the response to therapy.
- β -Agonists are effective in acute asthma from the first year of life and anticholinergics have been shown to provide additional benefit from at least 18 months of age.
- Non-steroidal preventer medications provide some benefit in early childhood asthma, but response is variable and dependent on severity.
- Inhaled corticosteroids are the most effective preventer medication in children with persistent asthma, but have not been shown to be effective in children with episodic viral wheeze.
- There is no convincing evidence to suggest that inhaled corticosteroids influence long-term outcome in childhood asthma.

What we need to know

- Can we distinguish different wheezing phenotypes at presentation (using clinical features or other markers of airway inflammation or airway hyperresponsiveness) in order to target therapy?
- What are the relative benefits of reliever and preventer medications in treating different wheezing phenotypes, and do all wheezing phenotypes require treatment?
- What is the dose-response curve for inhaled corticosteroids in infants and young children with asthma?
- Are infants and young children more susceptible than older children to growth suppression or other side effects from inhaled corticosteroids?
- Can early treatment with inhaled corticosteroids or non-steroidal medications influence long-term outcome in terms of asthma development and/or loss of lung function?

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what is the role of bronchodilators in infants with bronchiolitis? and (b) are β -agonists effective for treating children under two years of age with recurrent (not persistent) wheeze associated with upper respiratory tract viral infections? A recently completed Cochrane review of this issue concluded that there was no evidence of a clear benefit from using β -agonists in the management of recurrent wheeze in the first two years of life, although the available evidence was conflicting.⁶ The authors suggested that further studies should only be performed if the patient group could be clearly defined and there was a suitable outcome parameter for measuring a response.

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Anticholinergics

A Cochrane review of combined inhaled anticholinergics and β_2 -agonists for initial treatment of acute asthma in children aged 18 months to 17 years concluded that this combination of therapies, used in multiple doses, effectively improved lung function and also reduced hospital admissions, particularly in patients with severe acute asthma.⁷ For infants with airway obstruction, it has been suggested that anticholinergics may be more beneficial than β -agonists, because of the relatively high contribution of cholinergic-mediated mechanisms compared with the relative paucity of β -receptors in this age group. However, there is no consensus on this issue. The identification of specific subgroups of wheezy infants who respond better to this treatment may help clarify the role of anticholinergics in this age group.

Preventer medication

Non-steroidal medications

A recent systematic review of inhaled disodium cromoglycate (DSCG) as maintenance therapy in children with asthma aged 0–18 years concluded that there was insufficient evidence of benefit from DSCG and that it should no longer be recommended as a first-line prophylactic agent in childhood asthma.⁸ However, the review highlighted the variable methodological quality of the studies. Furthermore, the patients studied had moderate to severe persistent asthma, and daily symptom scores were used as the outcome measure.

In contrast, extrapolating from studies in older children, it appears that nedocromil sodium may still be of benefit in children with milder forms of asthma.⁹ The Childhood Asthma Management Program study demonstrated a significant reduction in urgent-care visits and prednisone courses over 4–6 years in the nedocromil-treated children compared with those receiving placebo.⁹

Leukotriene-receptor antagonists have also been shown to benefit children aged 2–5 years with persistent asthma,¹⁰ and may be a potential alternative to cromones and inhaled corticosteroids (ICS) in this age group. Given the apparent lack of efficacy of inhaled corticosteroids in children with predominantly episodic viral wheeze,³ further studies are required of the role of non-steroidal medications for children with this wheezing phenotype.

Inhaled corticosteroids

The role of inhaled corticosteroids (ICS) in the management of childhood asthma has recently been reviewed.¹¹ A systematic review of randomised trials examining the effectiveness of prophylactic ICS in children with asthma aged 0–18 years concluded that they were effective, compared with placebo, in improving both clinical outcomes (symptom scores and β -agonist use) and laboratory measurements (peak expiratory flow).¹² Most of the patients had persistent symptoms: there was a trend for ICS to be more effective in reducing symptoms when used at higher doses, and when

used in older children and in children with more severe disease.

In contrast, ICS have not been shown to benefit children with predominantly episodic viral wheeze³ (although only two randomised studies of children with this asthma phenotype have been performed to date, one of which was in preschool children). In particular, no reduction in hospitalisation, oral corticosteroid use or frequency and duration of acute episodes could be demonstrated. Thus, it is important to target the appropriate wheezing phenotype for treatment with ICS to maximise clinical benefit.

An important issue is whether ICS may have the potential for more side effects in infants and young children (particularly those with unresponsive wheeze) than in older children.¹ Of particular concern is statural growth. Although ICS have been shown to cause a short-term reduction in linear growth, especially in children with mild asthma,^{9,11} long-term treatment does not appear to affect final adult height.¹¹ However, these studies have been done in older children, and it is unclear whether initiating therapy in early infancy may have a more detrimental effect on growth. Furthermore, there is concern that early use of ICS in infancy may impair lung growth or enhance the development of the T_H2 -type immune response, thus promoting, rather than suppressing, the development of asthma.

Recent studies have suggested that targeted use of ICS according to wheezing phenotype may be useful.^{13–15} Kajosaari et al¹³ examined the effect of either seven days' or two months' treatment with nebulised budesonide during and after respiratory syncytial virus bronchiolitis. At two years' follow-up, 37% of children in the control group (symptomatic treatment only) were requiring asthma medication, compared with 18% in the seven-day budesonide group and 12% in the two-month budesonide group, suggesting a benefit of early treatment with ICS on subsequent wheezing episodes. Chavasse et al¹⁴ targeted infants with recurrent wheeze and a history of atopy (personal, or in a first-degree relative). In this group of infants, over a 12-week period, fluticasone provided a better outcome than placebo in terms of mean daily symptom scores and symptom-free days. In another study, Roorda et al¹⁵ found that the subgroup of wheezy preschool children (aged 12–47 months) most likely to respond to fluticasone were those with frequent symptoms and/or a family history of asthma. These studies demonstrate the importance of studying specific subgroups of young children with wheezing phenotype to better understand the role of ICS in their treatment.

Another unresolved issue is whether early treatment with ICS has the potential to prevent the persistent chronic inflammatory response that may lead to airway remodelling and impaired lung function.¹ The Childhood Asthma Management Program study,⁹ the first prospective study to examine this issue, failed to demonstrate any additional benefit of budesonide over nedocromil or placebo in terms of final lung function after 4–6 years of treatment.⁹ However, that study was undertaken in older children with mild to moderate persistent asthma and mean lung function in the normal range. As airway inflammation appears to commence early in life in children who go on to develop persistent wheezing, it may be important to target this

population in early childhood in order to prevent loss of lung function. Further studies are required in young children with the atopic wheezing phenotype to test this hypothesis.

Conclusion

If we succeed in developing methods of clearly distinguishing the different wheezing phenotypes at presentation, it will be possible to test the effectiveness of both reliever and preventer medications in these subgroups. We will then be able to establish with more certainty the role of these medications in treating early childhood asthma and to determine whether early use of preventer medication influences long-term outcome. At the same time, it will be important to determine whether the early use of ICS has any detrimental effects on growth or lung development in children.

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Therapeutic prospects for early asthma

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THE GLOBAL EPIDEMIC OF ASTHMA has triggered an international effort to understand the molecular basis of the disease and develop preventive or curative therapies. The pharmaceutical and biotechnology industries are investing billions of dollars in research to develop new classes of potential therapeutic agents. However, as our understanding of the molecular pathogenesis of asthma advances, the new insights gained into the disease may be best used to develop large-scale preventive interventions rather than new and expensive pharmaceuticals. We need to direct our efforts towards the most desirable therapeutic outcomes in early childhood, which include

- primary prevention of asthma;
- optimisation of lung function, especially in the first years of life;

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- suppression of disease exacerbations without impairing lung host defences;
- treatment of severe, refractory disease more safely and effectively;
- cure of established disease.

There is good evidence that immune deviation towards a net T_H2 cytokine pattern occurs early in asthma and contributes directly to disease (see page S47¹). However, in young children, mixed T_H1/T_H2 cytokine patterns have been found to be present concurrently. Physiologically, T_H1 - and T_H2 -biased immune responses reciprocally inhibit each other. It is a characteristic of lymphocyte immunobiology that during early immune deviation cytokine patterns remain plastic and can be realigned, but this plasticity is lost if stimulation is too intense or persists for too long.² In the early stages of asthma we perhaps have the best opportunity to use immune modulators to realign and fine-tune mucosal immunity away from an excessive T_H2 pattern and towards a neutral or balanced cytokine pattern. A fundamental ethical and medical issue is that almost all of the preventive agents currently envisaged would need to be given prophylactically to children at risk of asthma — yet our current