

Review Article

The use of inhaled corticosteroids in wheezy pre-school age children: Current practice and literature review

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Abstract

Preschool children and infants frequently suffer wheezy episodes, mostly associated with viral respiratory tract infections. There is no evidence to support the use of maintenance low dose inhaled corticosteroids to prevent or manage episodic mild wheeze caused by such viral infections. However, infants and young children with recurrent episodic wheeze and a positive asthma risk index (i.e. risk factors associated with a predisposition for the future development of asthma) should be considered for a short, three-month trial of an inhaled corticosteroid. Failure to respond to an inhaled corticosteroid should prompt its discontinuation and not an increase in the drug dose. Persistent wheezing should suggest a possibility of an alternate diagnosis and the child should be referred for further investigations. Some recurrently wheezy infants and children simply do not respond to inhaled corticosteroids and most symptoms remit spontaneously after the age of five years, especially among those who do not have an atopic predisposition. The use of large doses of inhaled corticosteroids in young children whose wheezing persists should be discouraged due to the significant risk of long-term effects.

Key words

Wheezing, pre-school age children, inhaled corticosteroids

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Introduction

The prevalence of asthma and other atopic diseases has increased dramatically worldwide over the last few decades but some investigators argue that the condition seems to be reaching a plateau.¹ However, asthma is still responsible for a significant degree of morbidity and to a lesser degree of mortality in the paediatric age group. The principles of management of asthma are aimed at the relief of symptoms and the suppression of the underlying chronic inflammatory processes in the airways. To this end, no drugs have been more successful in this than inhaled corticosteroids (ICS) and their use has heralded a new, effective and relatively safe management for the many patients who suffer from asthma. There is no doubt about the effectiveness of steroids in patients with asthma but the use of long-term inhaled steroids in pre-school age children and infants has raised several questions as to their effectiveness and possible long-term complications.

The management of wheeze in infancy is largely ignored in the asthma guidelines (Global Initiative for Asthma, GINA², and British Thoracic Society³, BTS), despite evidence of a differing aetiology and response to treatment when compared to older children.

Despite over one hundred therapeutic studies of bronchodilators and corticosteroids in infants and 40 studies using corticosteroids, clear consensus on best practice is lacking. Methodological issues, inappropriate outcome measures, and conflicting results have contributed to the uncertainty.⁴

This article will address the problem of wheezing in young infants and pre-school age children and review the literature on the use of ICS in the early years of life.

Background

Many young children and infants wheeze during the course of viral respiratory infections; however the pathogenesis of these episodes and their relation to the development of asthma later in life are not well understood.⁵ In a prospective study, the factors affecting wheezing before the age of three years and their relation to wheezing at six years of age were investigated in 1246 newborns in Tucson, Arizona. These children were assessed in infancy with measurement of cord-serum IgE levels, pulmonary-function testing before any lower respiratory tract illness had occurred, measurement of serum IgE levels at nine months of age, and questionnaires, completed by the children's parents when their offspring were one year old. Re-assessment

was performed again at six years of age. At the age of six, 51.5 % had never wheezed, 19.9 % had had at least one lower respiratory tract illness with wheezing during the first three years of life but had no wheezing at six years of age, 15.0 % had no wheezing before the age of three years but had wheezing at the age of six years, while 13.7 % had wheezing both before three years of age and at six years of age.

Children who had wheezing before three years of age but not at the age of six, had diminished airway function both before the age of one and at the age of six years and were more likely than the other children to have mothers who smoked, but not mothers with asthma; they did not have elevated serum IgE levels or skin-test reactivity. Children who started wheezing in early life and continued to wheeze at the age of six were more likely than the children who had never wheezed to have mothers with a history of asthma ($p < 0.001$), to have elevated serum IgE levels ($p < 0.01$) and normal lung function in the first year of life, and to have elevated serum IgE levels ($p < 0.001$) and diminished lung function ($p < 0.01$) at six years of age.

This long-term study has shown that the problem of wheezing in infancy and early childhood consists of two main groups of children. Patients with a parental history of asthma and serological markers for atopy were more likely to persistently wheeze after the age of six years. Patients who wheezed in infancy but did not have a parental history of asthma or markers for atopy were less likely to wheeze after the sixth year of life.

The majority of infants with wheezing have transient conditions associated with diminished airway function at birth and do not have increased risks of asthma or allergies later in life. In a substantial minority of infants, however, wheezing episodes are probably related to a predisposition to asthma.

There are several other studies that have investigated the natural history of wheezing disorders in infants and young children and results similar to those obtained by Martinez *et al.*⁶

Airway remodeling

Airway remodeling in established adult asthmatics and its subsequent irreversible negative effect on lung function has been addressed by several studies. The extrapolation of adult data to the paediatric age group is not possible as the duration and severity of symptoms are not common to both groups of patients. Although there are very few interventional studies with bronchoscopy and biopsy in children, several studies looking at long-term lung function have been performed.^{7,8} The conclusion from most of these studies was that the longer asthma symptoms persist and the longer the delay in introducing ICS, the more likely is the risk of irreversible changes in lung function.

The conclusions from several similar studies performed in the late 1990's lead to the concept of airway remodeling and long-term irreversible change in lung function. As a result, early introduction of inhaled corticosteroids was advocated and implemented. There is no doubt that this strategy is beneficial when asthma is established, especially when symptoms are

severe. It is of concern that in pre-school age children with wheezing, the effects of long-term ICS are not clear, when benefits and side-effects are considered. Little is known about the airway pathology of wheezing disorders in infants and preschool children, partly owing to the difficulty of undertaking invasive studies in this age group. If endobronchial biopsy is to be used to investigate the pathology of wheezing disorders in infants and preschool children, it is essential that the procedure is safe and that good quality biopsies can be obtained.

Asthma management guidelines are unsuitable for young children. Over the past decade, a number of guidelines have been published that are intended to help the clinician manage patients with asthma.⁹ Many guidelines recommend managing infants as if they were simply smaller versions of adults; with reference to preschool children, the GINA guidelines advice the use of a treatment algorithm similar to that used in school children, which, in fact, uses the same classification of disease severity as that used for adults. In the BTS guidelines, there is a warning concerning problems in the management of very young children that emphasizes the difficulty of diagnosis, the fact that most treatments have very poor efficacy, and that there are very few controlled trials of treatment in this age group.

Paediatricians have a particular problem in evaluating the severity of asthma in infants and young children, however, in the guidelines, this problem is ignored. Wheezing in infancy and early childhood cannot be fitted into the classification of asthma severity used by the guidelines aimed at treating older children and adults. Management should take into account the age and background of the child, the day-to-day disturbance to the life of the child and the family due to the wheezing or coughing attacks, as well as the response to a graded treatment strategy. The very common complaints of wheeze, cough, noisy breathing, and respiratory distress may also occur in young children with potentially more serious problems, such as foreign body aspiration, congenital airway or cardiac anomalies, and cystic fibrosis. The persistence of symptoms without remission and failure to thrive should suggest the possibility of a diagnosis other than asthma in a young child with atypical wheezing.⁹

Identification of infants and young children at risk of asthma

The majority of young children with wheezy lower respiratory tract infections have transient symptoms and a benign outcome. The health-related ethical and financial implications of blanket treatment of all young children and infants who wheeze is highly questionable. The task of identifying subjects at risk of future asthma in early life is hampered by the complex nature of the problem. Retrospective studies have helped identify markers and risk factors, which help the clinician answer the dilemma of which infant should be treated. As importantly, investigators who want to determine whether early treatment with anti-asthma therapy may change the natural course of the disease also need tools to identify those infants who may truly respond to such therapy.¹⁰

In 1999 Martinez proposed an algorithm (Table 1) similar to the Jones criteria for the diagnosis of rheumatic fever.⁵ The major and minor criteria are defined by their relative predictive power and those infants and young children with a positive asthma risk index should be considered at high risk for persistent wheezing after the age of six years and should be given a trial of inhaled corticosteroids. The criteria will also hopefully standardize selection of young children for future prospective studies on the effectiveness of ICS in the management of the young child with recurrent wheezing.

Studies on use of inhaled corticosteroids in young children

One of the major methodological deficiencies is that most studies have failed to make a distinction between infants and young children with an atopic predisposition and those with simple recurrent viral associated wheezing. In a study by Chavasse *et al.*, 148 U.K. based consultant paediatricians returned a questionnaire on how they manage wheezy infants. Salbutamol was the preferred bronchodilator for recurrent wheeze, whereas ipratropium was preferred in viral bronchiolitis. Doses of both medications varied widely and most respondents considered both inhaled and oral corticosteroids. There was an alarming range of doses unsupported by the literature and apparently paediatricians do not adhere to the current guidelines for asthma when treating wheezy infants. Inhaled corticosteroids (ICS) improve symptoms and reduce the number of exacerbations, even in toddlers with persistent wheezing, which strongly suggests the inflammatory nature of the disease. However, ICS generally do not provide full control in this age group.^{11,12} It is not known whether this is due to insufficient patient adherence, too low a dose of steroids, pharmacogenetic heterogeneity, or a distinct pathology in early asthma or in subgroups of wheezy young children. There are few reports on the inflammatory nature of persistent wheezing in young preschool children.

Table 1: Defining the asthma risk index. Children who meet one of the first two major criteria and any other of the major criteria and those who meet one of the first two major criteria and any two minor criteria should be considered to have a positive asthma risk index

Major criteria	Minor criteria
1. Hospitalization for severe wheezing / bronchiolitis.	1. Doctor diagnosed allergic rhinitis.
2. At least three wheezing LRI's during previous six months.	2. Wheezing apart from colds.
3. Parental history of asthma.	3. Eosinophilia >5%
4. Atopic dermatitis.	4. Male sex.

Recurrent episodic wheeze in association with viral upper respiratory tract infection (URTI) is a specific clinical illness distinct from persistent atopic asthma.

A wheeze that is recurrent and caused by a viral upper respiratory tract infection (URTI) is different to asthma. Episodic recurrent wheezing happens in children who have no symptoms in between episodes and is different to wheezing that is persistent. A Cochrane review of trials found that high-dose inhaled corticosteroids help treat mild episodic viral wheeze of childhood however there is no evidence to support the use of maintenance low-dose inhaled corticosteroids to prevent or manage episodic mild wheeze caused by viral infection.¹³

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The local situation reflects this theme in that children may be inappropriately placed on ICS therapy, and this was clearly demonstrated in a local audit performed in 2002.¹⁴ The study consisted of a retrospective analysis of clinical notes of 484 patients, less than 5 years of age who were started on inhaled steroids in the Outpatients Department in 2001. All new applications (468) were reviewed for demographic data and type of inhaled steroids prescribed. Out of these new applications, the clinical notes of 100 randomly selected patients were examined in detail.

These were further reviewed to identify when and what inhaled steroids were started and whether basic criteria for the introduction of inhaled corticosteroids were met. Finally an asthma risk index was calculated (as per Table 1) and this was related to the various age groups and the need for introduction of long-term inhaled steroid treatment.

Analysis of notes of 100 randomly selected patients

The number of patients less than two years of age totaled 174 while 340 patients were between the ages of two and five years. The patients less than two years of age included 96 who were less than one year old.

From a total of 100 patients 68% were male and 32% female. The age range was from 1 month to 60 months with a mean age of 22.7 months.

The total childhood population (Maltese) less than five years of age in 2001 was 21,748, and the number of children less than five years receiving inhaled corticosteroids was 484 (2.23%). Of the total number of patients whose notes were examined 45% had a negative asthma risk index while 55% satisfied criteria for a trial of prophylactic treatment.

The mean ages of both groups were 25 months and 22 months respectively.

It is clear from the results of the audit that an alarming percentage of children (2.23%) under the age of five years have been prescribed long-term inhaled corticosteroids without satisfying minimum criteria or adequate follow to assess the true impact of ICS on their wheezing.

Management approach

Wheezing in infancy and early childhood cannot be fitted into the classification of asthma severity used by the guidelines for older children and adults. Management should take into account the age, the disturbance to the everyday life of the child and the family due to the wheezing or coughing attacks, and the response to a graded treatment approach.

There will be symptom-free intervals lasting for weeks or months between attacks, during which treatment can be reduced or stopped. Some wheezy infants and children simply do not respond to treatment without necessarily having an alternative diagnosis. When a child is not responding to treatment, especially an inhaled corticosteroid, there is no reason for it to be continued.

Treatment is given, as needed using an inhaled selective beta₂-agonist bronchodilator until the attack is over using an appropriate inhalation device. A short course of corticosteroids may be useful especially in patients who have a recurrent history of wheezing. Those infants and young children with recurrent episodic wheeze and a positive asthma risk index should be considered for a short three-month trial of an inhaled corticosteroid.

When a child is not responding to an inhaled corticosteroid there is no reason for it to be continued. Persistent wheezing should suggest a possibility of an alternate diagnosis and the child should be referred for further investigations. Some typical wheezy infants and children simply do not respond to treatment without necessarily having an alternative diagnosis. Most of these young patients remit spontaneously after the age of five years especially those without an atopic predisposition. The use of large doses of inhaled corticosteroids in young children whose wheezing persists should be discouraged.

Conclusion

Persistent wheezing is the most common chronic disease in young pre-school children and a considerable burden to the child and health services. It is also a diagnostic and therapeutic challenge to health care providers. This is an area in which there is minimal investigation and evidence of efficacy of therapeutic measures and hence little data on which to make treatment decisions. Subgrouping wheezy children is helpful and may be attempted from the clinical picture and predisposition to atopy.

Inhaled corticosteroids provide only modest beneficial effects in such children and further studies are required to define their role. The use of criteria for the identification of an atopic predisposition and hence a positive risk of developing asthma in later life should be encouraged.

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