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Arch Dis Child Educ Pract Ed published online July 30, 2010
doi: 10.1136/adc.2009.171272

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The use of inhaled corticosteroids in the wheezy <5-year-old child

B R Davies,¹ W D Carroll²

¹Nottingham University Hospitals NHS Trust, Nottingham, UK

²Derbyshire Children's Hospital, Derby, UK

Correspondence to

Dr Will D Carroll, Derbyshire Children's Hospital, Uttoxeter Road, Derby DE22 3NE, UK; will.carroll@nhs.net

Accepted 7 April 2010

ABSTRACT

Inhaled corticosteroids are established as the most effective long-term anti-inflammatory therapy for asthma. National and international treatment guidelines recommend the use of these agents for long-term asthma control in children. In children <5 years, there are significant difficulties in diagnosing asthma. There are multiple non-asthma causes of wheeze, and there remains a lack of consensus in the description of wheezing phenotypes in this group of children. There is also a relative paucity of data concerning the short- and long-term effectiveness and side-effects in the under-fives: treatment recommendations have drawn heavily from experience of asthma treatment in school-age children and remains controversial. This article discusses the important recent advances in the evidence-base and current expert opinions which are helping to delineate improved outcomes for young children with wheeze.

Wheeze is a very common symptom in the pre-school child. Birth cohort studies have demonstrated that approximately one third of children aged between 1 and 5 years suffer recurrent episodes of respiratory symptoms including wheeze.¹ Wheezing prevalence in UK children has increased twofold to threefold during the past 40 years but may have stabilised or even peaked in the early 1990s.² Fortunately, the majority of young children with wheeze tend to have only transient symptoms and do not have subsequently increased risk of asthma or allergy in later life.³ Childhood wheeze nevertheless presents a major burden of morbidity during preschool years, and there is significant progression from some childhood wheeze to adult asthma. More than 25% of an unselected birth cohort of children had wheezing that persisted from childhood into adulthood or that relapsed after remission.⁴ Despite the prevalence of childhood wheeze, controversy and confusion exist over which treatments are effective in an individual child. This review attempts to discuss the role of inhaled corticosteroids (ICS) in management of wheeze of children <5 years.

SOURCES AND SELECTION CRITERIA

We searched PubMed and Cochrane databases using the terms "asthma", "wheeze" and "inhaled corticosteroid" limiting the age range to children (or "preschool children" where available) and selecting what we deemed to be clinically relevant articles. We also used the evidence based GINA and BTS/SIGN guidelines which we recommend

to readers. Citation searching of publications identified by database searches and guideline review identified important recent related references. We drew on our personal archive of references and included pertinent evidence from older children and adults when data are lacking in preschool children.

THE DIAGNOSIS OF ASTHMA IN CHILDREN

Diagnosis of asthma in the under-fives is challenging due to the multiple non-asthma causes of early childhood wheeze and relies heavily upon clinical judgement since it is difficult to measure airflow obstruction in this age group. Features suggesting important alternative diagnoses include neonatal onset of wheeze, focal cardiovascular or respiratory signs, symptoms associated with vomiting and failure to thrive. Such cases merit further investigations to rule out the diagnoses listed in table 1.

Recent asthma management guidelines have moved beyond the exclusion of alternative causes of airway obstruction towards acknowledgement that the diagnosis of asthma in children is probability-based. Clinical indices such as the Asthma Predictive Index (API) have been developed based upon easily obtainable clinical parameters such as the presence of wheeze <3 years, parental history of asthma or eczema, eosinophilia, interval wheeze and allergic rhinitis.⁵ Their use is recommended for the early identification of serially wheezing patients at high risk of developing persistent asthma symptoms.⁶ There are concerns that such indices are insufficiently powerful to be of clinical value for individual patients.^{7 8} The most recent iteration of the British Thoracic Society/SIGN Asthma guidelines give treatment recommendations based upon a risk stratification of patients into high, intermediate and low probability of asthma groups, and ICS are mainstay therapy in the treatment of childhood asthma.⁹

However, "all that wheezes is not asthma"—particularly in the <5-year-old where clinical assessment and management is most appropriately determined by "wheezing phenotype". A recent consensus statement from the European Respiratory Society has discouraged the use of the term "asthma" in preschool children (<5 years) altogether.⁷ There is insufficient evidence showing that the pathophysiology of preschool wheezing illness is similar to that of asthma in older children and adults.¹⁰ For this reason, consideration of the wheezing preschool child may best be considered with respect to history and symptoms

Table 1 Alternative causes of recurrent wheeze in infancy

Recurrent viral infection
Recurrent aspiration of feed/foreign body aspiration
Gastro-oesophageal reflux
Prematurity
Tracheobronchomalacia
Cow's milk protein allergy
Tuberculosis
Immune deficiency
Cystic fibrosis
Congenital abnormality of lung, airway or heart
Primary ciliary dyskinesia

alone since little benefit is gained from investigations such as lung-function testing or bronchial challenge.^{7 11}

WHEEZING IN THE PRESCHOOL CHILD

Descriptions of patterns of wheezing in preschool children first arose from longitudinal population surveys of wheeze in the Tucson Children's Respiratory Study.³ The initial phenotype description encompassed *transient early wheeze* (presenting <3 years and commonly outgrown by the age of 6), *persistent early-onset wheeze* (presenting <3 years and persisting into late childhood) and *late-onset wheezing* (not present by 3 years but reported at age 6). These phenotypes have been refined and expanded over the years and other wheezing phenotypes (intermediate onset and prolonged-early wheeze) have also been proposed.¹² There has been a lack of consensus in the definition of some of these phenotypes. With respect to clinical management of a wheezy <5-year-old, such phenotypes may prove confusing for the clinician and there is controversy over their prospective validity. A simpler, two-phenotype, descriptive system for children <5 years has recently been proposed.⁷

Episodic (viral) wheeze describes those children who wheeze in discrete episodes, commonly 2–4 weeks in duration, but are well between episodes. The trigger for such episodes is commonly viral upper respiratory tract infection. *Multiple-trigger wheeze* describes those who similarly wheeze during discrete episodes and have intermittent symptoms between episodes. Symptoms include nocturnal wheeze or cough and triggers may include cold air, exercise, laughing or crying. Classification may be made by the clinician based solely upon the history. Children may not fit clearly into either category, and there is necessarily overlap between these phenotypes which describe the extremes of a clinical spectrum in preschool children and reflect the multifactorial nature of wheeze. They are not fixed diagnoses but aids to communication, management recommendations and future research; children may thus “move” from one phenotype to another.

While this simplicity may enable a rational approach to treatment, the classification does not allow for a prediction of the likelihood of subsequent development of “true asthma”; that is, persistent,

atopic, multiple-trigger wheezing. It is the clinical progression from episodic to multiple-trigger, unremitting wheeze with atopic features such as dermatitis, aeroallergen sensitisation and impaired lung function that defines asthma—not the clinical presentation of early wheezing episodes.⁸

The evidence base for therapies such as ICS in wheezy preschool children is complicated by mixed and inconsistent recruitment of patients with conditions ranging from viral wheeze through asthma to bronchiolitis.^{8 13} Use of the terms episodic and multiple-trigger wheeze should allow clear communication and facilitate future therapy trials.

Respiratory viral infections are likely to play an important role in the development of wheeze and asthma.^{14 15} Infection with respiratory syncytial virus in early life is an independent risk factor for wheeze (though not for atopic asthma), and the importance of rhinovirus is increasingly being recognised.^{16–19} Rhinovirus infection has been implicated in the “September Bounce” phenomenon—the epidemic of paediatric asthma exacerbation requiring hospitalisation between the end of September and early November in many northern hemisphere countries. Asthma control medications—particularly ICS—appear to be protective against hospitalisation through viral-associated symptom exacerbation.²⁰ In children with atopic asthma (3–17 years), treatment with ICS protected against acute exacerbation (OR 0.2, 95% CI 0.1 to 0.6; $p=0.002$).²¹

AIMS OF THERAPY IN THE WHEEZY PRESCHOOL CHILD

Despite initial enthusiasm for ICS, it is now well established that no disease-modifying therapy for wheezing in preschool children exists. Two-year ICS treatment of <4-year-olds with a positive API resulted in no subsequent disease-modifying impact after discontinuation of therapy.²² Therefore, treatment of this age group is aimed at the relief of symptoms to allow the child to lead as normal a life as possible with as little medication and disruption of family life as possible. Short-acting β_2 -agonist therapy is the treatment of choice for acute symptoms of wheeze (episodic and multiple trigger). Regular, maintenance ICS in multiple-trigger wheeze result in improved symptoms, exacerbation rates and lung function, but the use of intermittent ICS is more controversial.²³

The intermittent use of ICS (budesonide at daily doses >400 μg) in wheezing preschool children has been demonstrated to provide no measurable clinical benefit in two separate randomised controlled trials,^{24 25} although there is some evidence for modest improvement in breathing difficulty and activity limitation in those patients with a high API.^{25 26} A third, smaller study using high-dose fluticasone (750 μg twice daily) found evidence of a reduction in the requirement for rescue oral steroid use in preschool children with episodic

viral wheeze.²⁷ Given that the receipt of four or more courses of oral prednisolone during childhood increases fracture risk by 32%,²⁸ ICS use to minimise oral steroid requirement may prove important in the future. However, this preventive rationale for ICS cannot be currently recommended due to current uncertainty regarding the long-term bone health effects of very high-dose ICS themselves. Current consensus opinion is that the use of high-dose, intermittent ICS should be decided on a case-by-case basis, especially in children with a positive API.¹³ Montelukast is recommended at the start of an episode of viral-induced wheeze while regular maintenance ICS are of benefit for multiple-trigger wheeze.⁷ Overlap and clinical evolution between episodic and multiple-trigger wheeze mean it is reasonable to attempt a trial of montelukast and ICS in any preschool child with recurrent wheeze. Therapy should be subsequently modified on the basis of clinical benefit.

Assessment of clinical response in older children has been aided by the development of validated clinical control assessment tools. A seven-item questionnaire has been developed and validated for children between the ages of 4 and 12.²⁹ No validated tool exists for children <4 years, although working guidelines based upon frequency of symptoms, exercise limitation and need for reliever therapy have been developed for use in the under-fives.¹¹

INHALED CORTICOSTEROID THERAPY

ICS are prescribed for an intended "topical" action. Significant established effects of ICS include up-regulation of β_2 -receptors and inhibition of the inflammatory response in a wide variety of cell types including mucosal mast cells, eosinophils, fibroblasts and macrophages.^{30–33} It is postulated that ICS may cause symptomatic relief through vasoconstriction in the bronchial mucosa and decreased airway oedema.³⁴

The major proportion of administered ICS is swallowed.³⁵ Different corticosteroids vary in terms of the bioavailability of this swallowed proportion—for example, fluticasone propionate is largely destroyed by first pass metabolism—and in several other key factors impacting their clinical efficacy, toxicity and side effects.³⁶ In vitro studies of corticosteroid anti-inflammatory activity consistently demonstrate potency differences among different corticosteroids.³⁷ There is wide variation between available ICS in terms of lipophilicity, lung delivery profiles and receptor-binding pharmacodynamics; this might suggest varying clinical efficacy. Current evidence suggests that the available ICS provide similar efficacy at low to medium (less than 400 μg of beclomethasone equivalent) doses.³⁷ Side effects vary according to oral absorption, lung deposition profiles, systemic bioavailability of the inhaled proportion, half-life and pharmacokinetic differences such as fatty acid esterification (ICS such as ciclesonide are delivered as inactive precursor molecules requiring activation by airway esterases). Variations in lung

deposition may have a marked effect upon clinical efficacy and side-effect profile. There are suggestions that ciclesonide (widely available in other European countries but not currently licensed for paediatrics in the UK) may achieve greater pulmonary deposition, cause fewer adverse oropharyngeal effects, deposit less biologically active drug in the systemic circulation and have less potential for adrenal suppression than fluticasone dipropionate.³⁸

The choice of ICS in the under-fives is limited by licensing restrictions and a paucity of data: dose–response relationships for different ICS are seldom available for the under-fives. Table 2 summarises consensus (from guidelines and manufacturer information) dose recommendations in older children and adults compared to the limited "low daily dose" recommendations for under-fives.

DIFFICULTIES WITH INHALED THERAPY IN THE UNDER-FIVES

It is important to consider the practicalities of the administration of ICS to children <5 years. There may be factors intentional and non-intentional that may undermine the benefits of ICS therapy in the very young. Parental concerns about steroid therapy adversely affect adherence and inhaler therapy adherence progressively declines when continued for longer than 3 months.^{39,40} This reinforces the importance of family education and the development of asthma management plans to optimise treatment adherence.

Administered dose of ICS in young children is controversial as previously considered. Adults and children <5 years given the same inhaled dose of budesonide demonstrate similar plasma concentrations which suggests that doses similar to adult recommendations may be safe in children.⁴¹ Initial ICS dosage recommendations for the under-fives are 100 μg of beclomethasone or fluticasone propionate or 200 μg of budesonide.¹¹ If control is not achieved after 3 months, dosage doubling may be considered,^{11,42} although inhaler technique and consideration of different ICS formulations may prove more beneficial.

The major factor limiting ICS therapy in the under-fives is cooperation. Aerosol lung deposition may be as low as 0.1% in a screaming, uncooperative child, but as high as 5% in a calmly breathing child.³⁵ Inhaled particle size may also be an important determinant of effective delivery, with small particles possibly more likely to reach the small airways.⁴³ There is currently no randomised-controlled-trial evidence to support the use of smaller aerosol formulations in young children.

There are considerable challenges in ensuring optimal delivery of inhaled medications to the lungs of small children. The use of age-appropriate spacer systems to improve cooperation and small aerosol particle drug formulations may improve lung deposition in young children.⁴⁴ Although nebulisers have been used in some studies,⁴⁴ the

Table 2 Dose comparisons of inhaled corticosteroids in order of increasing lipophilicity

Drug	Low daily dose (µg)*	Medium daily dose (µg)†	High daily dose (µg)‡
Budesonide	200	200–400	>400
Beclometasone dipropionate	100	200–400‡	>400
Fluticasone§	100	100–200	>200
Mometasone furoate¶	200	200–400	>400
Ciclesonide¶	80	80–160	>160

*Low daily doses recommended by GINA as those doses not associated with clinically adverse effects in trial evidence.

†Consensus doses for older children or adults.

‡Note differing potency of non-CFC propellant formulations QVAR and Glenil Modulite.

§Fluticasone is not licensed in children <4 years.

¶Mometasone furoate and ciclesonide are not currently licensed for children <12 years in the UK.

provision of home nebulisers to families is often counterproductive in our clinical experience as it encourages parents to seek medical review later than they might do otherwise.

SIDE EFFECTS OF INHALED CORTICOSTEROIDS

Much of the literature evaluating potential side effects of ICS has involved children >5 years. Presently available evidence suggests that low and medium doses (<400 µg beclometasone equivalent) of ICS are effective and safe with potential risks outweighed by clinical benefits.¹¹

Concerns regarding possible retardation of growth by long-term steroid therapy were initially raised by studies with follow-up periods of less than a year.^{45–46} Evaluation of childhood growth rates is, however, notoriously difficult, and satisfactory assessment cannot be made over periods of <1 year.⁴⁷ Decreased growth rate during the first year of ICS therapy (200 µg budesonide) has been robustly demonstrated in children >5 years, but this retardation is not apparently maintained during subsequent therapy.⁴⁸ A 10-year prospective study of children receiving regular inhaled budesonide (variable dose with mean dose 412 µg) until attainment of adult height revealed an initial decrease in growth velocity during early budesonide therapy but found no statistically significant difference between attained and predicted adult heights.⁴⁹ Uncontrolled asthma and socioeconomic class appear to have a more significant impact upon growth velocities and adult height than ICS.

Caution is needed in applying such data to the use of ICS in the under-fives as growth patterns before and after the age of 3 are quite different.⁵⁰ A 1-year study found no significant alteration in annual growth velocity in wheezy 1–3-year-olds taking 100 µg of fluticasone propionate twice daily.⁵¹ Another study demonstrated a significant, but apparently temporary, decrease in growth rate in preschool children treated with 88 µg fluticasone propionate twice daily.²² Long-term data studying the effect upon adult height of corticosteroid therapy on wheezing in the under-fives is unavailable. There remains the potential for growth retardation with high-dose ICS, but anxious parents may be reassured that children

treated with recommended dose ICS attain their predicted adult height—but at a later age.^{6–52}

Observational studies and randomised trials in adults have identified osteoporosis and increased fracture risk as potential adverse effects upon bone health associated with corticosteroid use. Evidence regarding bone health and corticosteroids in children <5 years is limited.

Case-control analysis of the UK General Practice Database (3744 cases and 21 757 controls) found no increased incidence of fractures in children ranging between 5 and 17 years old who had used ICS for any period of time.⁵³ A randomised controlled trial of 2 years of fluticasone (200 µg daily) versus nedocromil therapy in children between 6 and 14 found no significant differences in bone growth or the increase of bone mineral density.⁵⁴ No correlation has been demonstrated between dual energy x-ray absorptiometry measures of bone growth and budesonide treatment (mean dose 504 µg) for up to 6 years.⁵⁵ There may even be a protective effect of inhaled steroid therapy upon bone health: uncontrolled asthma reduces bone metabolism and mineral density through direct effects on osteocalcin and through reduced physical activity in children.⁵⁶

No overall adverse effect upon bone mineral density from ICS has been identified in studies in older children. There have been no long-term prospective studies following children using inhaled steroids early in life through to attainment of maximal adult bone density.

Other ICS side-effects seen in adults and older children such as voice hoarseness and candidiasis have been seldom reported in children <5 years.⁵¹ There is no evidence for increased occurrence of cataract development in children with inhaled budesonide.^{48–55} At higher doses, there is some evidence that ICS (in particular fluticasone propionate at doses higher than 500 µg daily) may precipitate acute adrenal crisis.⁵⁷

Up until recently, it has been commonly believed that decreased airway function in wheezy infants is secondary to airway narrowing and that the responsiveness of symptoms to ICS reflects wheeze aetiology: allergic/asthmatic inflammatory wheeze demonstrating good response to steroids and viral wheeze with decreased airway calibre being less responsive.⁵⁸ This may be an oversimplification since high-resolution computerised tomography of children with recurrent wheeze has demonstrated that decreased airway function in wheezy infants is not related to reduction of airway lumen.⁵⁹ The observed decrease in forced expiratory flow may result instead from alternative mechanisms such as reduced alveolar septation, decreased pulmonary elastic recoil or increased airway collapse. Altered lung microanatomy in childhood wheeze may prove very significant given epidemiological suggestions of a link between early childhood wheezing and adult chronic obstructive pulmonary disease.^{60–61} There is no suggestion that ICS have protective effect upon

this possible link, but animal studies have demonstrated the potential sensitivity of lung development to corticosteroids.⁶² Corticosteroids may adversely impact upon lung growth and have detrimental developmental effects upon airway wall thickness and lung microanatomy. ICS in early childhood, therefore, have the potential to be another paediatric factor predisposing to adult respiratory disease.

CONCLUSION

Recent expert opinion has moved away from early diagnosis of asthma as it is clear that no therapy exists that can modify progression from preschool wheeze to asthma. The use of the term "asthma" should be limited to those children with a clear personal or family history of atopy. Wheeze in the under-fives might be most usefully described as either episodic or multiple-trigger wheezing and this simple classification might enable a clearer vision of appropriate management strategies in the future. Assessment of potential side-effects of ICS in the under-fives is largely extrapolated from studies in older children as there is currently limited data in the preschool age group. Long-term follow-up studies are needed to assess impact upon bone health and alveolar development.

Intermittent ICS remain of controversial benefit and must be considered on a case-by-case basis. Regular maintenance ICS therapy may have significant clinical benefits, particularly in multiple-trigger wheeze or children with a positive API.

In reality, recurrent wheezing in children <5 years is caused by a number of overlapping clinical syndromes which respond variably to treatment with ICS or montelukast. The key to successful management of these children requires careful assessment of the wheeze phenotype, close monitoring of clinical response to any treatment strategy and subsequent adaptation of therapy. As with all medicines, the potential transient benefits of ICS must be weighted against the risks of short- and longer-term side effects.

Practice Points

- ▶ Inhaled corticosteroids have dose-dependent and predictable side effects. In younger children, the variability in dose delivery increases.
- ▶ Careful monitoring of children's growth is a useful guide as adrenal suppression is often associated with faltering growth.
- ▶ If high doses (>400 µg of beclometasone equivalent) are used then the risks are greater, and it is important to discuss potential side effects with the family.
- ▶ There are clinical potency differences between different ICS and also between different formulations of the same ICS—for example, the CFC-free Beclometasone inhalers QVAR and Glenil Modulite are not equipotent and should not be prescribed generically.

Competing interests BRD has no potential conflict of interests. WDC has received payment for advisory board work and speaker fees from GlaxoSmithKline, Merck Sharpe Dome, Nycomed, Novartis and Schering Plough.

Contributors Both authors contributed equally to this work.

Provenance and peer review Commissioned; externally peer reviewed.

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