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**DISCUSSION PAPER**

# Pro-con debate: Inhaled corticosteroids should not be prescribed in primary care to children under two years of age – the case for

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**Abstract**

Inhaled corticosteroids (ICS) are effective treatment for older children and adults with asthma. Pathological studies have established that eosinophilic inflammation is important especially in mild to moderate asthma, thus providing a rationale for ICS treatment. However, we have wrongly concluded in the past that early and aggressive treatment of asthma is needed to prevent irreversible scarring and airflow obstruction. We have increasing evidence from all age groups that there are non-eosinophilic asthma phenotypes, that remodelling is independent of inflammation, and that steroids do not prevent children developing progressive airflow obstruction. Asthma treatments that are valuable in adults may not be effective in children, and safe prescribing requires paediatric clinical trials. In young preschool children, the evidence for any eosinophilic airway inflammation is scant, the symptomatic benefit of inhaled steroids is meagre, and there is clear evidence that ICS do not modify the natural history. There is also the potential for steroids to interfere with the developing lung. Thus, we believe that ICS should not be prescribed in primary care for children under two years of age, and that if these children are thought to need more than intermittent therapy with beta-agonists or possibly leukotriene antagonists, specialist referral is mandatory.


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**Keywords** asthma, preschool wheeze, inhaled corticosteroids, hypoglycaemia, side effect, leukotriene antagonists

## Introduction

The history of the treatment of children with inhaled corticosteroids (ICS) includes much inappropriate and overuse of this precious asset. Whilst this has also occurred with other respiratory treatments, inappropriate use of ICS has arguably had the greatest implications. Paediatricians and primary care clinicians alike have been guilty of swallowing uncritically the proposition that steroid responsive inflammation is the root of all asthma (and even wheezing illness), that all asthmatics must therefore be treated with anti-inflammatory medications, and that failure to prescribe anti-inflammatory therapy is akin to Nero fiddling while Rome burned because the patient's airways would remodel and scar and irretrievable damage would be done if ICS were not prescribed. As a result, a treatment (ICS) which is undoubtedly highly beneficial when appropriately used has been inappropriately prescribed, and children in particular have been put at unnecessary risk.[1,2] How did this happen, why were we taken in, and what lessons can be learned? The aim of this paper – which is a personal view based on a review of important new evidence – is to contrast current recommendations, in the light of this new evidence, with past and present clinical practice.

## Asthma as an inflammatory condition?

There is no doubt that the early bronchoscopic studies which established that very highly selected groups of patients with asthma had eosinophilic airway inflammation were truly ground-breaking.[3-6] They established a rationale for the use of anti-inflammatory therapy for asthma, rather than merely

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papering over the cracks with bronchodilators.

However, from the solid rock of careful observation sprung a veritable tidal wave of speculation which has since carried us far from our base. Thus, it was assumed without caveat that airway inflammation caused bronchial hyper-responsiveness, which caused asthma. The cardinal rule of the great Dr Richard Asher – never to mix the clinical and the pathological in definitions – was discarded, and inflammation was built into the definition of asthma, which had hitherto been clinical and physiological.[7] As Asher pointed out, once thinking becomes corrupted, loose talking follows, so it was uncritically assumed that all asthmatics, and worse, all patients who wheezed, had inflamed airways.

Next, the pathological changes of remodelling were assumed to be the results of repeated bouts of inflammation, cycles of inflammation repair and regeneration, an argument for which at the time there was not one scintilla of evidence, and which is now becoming increasingly discredited.[5,8] An excellent study attempted to show that if there was a delay of two years or more in initiating ICS therapy in asthma, then long term airway function would be impaired.[9] This study inevitably suffered from patients crossing over between groups, and in any case, did it really have a message for the treatment of children? It appeared to be confirmed by a retrospective, uncontrolled, non-randomised observational study in children from Copenhagen, in which it appeared that those children treated for more than two years with prophylactic therapy other than ICS (chromones, theophyllines) had worse lung function than those treated from an early stage of asthma with ICS.[10] As "steroid fever" reached its height, the 2nd iteration of the British Thoracic Society (BTS) guidelines encouraged the early use of inhaled steroid therapy at a high dose, subsequently stepping down to find the minimum controlling dose, despite the lack of any evidence whatsoever that this was beneficial in terms of any outcome measure.[11]

However, the absence of evidence has not precluded the prescribing of high doses of ICS in children, as shown by a recent UK primary care database study of data from 2003 showing that over 5% of children aged under five who received treatment with ICS were being prescribed doses greater than 400 mcg per day.[12]

## The damping down of "steroid fever"

*On fire that glows, With heat intense, I turn the hose, Of common sense, And out it goes, At small expense*

Thus wrote WS Gilbert, and this was a favourite quotation for Dr Asher. There are gratifying signs that the steroid fever is abating, and that ICS are being restored to their proper (and highly beneficial) place, with less children receiving them today than in the early 1990s.[13]

Firstly, it has become clear that there are different cellular phenotypes of asthma – eosinophilic, granulocytic, mixed cellularity, pauci-cellular – and that not all benefit from treatment with ICS.[14,15] Indeed, in severe asthma, cellular inflammation may be rare, despite ongoing symptoms.[16] We do not expect primary or indeed secondary care to be able to differentiate between these phenotypes easily, but we do expect an acknowledgement that not all wheeze is due to airway eosinophilia.

Secondly, it has been noted that at least some elements of remodelling were fully developed in childhood, and that these were independent of disease duration, any marker of inflammation, or anti-inflammatory therapy.[5,6] Symptoms and bronchodilator reversibility precede inflammation and remodelling,[17] and both are apparent by the age of three,[8] corresponding neatly with the findings of cohort studies of the evolution of lung function changes in asthma.[18,19] Furthermore, in mild paediatric asthma, there is no real advantage to lung function in a group prescribed ICS,[20] nor did ICS prevent the deterioration in lung function that occurred in about 25% of the children studied.[21] The hypothesis that inflammation causes airway hyperreactivity unravelled when it was shown that there was little correlation between the two,[22] that inflammation could be reduced without change in airway reactivity by treatment with anti-IgE (omalizumab),[23] and that airway reactivity could improve (with etanercept) with no change in airway inflammation.[24] Consequently, the latest BTS guidelines have become much more cautious about starting treatment with high dose ICS.[25]

Finally, adult physicians have discovered a factor which leads to a 100-fold reduction in overall ICS dosage with no adverse effect on any major asthma outcome – prescribing ICS for as-needed rather than regular use...[26]

## The importance of having appropriate data

Before we turn to prescribing in small infants, we need to address the lessons of the past just as another potential storm-cloud lurches over the horizon – prescribing for young children with wheezing disease. We have made mistakes with the prescribing of ICS in the past through:

(a) being guilty of muddled thought about the different types of asthma encountered, particularly in infancy; and
(b) accepting without critical thought concepts which may (or may not) be relevant in adults, but for which there are no data in childhood.

The prescribing of long-acting $\beta_2$-agonists in young children could become a similar issue; there are good studies in adults testifying to their efficacy, but the current data in children are far less convincing.[27-30] So, we need to insist that

good data is obtained. Hopefully, this will be easier in the wake of new European Union legislation which should abolish this reverse ageism.[31]

## Recent evidence on the use of ICS in children aged two years or under

What are the implications for children in the first two to three years of life? Inhaled steroids might be justifiable if they prevented disease progression (from intermittent to continuous, multi-trigger wheeze), prevented flare-ups of disease, or provided current symptom prevention. Four good studies have shown that neither continuous nor intermittent inhaled steroid prevents disease progression.[32-36] In fact, oral steroids given acutely have failed to show benefit. In a placebo-controlled trial where they were used intermittently in wheezing children aiming to prevent hospitalisation the opposite was in fact found, with a trend towards greater hospitalisations in those given oral steroids.[37]

What about present symptoms? The key study which illuminates this looked at infants at high risk for progression to asthma, the very group that would be expected to benefit from inhaled corticosteroids. After two years of treatment, the beneficial effects had built up to a clinically unimpressive 2-3 extra symptom free days per month, or the difference between 1-2 days or 3-5 days of symptoms per month.[34] This statistically significant, but clinically trivial effect, came with a price – a reduction in linear growth, trivial in itself, but worrying evidence of a systemic effect. What might have been the effect on the developing adrenals (not measured) or other vulnerable organs? Furthermore, what might be the effect on alveolar development? The vast majority of alveoli develop postnatally, in the first 18 months of life in particular. In animal models, parenteral and nebulised steroids impact adversely on alveolar development;[38-39] we simply do not know about the risks of inhaled steroids in this setting. The IWWIN study[36] reported evidence of increased airflow obstruction in their fluticasone-treated group; these data are difficult to interpret since there were no pre-treatment lung function tests, but is it possible that the ICS adversely affected alveolar development, reducing alveolar attachment numbers and thus causing airflow obstruction?[40]

Thus, in the first two years of life, the risks of ICS are not known but could be significant, and the benefits are minimal, even in a group that would be predicted to have the greatest benefit. What then is the logic of using a therapy which is powerfully anti-eosinophilic? At age one year, a group of really severe wheezers who were atopic and had bronchodilator reversibility, had no evidence of eosinophilic inflammation.[17] Bronchoalveolar lavage studies have also failed to show eosinophilic inflammation in children with preschool wheeze, instead revealing a neutrophilic cellularity similar in magnitude to a group of children with cystic fibrosis,[41] a condition in which inhaled steroids are notably ineffective.[42] Steroids may in theory actually increase neutrophilic inflammation by prolonging their lifespan by reducing programmed cell death (apoptosis).[43]

## Recommendations

Thus, we suggest that a child in this age bracket in whom the prescription of regular ICS therapy is contemplated, should be seen by a specialist for two main reasons. Firstly, it is necessary to exclude important differential diagnoses, the most common being 'Nursery school syndrome' in which a series of coughs and colds merge into a hideous continuum that is non-responsive to all therapies including ICS. The differential diagnosis of pre-school wheeze has recently been discussed in this Journal.[44] The second reason for referral is to monitor response to therapy, including a trial without therapy. In fact, two studies, undertaken with broad representative populations drawn from primary care, have failed to provide evidence of any efficacy for ICS in young children.[45,46] However, this is not meant as an argument that all infants who have symptoms with colds which are unresponsive to bronchodilators and leukotriene receptor antagonists should be seen in secondary care; rather, they should not be given ICS, other than for such exceptional reasons that a specialist review is mandated first. This specialist review can occur in either primary or secondary care.

Intermittent symptoms should be treated intermittently as there is no evidence of benefit with regular inhaled steroids;[47,48] bronchodilators or possibly leukotriene receptor antagonists[49] should be used in those with recurrent disease and significant morbidity, assuming that the child merits treatment at all – the emphasis purely being on relief of current symptoms and their impact. A funny noise is not in itself sufficient evidence that medication is required. If the child apparently has continuous symptoms, then what is needed is a diagnostic review, not ICS. In many cases symptoms will be non-specific in a well, thriving child, and reassurance is all that is needed and all the parents want. However, it may be that there is a more serious underlying diagnosis, such as chronic bacterial bronchitis, which needs different treatment.[50,51] It may be that there are a very, very few atopic two-year old children who genuinely benefit from ICS; but we suggest that the safe option is for them to be identified only after a specialist review.

John Buchan, of *The Thirty Nine Steps* fame, declared that his father, a Scottish minister, was terrified of finding himself on a side which was superior in numbers.[52] Those who have taken the majority view in the past about the prescription of ICS in young children might do well to reflect on these words, as we do.

### Conflict of interest declaration

AB has no financial conflict of interest with regard to the subject of this manuscript. DP has no shares in pharmaceutical companies. He has received speaker's honoraria for speaking at sponsored meetings from the following companies marketing respiratory products: 3M, Altana, AstraZeneca, BI, GSK, IVAX, MSD, Novartis, Pfizer, Schering-Plough. He has received honoraria for advisory panels with; 3M, Altana, AstraZeneca, BI, GSK, IVAX, MSD, Novartis, Pfizer, Schering-Plough. He or his research team have received funding for research projects from: 3M, Altana, AstraZeneca, BI, GSK, IVAX, MSD, Novartis, Pfizer, Schering-Plough, Viatris.

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