IT IS NON-ETHICAL TO TREAT CHILDREN UNDER 3 YEARS WITH INHALED CORTICOSTEROIDS: PRO

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Treatment may be given as primary prevention (to pre-empt the development of a disease), for symptomatic treatment, and as secondary prevention (to prevent the development of complications of a disease which is present). There is no suggestion that inhaled steroids should be used as primary prevention, so the debate centres on symptomatic treatment and secondary prevention. This manuscript begins with some context on the pathophysiology of wheeze in the under three, before discussing secondary prevention and symptomatic treatment.

Context: What do we know about wheeze aged 0-3 years old?
Preschool wheeze usually starts with intermittent, viral associated symptoms. A proportion of infants progress to multi-trigger wheeze as they get older. The evidence is that the substrate for pre-school wheeze lies antenatally. Studies have shown that maternal smoking, maternal atopy, and maternal pregnancy hypertension are all associated with airflow obstruction in the newborn period [1-3]. The anatomical basis of this is not known, but may be related to a reduction in alveolar tethering points on the airway [4]. Furthermore there are data showing that maternal smoking has immunological effects including leading to lower cord blood IL-4 and IFN-γ [5], and also increased cord mononuclear cell proliferation to house dust mite [6]. Other cord blood studies showed that maternal smoking was associated with increased IL-13, and reduced IFN-γ mRNA responses by stimulated cord blood cells [7]. The Perth group [8] have investigated the effects of maternal smoking on fetal Toll-like receptors (TLRs) and their signalling. Smoking during pregnancy was associated with reduced TLR2 mediated IL-6, IL-10 and TNF-α production. TLR 3 and 4 mediated signalling of TNF-α, but not IL-6, IL-10 and IL-12 were reduced in the infants of mothers who smoked. In terms of TLR9 responses, there were attenuated IL-6 and increased IFN-γ responses in the infants of smoking mothers. In summary, maternal smoking has profound effects on the immune responses of the newborn. Furthermore, maternal hypertension or pre-eclampsia is associated with an increased risk of transient early wheezing, persistent wheezing and late-onset wheezing. Use of antibiotics for urinary tract infections was associated with transient early wheezing, and antibiotic administration at delivery was associated with both transient early wheezing and persistent wheezing [9]. Children who had a mother with diabetes were more likely to have persistent wheezing [9]. Amniocentesis or chorionic villus sampling was associated with the subsequent development of wheezing [9]. Thus multiple lines of evidence suggest that the substrate for pre-school wheeze comes antenatally, long before it can be modified by pharmacotherapy.
The postnatal progression of pre-school wheeze has been studied in birth cohorts, which have given conflicting results, but the most generally accepted classification comes from Tucson [1], Table 1. In summary, infants who turn out to have transient wheeze (usually virus-associated) have evidence of airflow obstruction shortly after birth, before their first wheezing episode; by age six years there has been some catch-up in lung function, but airflow obstruction persists to at least the early twenties, with lung function tracking [1,10,11]. Those with persistent wheeze have normal lung function at birth (although others dispute this [12]), but by age six years have established airflow obstruction, which also tracks into the teenage years. The pathological counterpart of these epidemiological observations has recently been established. At a median age of one year, even atopic infants who have airflow obstruction reversing with acute bronchodilator administration have no evidence of eosinophilic airway wall inflammation or reticular basement membrane thickening [13]. By age 3 years, these changes are emerging, although they are not as marked as those found in older asthmatic children [14]. Studies in peripheral blood, nasal lavage and bronchoalveolar lavage have also established that the inflammatory phenotype of pre-school wheeze is neutrophilic, and not eosinophilic [15-18].

**Secondary Prevention**

Are inhaled corticosteroids disease modifying, in other words, do they prevent the progression from intermittent, viral associated wheeze to multi-trigger wheeze? This would seem to be a logical approach, given the proven efficacy of inhaled corticosteroids in treating established asthma in older children and adults. However, despite admirable logic, the concept has been discredited. A total of four randomised controlled trials have shown that neither continuously administered [19-22] nor intermittent therapy with inhaled corticosteroid [23] modify this disease progression. In the PEAK study [21], 285 participants two or three years of age with a positive asthma predictive index were randomly allocated treatment with fluticasone propionate (88 µg twice daily) or placebo for two years, followed by a one-year period observation without study medication. The primary outcome 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. Thus in preschool children at high risk for asthma, two years of inhaled-corticosteroid therapy did not change the development of asthma symptoms or lung function during a third, treatment-free year. Although conceivably higher doses may have been disease modifying, significant side-effects in this low dose study are likely to preclude this being investigated. The Manchester study was more complex [22]. It was a randomised, double-blind, placebo controlled study of inhaled fluticasone propionate 100 µg twice daily in young children who were followed prospectively and randomised after either one prolonged (>1 month) or two medically confirmed 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 the parents or guardians were given questionnaires, and the children's lung function and airway reactivity was measured. 173 (85 treatment, 88 placebo) of 200 randomised children completed the follow-up at age five
years. There was no treatment effect at age five 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. Thus here too, the early use of inhaled fluticasone propionate for wheezing in preschool children had no effect on the natural history of asthma or wheeze later in childhood, and did not prevent lung function decline or reduce airway reactivity. Similar conclusions were reached in a Dutch study using nebulised budesonide, with regular salbutamol as the comparator, more than 15 years previously [19, 20]! Children who go on to persistent wheeze and atopic asthma often start with a phase of recurrent episodes of wheezing during the first years of life, usually in association with a viral infection, and with no symptoms between viral colds. Hence inhaled corticosteroid therapy during symptomatic episodes in this early phase might delay progression to persistent wheezing. 411 one-month-old infants were randomly assigned to treatment with two-week courses of inhaled budesonide (400 µg per day) or placebo, initiated after a three-day episode of wheezing, in a single-center, randomized, double-blind, prospective study lasting three years [23]. 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 who went on to persistent wheezing. This latter finding that was unaffected by the presence or absence of atopic dermatitis. There were no safety issues. Intermittent low dose inhaled corticosteroid therapy had no effect on the progression from episodic to persistent wheezing and no short-term benefit during episodes of wheezing in the first three years of life. I still feel there is a need for a proper trial of short term, high dose inhaled steroids at the time of viral wheeze, for example budesonide 1 mg bd for five days; this might improve symptoms, but I doubt would be disease-modifying.

Thus there is no justification at all for administering inhaled corticosteroids to infants in order to try to prevent them getting asthma. Indeed, currently we have no means of preventing this transition. Furthermore, even the best asthma predictive indices have a low positive predictive value [24], although a better negative predictive value, so using these scores would lead to over-treatment of many infants who would not go on to develop asthma.

Symptomatic therapy of pre-school wheeze
A large number of studies have given conflicting results, but the Cochrane review [25] summarizing them suggests there is little if any evidence that continuous use of inhaled corticosteroids in the under threes is particularly efficacious; very high dose intermittent therapy may have a place, but side-effects are not unlikely, and the lack of efficacy of parent initiated prednisolone therapy militates against the likely efficacy of this approach [26]. Continuous inhaled corticosteroid therapy is not effective against episodic wheeze. Studies have in the main been of short duration, with relatively soft end-points. In the PEAK study [21] during the treatment period, fluticasone 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 (an overall 1-2 extra days per month without symptoms), but slowed growth, albeit temporarily and not progressively. The individual data were not published, so possibly within this group there were some individuals who benefited greatly. However, overall, benefit was trivial, even in a very high risk group. This accords with the pathological evidence that the inflammatory process is neutrophilic, not eosinophilic; and inhaled steroids are notoriously unhelpful in primarily neutrophilic diseases.

So should inhaled steroids ever be used in this age group? There is no evidence that they have any effect on viral induced exacerbations; in older children there is an effect on asthma control, which is different from exacerbation. Thus if a child under three who is atopic has genuine multi-trigger wheeze, a trial of inhaled corticosteroids may be worthwhile considering. If a therapeutic trial is to be undertaken, then I suggest the following safeguards:

1. Isolated cough, without wheeze or breathlessness, is rarely due to asthma, even in atopic children, and should not be treated with inhaled corticosteroids
2. If the child is non-atopic, and there is no first degree history of atopy, then the diagnosis of multi-trigger wheeze that responds to inhaled steroids is probably wrong
3. The younger the child, the less likely is benefit, and certainly inhaled steroids should only be given by a real expert to babies less than 12 months of age.
4. If a therapeutic trial is believed to be indicated, then I would start with a relatively high dose (e.g. budesonide 400 mcg bid) for a strictly defined period, say two months.
5. At the end of two months, irrespective of apparent response, the therapy is stopped. If there has been no symptomatic response, the diagnosis of steroid sensitive asthma is wrong; if there has been an apparent response, then spontaneous recovery needs to be excluded.
6. If symptoms return on stopping inhaled steroids, and respond again to a re-introduction, then probably this can be taken as evidence of benefit.

**Summary and conclusions**
We currently have no strategy to prevent progression of intermittent (virus associated) wheeze to persistent (multi-trigger) wheeze. We know inhaled steroids are not effective. We also need better biomarkers to define a high risk group for when an effective intervention becomes available. The younger the child, the less likely are inhaled steroids to be effective. So, although there may be a very few atopic infants age less than three years of age who have genuine multi-trigger wheeze which is steroid responsive, in general, therapy with inhaled steroids in this age-group is ineffective, with proven side-effects, and is thus unethical!
Table: Phenotypes of pre-school wheeze

<table>
<thead>
<tr>
<th></th>
<th>Wheeze age 0-3 years</th>
<th>Wheeze age 3-6 years</th>
<th>Lung function at birth</th>
<th>Lung function age 6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient wheeze</td>
<td>Yes</td>
<td>No</td>
<td>Reduced</td>
<td>Reduced (some catch-up)</td>
</tr>
<tr>
<td>Persistent wheeze</td>
<td>Yes</td>
<td>Yes</td>
<td>Normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Late onset wheeze</td>
<td>No</td>
<td>Yes</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

References
11. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. Lancet. 2007; 370: 758-64