

Original article

Efficacy of steroid treatments in the asthmatic preschool child

Asthma represents the most common chronic disease in preschool children. Hospital admission for wheezy disorders is the most common paediatric chronic disease causing hospital admission and more common in young children than later in life.

H. Bisgaard

Department of Paediatrics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Key words: child; efficacy; infant; preschool; steroid.

Professor Hans Bisgaard
Department of Paediatrics
Copenhagen University Hospital
Rigshospitalet
DK-2100 Copenhagen
Denmark

COPenham Studies on Asthma
in Childhood – COPSAC

Diagnosis

It is the aim of medical diagnoses to ensure the correct treatment, and imprecise terminology causes under- or over-treatment.

The asthma diagnosis may be based on a pragmatic approach based on typical symptoms and response to treatment after considering relevant differential diagnoses.

Differential diagnoses are numerous. The important differential diagnosis never to miss is foreign body, although a proper anamnesis often reveals a brief and abrupt history. Cardiac diseases may manifest themselves with dyspnoea during exercise. Anatomical malformations are rare, but should be considered if symptoms are resistant to treatment. The inspiratory nature of the obstruction in malacia and croup differentiates these ailments from asthmatic disorder. Cystic fibrosis is an important, albeit rare, differential diagnosis, predominantly in Caucasians. Recurrent bronchitis is by far the most common disorder mimicking asthmatic symptoms.

The effect of controller treatment supports the diagnosis, because such treatment has no effect in any of the differential diagnoses. However, regression towards the mean is a common deceptor of paediatric medicine. Therefore, relapse upon withdrawal of controller treatment should be ascertained before the asthma diagnosis can be considered likely. Such a pragmatic approach to diagnosis delineates asthma in young children as a syndrome. It carries no implications for prognosis or underlying pathology, but is an operational term relating to the most beneficial treatment, i.e. anti-asthmatics. As in other syndromes, it is probable that such a grouping comprises entities other than bronchial asthma.

A separate diagnosis might be appropriate for the young asthmatic child considering the uncertainties related to this disease entity. However, the use of nonspecific terms such as asthmatic bronchitis may lead to the use of ineffectual antibiotics and antitussives. With the aim of assuring appropriate anti-asthmatic therapy, asthma is therefore the appropriate diagnosis. Issues specific to asthma in the young child which differs from asthma in older children and adults should be pointed out to the family, but this is no different from many other diseases which often have different presentations in various age-groups.

Symptoms

Young asthmatic children may present with wheezing and coughing during airway infections and these symptoms may also be provoked outside infections by physical exertion, crying and laughing. Symptoms are often aggravated during the night. During severe attacks the child suffers prolonged expiration and laboured breathing. Lower airway infections cause not only the symptoms but may also be a complication of the disease. The asthmatic young child is typically moody, with little appetite during exacerbations. The symptoms may be severe and persistent in a manner leaving few in doubt of its asthmatic nature. At the other extreme symptoms are revealed only during infectious episodes. A careful history often reveals that what may seem an episodic disease in fact presents its more subtle symptoms between attacks, and the separation into episodic or persistent symptoms may become somewhat arbitrary in the individual case.

Subgrouping

It's best to know what you are looking for before you look for it
(A.A. Milne, *Winnie the Pooh*)

A Babylonian confusion exists on the diagnosis of asthmatic preschool children and the medical definitions are ambiguous, one of the reasons being that few objective measures are available and none is widely used. The symptoms are nonspecific and mimic common colds and other airway infections. In fact, the asthma child is more typically coughing than wheezing. The clinician depends on second-hand symptom description reliant on the caretaker's ability to observe and report intelligibly the symptoms presented by the child. Moreover, the child is often away from the primary caretaker for large parts of the day. Eventually there is no common language shared between or within cultures to describe the symptoms. Wheeze does not exist as a term in all languages and even where it does it rarely conveys a specific meaning in lay terms (1, 2). Therefore, subgrouping and diagnosis are inconsistent and most confusing.

The first acute attack of wheeze in a child less than 2 years old with viral pneumonia is defined in Anglo-Saxon textbooks as bronchiolitis, while this term is used in a less strict sense in other countries, referring often to any infant with viral pneumonia. Evidence from such cases is sometimes confused with evidence on asthma.

Asthma in the preschool child is often defined from the clinical picture depending on symptom intensity or triggers, or from epidemiological evidence depending on long-term prognosis and risk factors.

The asthma diagnosis has been restricted to the third attack (3). Such an approach is complicated in real life by the fact that the first symptoms may clearly be asthmatic in nature.

Allergy has been used to separate asthma from non-asthma. Yet, even though asthma with or without concurrent allergy may be a valid distinction in any age group, it is only in preschool children that the presence of allergy has been used to define or exclude asthma. Certainly in older children and adults asthma may be present without allergy; also allergy may be present without asthma. Furthermore, there is no indication in any of the available trials suggesting that treatment response relates to the presence of allergy. Therefore allergy is neither a specific nor sensitive marker for asthma.

"*Viral-induced wheeze*" is often used in preschool children to denote a disease entity separate from asthma. It is used to imply a child prone to asthmatic symptoms associated closely with viral infections but with no clinical symptoms outside such infections. However, the clinical separation of this subgroup is not well defined. Most asthma symptoms are virally driven in young asthmatics, and virus is known to be the predominant trigger of asthma exacerbations, even in older children with definite asthma. Viral-induced wheeze may be a different disorder

or may represent a mild and transient form within the spectrum of asthma immunopathology.

Epidemiological evidence suggests different subgroups defined from onset and persistence of symptoms, as supported by differences in risk factors (4). Therefore the terms transient wheeze, persistent wheeze and late onset wheeze is used in preschool children. However, this seems of little help to the clinician, who would prefer to categorize the child before it grows up and its history becomes apparent.

Prognosis is often used to decide on the diagnosis. It is argued that prognosis is benign and that most preschool children will outgrow their asthmatic symptoms. However, there is no evidence to suggest that children who later outgrow their symptoms are less responsive to treatment than those who continue their asthma carrier. Schoolchildren often outgrow their asthma as well. Nevertheless, a good prognosis is clearly no good reason to withhold treatment for the years during which they are troubled by asthma symptoms. Prognosis should not be used to make a diagnosis, but a diagnosis should be used to suggest a prognosis.

Risk factors are often argued as useful for the diagnosis of asthma. Certainly persistent asthmatic symptoms are associated with a number of risk factors including parental history of asthma, atopic dermatitis, eosinophilia, allergic rhinitis, wheezing apart from colds, more than three episodes of wheeze during the previous 6 months, male sex and sensitization to specific allergen(s). It has been suggested to base the diagnosis on an algorithm to define children with wheeze who have a high probability of having asthma (5). However, it is not known how this algorithm relates to treatment response, and its clinical value still needs to be evaluated.

Immunopathology of asthmatic preschool children is poorly understood. It is essential that any subgrouping is based on differences in pathology. However, there is as yet no such evidence on different subgroups of asthma immunopathology within age-matched groups. Indirect measurements have attested to the general inflammatory nature of asthma from early age. Exhaled nitric oxide was increased significantly in asthmatic young preschool children. It increased further subsequent to dose reduction of inhaled corticosteroid (ICS). Virally induced wheezers also had increased exhaled nitric oxide (6). Direct evidence of inflammation has been provided by studies of bronchial lavage, which have reported increased total cell counts in groups of young preschool children with virally induced wheeze as well as groups of allergy-driven asthma (7, 8). In a recent study data on bronchoalveolar lavage (BAL) in very young preschool children (mean age 15 months) with asthma were compared with age-matched controls without any lung symptoms (9). The children had a history of persistent wheeze, relief of symptoms from bronchodilator treatment and relapse following withdrawal of medication, as well as repeated severe attacks requiring prednisolone.

This suggests a pragmatic diagnosis of asthma, and the children represent the more severe end of the spectrum. These children had a threefold increase of total cell numbers, mainly from increased macrophages and lymphocytes. The proportion of eosinophils was only marginally increased. Eicosanoid levels were generally upregulated in the asthmatic children compared with normal controls, with large increases in mediators derived potentially from the epithelium. The cellular and eicosanoid findings support a nonspecific inflammatory response, possibly involving epithelial activation. However, the numbers of children studied were small, and subgroups could be difficult to discern with this number of subjects. It is noteworthy that the use of ICS was not associated with significant effects on cell differentials or on the concentration of eicosanoids (7–9), which may reflect incomplete control by ICS on this type of inflammation. The evidence available suggests that asthma, when defined pragmatically from symptoms and treatment response, reflects a chronic airway inflammatory condition from a very early age. Interestingly, the data suggest a nonspecific inflammation, implying that the eosinophils may not be as predominant an inflammatory cell in very early asthma compared with the pathology in older schoolchildren. Pathology with absence of or low-level tissue eosinophilia, increased macrophages with some evidence for epithelial activation, is reminiscent of the pathology of viral infections, and may suggest a virally driven pathology in asthma in early life even in the steroid-responding severe end of the spectrum. It may even reflect the initiating or causative events of asthma. Are we indeed witnessing the fingerprint of the “asthma microbe” in analogy with *Helicobacter pylori* of the ventricular ulcer? We have recently reported findings suggesting that infants and toddlers of mothers’ colonized with *Ureaplasma urealyticum* had an increased risk of hospitalization for an asthma-related diagnosis (ICD-10 J45 and J46) during the first 3 years of life. The aetiological fraction was 0.3 (0.1–0.6), equivalent to a reduction by 1/3 if *U. urealyticum* been eradicated (10). Colonization by this or other microbes may contribute a causative or initiating role in early airway inflammation of asthmatic preschool children.

In conclusion, there is no consensus on subgrouping of asthmatic preschool children. Many subgroups are used interchangeably but none are exhaustive or exclusive. There is no consistent evidence of airway immunopathology to support separation into different subgroups of asthmatic symptoms, such as virally induced vs allergy driven asthma or transient vs persistent subgroups. It is essential that any subgrouping is based on relevant differences in immunopathology. Lack of strict diagnostic criteria relevant for the disease immunopathology is an important cause for the paucity of scientific data in this area as well as a cause for under- or over-treatment and poor disease control.

Prognosis

Most young wheezers outgrow their symptoms, but most older children and adults with asthma have had their debut as young preschool wheezers.

The prognosis reported depends on the population from which the cohort is selected. Hospitalized index cases obviously differ from children attending a general practice, which differs from survey data. It may be maintained that young asthmatic children often outgrow their symptoms. On the other hand, 80–90% of schoolchildren with chronic asthma have had their debut before age 5 and approximately two-thirds before age 3. Accordingly, this group of young children comprises those later becoming chronically asthmatic schoolchildren as well as those outgrowing their symptoms before school age. At present the two groups cannot be distinguished.

Epidemiological evidence is sparse. In a milestone study Martinez et al. (4) posted a questionnaire around age 1.5 years to a random population of 826 infants in Arizona, USA, asking “Did the child’s chest ever sound wheezy or whistling apart from colds?” A second questionnaire was posted around age 6.5 years in this cohort asking if the child had had: “One episode of wheezing during the previous year”. Based on the returned responses the authors suggested a subgrouping of preschool wheeze into “never wheezers” (answering no and no), transient early wheezers (answering yes and no), persistent wheezers (answering yes and yes) and late-onset wheezers (answering no and yes). This subgrouping related eventually to different predisposing factors. Those with a “transient early wheeze” related to small airway diameter and mothers smoking, whereas those with persistent wheeze related to mothers asthma and other atopic manifestations in the child. Since such differences in predisposing factors could be shown, the subgrouping may actually reflect differences in immunopathology. Although this is a very important finding a caveat should be observed, as it builds on a small number of index cases (14 children had “persistent wheeze”), a very limited history-taking through posted questionnaires, no objective measurements, and the special geographic circumstances in Arizona may account for the apparently high prevalence of symptoms, with 40% of preschool children reporting wheezing at sometime during the first 6 years of life.

In a cross-sectional study of lung function (whole-body plethysmography) in clinically asymptomatic asthmatic preschool children, lung function was abnormal in many children despite apparent clinical control, and this was significantly more common among children of 2–3 years compared to children of 4–5 years (11). Furthermore, at follow-up 3 years later threefold more children studied initially at age 4–5 were still on controller therapy compared to those studied at 2–3 years of age. This observation supports a hypothesis of a large group of transient early wheezers associated with reduced airway calibre but a good prognosis.

Some early transient wheezers are related probably to the effect of a viral pneumonia. Respiratory syncytial virus (RSV), but also other viral pneumonia, was shown to cause an increased risk of recurrent wheezing throughout early childhood (12).

In summary, two major groups of recurrent wheezers in early life may be separated: in one group wheezing is simply an early manifestation of asthma. These children normally continue with persistent symptoms later in life and they tend to have an increased prevalence of a family history of atopy, allergic markers and bronchial hyper-responsiveness. Without any treatment a significant deterioration in lung function during the first 6 years of life is seen in this group. Often these children also have some symptoms between episodes of more severe wheeze. In the other group wheezing is associated with lower airway calibre which is present from birth, but which in contrast to the asthma group does not deteriorate further in spite of the recurrent symptoms. These children normally come from a nonatopic background, do not show bronchial hyperresponsiveness and they tend to have a good prognosis, the vast majority growing out of their symptoms before the age of 3 years. Symptoms between acute attacks of wheeze are rare in this group, and viral infection may be causative in some of these children. Unfortunately, it does not appear that the two conditions are entirely separate or easily distinguishable from a clinical point of view. Symptoms and treatment response may be similar. They share several predisposing factors such as exposure to environmental tobacco smoke and an increased risk in males. Furthermore, the most common triggering factor of both conditions is viral infections. Therefore, only population risk factors for these conditions are available, and the separation in individual patients may be difficult to apply in clinical practice.

Objective measurements

Health outcomes have been the primary outcome of most clinical trials in young asthmatic children. Exacerbation rate is a most useful outcome, which despite various definitions has discriminated treatments most clearly and showed a dose-response relation (13). Other useful health outcomes are hospital admission, use of rescue treatment and some composite measure of asthma control reflecting days with no symptoms, use of treatment or health-care utilization.

Lung stethoscopy is rarely of use for diagnosing or monitoring asthma in young children. Signs of obstruction are heard only during exacerbations, while the common finding of normal lung sounds carries a very high risk of a false negative outcome. Lung function and oxygen saturation may fall by 30% before wheezing becomes audible (14, 15). Lung stethoscopy therefore cannot be used to exclude asthma.

Lung function by forced expiration can seldom be performed reliably before age 6 years. To be applicable in young preschool children lung function measurement techniques should be noninvasive and acceptable in the awake child, requiring only passive cooperation with no need for verbal instructions. Several techniques are candidates for such a method, including whole body plethysmography for measuring the specific airway resistance, the interrupter technique for measuring respiratory resistance and the impulse oscillation technique for measuring respiratory resistance and respiratory reactance (16, 17).

Specific airway resistance ($sRaw$) is measured in whole-body plethysmography where the subject is seated inside an airtight chamber breathing through a pneumotachograph. The variations of pressure within the plethysmograph due to compression and rarefaction of the air during the breathing cycle are measured together with the corresponding flow through the pneumotachograph. The pressure changes within the box mirror the volume changes of the thorax. Airway resistance is reflected in the volume changes driving airflow, and measured from this ratio. In children who refuse to enter the whole-body plethysmograph alone measurements may be attempted with an adult accompanying the child inside the plethysmograph, which can be performed without introducing a bias (18).

The interrupter technique for measurements of respiratory resistance (R_{int}) is performed with a pneumotachograph mounted with a shutter-device. R_{int} is measured as the ratio between airflow and mouth pressure during a brief interruption. The pressure driving the airflow is measured during a brief interruption of the airflow by a shutter. Pressure equilibration between alveolar pressure and mouth pressure is assumed. Airflow is measured at an operator-defined time before or after this interruption. Because recordings of respiratory airflow and airway pressure are separated in time they are not accurate reflections of the corresponding flow and pressure. The method suffers particularly from a lack of recognized standard settings (16).

The impulse oscillation technique (IOS) is a modification of the forced oscillation technique, which is based on measuring the response of the respiratory system to an externally applied pressure pulse. Such a pressure pulse is applied at the mouth by means of a "loudspeaker". The imposed variations in airway pressure and the corresponding flow variations are recorded by a pneumotachograph equipped with a separate pressure transducer. Pressure pulses are applied repeatedly during the child's tidal breathing. The relationship between pressure and airflow constitute respiratory impedance, which can be subdivided into respiratory resistance (R_{rs}) and respiratory reactance (X_{rs}) (16).

Acceptability and validity of these techniques are good in young preschool children. Measurements can be achieved in more than 50% of untrained healthy 2-year-olds

and in most asthmatics accustomed to facemasks (19). The methods compared well to spirometry as a “gold standard” during methacholine challenge in a highly selected group of young asthmatics able to perform spirometry (16).

Discriminative power between healthy and asthmatic was generally good using these lung function measurements. Sensitivity to methacholine-induced bronchoconstriction indicated better sensitivity and repeatability of the sRaw and IOS measurements compared with Rint (16, 17), while IOS and Rint provided better separation of baseline lung function measurements between healthy and asthmatic young children (11, 20).

The bronchodilator response to inhaled short-acting beta-2 agonists measured by sRaw provided a sensitivity of 66% and a specificity of 81% (21).

Bronchial hyperresponsiveness (BHR) may be tested in infants and young children by inhalation of aerosols of methacholine or histamine in incremental doses. Adenosine monophosphate may provide an improved discrimination between healthy and asthmatic young children, as suggested in studies of adults, but no data are available as yet in young asthmatic children.

Exercise cannot be standardized sufficiently in preschool children to assure the necessary submaximal workload, as the child is unlikely to cooperate with such a demanding workout.

We recently adapted a single-step, cold, dry air hyperventilation method, which induces a brief bronchoconstriction in asthmatics. Computer animation is used to engage the child and assure compliance with the demanding 4-minute hyperventilation. It is acceptable for young children from the age of 2 and allows a separation between healthy and asthmatic young children, with a sensitivity of 68% and a specificity of 93% (22). The method is appealing as it mimics a clinically relevant asthma trigger.

In conclusion, sRaw, Rint and IOS are all applicable in clinical practice for measurements of lung function in young awake children from 2 years of age. sRaw seems to provide a better separation between healthy and asthmatic young children when used in conjunction with tests of airway responsiveness and bronchodilation. Cold, dry air hyperventilation provides a convenient method to test the airway responsiveness in young children. Introducing these methods may help define asthma in this clinically difficult group of young wheezy children.

Inflammatory markers

Blood eosinophils may substantiate the diagnosis but are raised only in severe cases. Plasma or urine eosinophil cationic protein may prove more sensitive than crude blood eosinophils, but has so far proven neither sensitive nor specific for asthma diagnosis in young children (23).

Exhaled nitric oxide seems to reflect airway inflammation and is being developed for use even in uncooperative

young children. Exhaled nitric oxide was significantly increased in asthmatic young preschool children. It increased further subsequent to dose reduction of ICS. Virally induced wheezers also had increased exhaled nitric oxide (6). It is currently applicable only in research centres but appears to have the potential as a simple clinical tool supporting the diagnosis and monitoring of asthma in young children. Studies are required to document the validity of such tests before they can be introduced into clinical practice.

Pharmacological intervention

Primary prevention

Pharmacological intervention aims normally at secondary prevention, i.e. controlling established asthma disease. However, increasing interest is devoted to primary prevention, i.e. preventing the development of asthma by pharmacological intervention.

A prospective controlled trial evaluated a possible prophylactic effect on asthma development from 18 months of regular antihistamines treatment in 817 young children with eczema but without asthma (24). The conclusion of the study was that there was no difference between placebo or antihistamine treatment (38% developed asthma in both groups). However, a subsequent subgroup analysis in children with eczema who were also sensitized to grass pollen or house dust mites revealed a significant difference between the two groups in favour of the active treatment: 26 of 92 children (28.3%) in the active group and 55 of 102 (53.9%) in the placebo group developed asthma. Similar findings were not seen in those sensitized to cats. Further prospective studies are needed in sensitized children with eczema to confirm this finding, and evaluate the long-term effects to determine whether such treatment prevents or delays asthma. The cost-benefit should be assessed balancing the screening procedure involving large numbers of allergy tests required to define the intervention group with the size of the potential target group of such distinct high-risk babies. Those high-risk children with eczema and defined allergies constitute a very small minority of the actual asthma population. However, the findings are exciting as early examples of a possible primary prevention of asthma through pharmacological intervention.

There are no randomized controlled trials (RCT) reported on a possible preventive effect of inhaled steroid on the development of asthma, but a number of such pivotal trials are currently ongoing with expected outcomes around 2003–5.

Secondary prevention

Oral steroid has been reported effective in the treatment of acute exacerbations of recurrent wheezing in children from the age of 2 months in several double-blind RCT

(D-B RCT) whether viral induced (25, 26) or otherwise (27, 28), although some were unable to detect any effect (29, 30).

Inhaled corticosteroids. Health outcomes have generally shown significant and clinically relevant improvements in D-B RCT in young asthmatic children treated with ICS (13, 20, 31–38). Treatment effect has reflected in day- and night-time symptom scores of cough, wheeze and dyspnoea, physical activity and happiness, use of rescue treatment and use of healthcare resources.

BUD and FP administered from pMDI and spacer devices have shown beneficial clinical improvements in young asthmatic children of 0–3 years in six D-B RCT (13–35), comprising a total of 469 young children as well as in studies of slightly older children (20, 39).

Nebulized BDP suspension from a jet-nebulizer failed to show convincing effects in two D-B RCT in young asthmatic children of 1–6 years (40, 41), due probably to inefficient nebulization of this particular steroid preparation (42). However, nebulized BDP was reported to reduce the frequency (but not the severity) of respiratory symptoms in infants with postbronchiolitic recurrent wheezing (43).

Nebulized BUD from a jet-nebulizer has shown a significant steroid sparing effect (44) as well as improvement of other health outcomes in children of 0.5–8 years in a number of large parallel D-B RCT of 178 (38), 480 (37) and 359 (36) children. However, the older group of children could have driven the effect in these studies. Nebulized BUD failed to show effect in 23 infants aged 3–17 months, who were randomized into the study based on the criteria that they were unresponsive to inhaled beta-2 agonists and ipratropium bromide (45). This peculiar inclusion criterion, together with the small sample size and the risk of carry-over effect within such a short-term 4-week cross-over design, probably explains the lack of treatment effect reported.

Nebulized flunisolide nasal preparation also indicated improved health outcomes in young asthmatics in a pilot study (46).

Subsets of young children may not benefit from the treatment. Generally, the study groups of young asthmatic children do not become symptom-free. ICS typically reduce the number of asthma exacerbations by half (13, 34), but does not prevent exacerbations completely. Whether this is due to insufficient adherence, too low doses or subsets of wheezers unresponsive to treatment is the important focus of future studies.

The variable nature of recurrent wheeze in young children and strong seasonality are part of the reason for the difficulty in performing clinical trials and also reflect the difficulty in clinical practice. Often patients are put on preventer therapy or included in a trial during periods of exacerbations, typically during the winter season. Simple regression towards the mean is exaggerated in such children by the strong seasonality and variable course

of the disease. This is reflected very clearly in the pronounced improvements in placebo treatment in most trials on this entity.

Dose-response effects are generally difficult to define from ICS in any age group of asthmatics. We showed a dose-response relation on exacerbation rate from a daily dose of 100 µg vs 200 µg of fluticasone propionate delivered from Babyhaler (13). As we applied only two dose-steps we were unable to define the plateau of the dose-response relation, so we can conclude only that the doses chosen are at the steep part of the dose-response relation, but higher doses may be required to obtain a full effect. Comparison of 0.25 mg, 0.5 mg and 1.0 mg nebulized budesonide once daily (36) and twice daily (38) showed significant improvement over placebo treatment but failed to indicate a dose-response relation, as similar improvements were found from the low and the high doses. However, one similar study suggested a dose-relation from 0.25 to 1.0 mg nebulized budesonide bid (37).

Dose-finding studies have been performed with nebulized budesonide (47, 48). Marked individual variations were seen and the conclusion of both studies was that the dose of nebulized budesonide must be individualized.

In summary, the evidence shows a convincing dose-related effect of ICS on health outcomes although a defined subgroup apparently achieves no or little response.

Lung function and BHR have been reported as primary endpoints in six D-B RCT of ICS in young wheezy children.

BDP nebulized suspension was used in two trials although this is a comparatively inefficient steroid regime (*vide supra*). Nevertheless, Maayan et al. (49) reported improvement from nebulized BDP of the airway conductance measured in whole-body plethysmography in nine sedated infants with persistent wheeze, aged 15–36 weeks. De Baets et al. measured sRaw by whole-body plethysmography in 15 awake children 3–5 years of age with a history of recurrent wheezing and determined bronchial hyperresponsiveness to histamine (50). Nebulized BDP failed to affect bronchial hyperresponsiveness, although an improvement in symptoms was reported.

BDP pMDI from a spacer has been applied in two studies in infants with recurrent wheeze. Stick et al. used the rapid thoracoabdominal compression technique to measure flow at functional residual capacity, and estimated BHR to histamine (51). Thirty-eight infants aged 5–18 months with a history of three discrete episodes of wheezing or persistent wheezing for more than 4 weeks were treated in a placebo-controlled, parallel D-B RCT with a daily dose of 400 µg of BDP pMDI via a spacer with facemask. BHR improved significantly from active treatment compared to placebo, although symptoms were not found to improve. Kraemer et al. reported improvement of thoracic gas volume and airway conductance

(whole-body plethysmograph) in a study of 29 infants aged 2–25 months with recurrent wheezing (52).

BUD pMDI via a spacer has been studied in two trials in young asthmatic children. Greenough et al. reported the effect of a 400 µg daily dose of budesonide pMDI via a spacer in a D-B RCT of 19 asthmatic young children aged 2–6 years, looking at the functional residual capacity measured by helium dilution as the primary outcome (53). The results suggested that ICS reduced hyperinflation in young asthmatic children. We reported recently the effect of budesonide inhaled from a metal spacer (800 µg daily dose) on airway resistance measurements and BHR to cold, dry air hyperventilation and methacholine in 38 young asthmatics aged 2–5 years in a comprehensive parallel D-B RCT (20). Symptoms improved significantly, with exacerbation rate as the best discriminator between active and placebo treatment. Rint and IOS measurements of resistance and reactance mirrored this clinical effect on the baseline lung function. Bronchial hyperresponsiveness improved significantly as measured by the cold, dry air hyperventilation method, but not by methacholine challenge. The beneficial effect of inhaled budesonide on bronchial hyperresponsiveness to cold, dry air hyperventilation was reflected in sRaw as well as Rint and IOS measurements of resistance and reactance.

In summary, the available evidence suggests that lung function and BHR in young wheezy children are improved by ICS.

Inflammatory markers: we have reported recently a study showing a significant rise in exhaled NO subsequent to dose reduction of ICS in young asthmatic children of 2–5 years (6). This attests to the inflammatory nature of the disease and the anti-inflammatory control by ICS in young asthmatics. None of the available studies on ICS in young children has reported on the effect on blood eosinophils or markers thereof.

In conclusion, there is suggestive though very limited evidence on the anti-inflammatory effects of ICS in young asthmatics.

Viral-induced wheeze and ICS are much debated, partly because of confusion in terms. The distinction should be made between the steroid effect on acute viral-induced exacerbation in children with a history of recurrent wheeze, and the treatment of wheeze associated with viral pneumonia in previously healthy children (bronchiolitis). Although the latter may present the first asthma attack where a steroid effect is to be expected, the majority of such incidents are associated with common viral infections in otherwise healthy children and cannot be expected to benefit from steroid treatment. Repeated D-B RCT have found no short- or long-term clinical benefits from the administration of systemic (54–57) or inhaled steroids (58–62) during the acute phase of viral-induced wheeze in previously healthy infants, although some short-term improvements have been reported in other studies (26, 63).

On the other hand, viral-induced symptoms in young children with moderate to severe persistent wheeze have been shown to respond to steroid treatment, inasmuch as most of the exacerbations in the preschool asthmatic children are virus-related. The exacerbation rate provided the best discrimination between steroid and placebo in the studies of preschool asthma reviewed above. In addition, acute severe exacerbations of young children with a history of recurrent wheeze showed a good response to oral steroid (*vide supra*).

Viral-induced symptoms in young children with recurrent but mild episodic wheeze are probably part of the asthmatic spectrum in the young child. Intermittent high-dose ICS administered for 1–2 weeks in association with virus-induced wheeze significantly reduced the severity of the symptoms (64–66). The differences between placebo and inhaled steroids were statistically significant, although generally small, and inhaled corticosteroids did not reduce the need for oral steroids or frequency of hospitalization. One study reported no apparent effect from regular steroid ICS treatment on viral-induced wheeze (67). However, this study included 41 children aged 0.5–6 years with very mild episodic wheezing. They were included if they presented two disturbed nights over 3 months due to lower airway symptoms. Children requiring more than four inhalations of beta-2 agonist within 1 week were excluded. Despite the very mild and episodic nature of the disease, inhaled budesonide showed a trend of reduced symptoms ($P = 0.09$) and days without symptoms ($P = 0.08$). The risk of a false negative outcome is obvious considering the very mild nature of the disease, the small number of patients included and the heterogeneity of the age groups involved. Clearly, this study group of mild intermittent wheezers did not qualify for daily preventer therapy and could hardly be expected to adhere to such treatment. The trend revealed in the study suggests that the mechanism of the disease may be similar to the more severe end of the spectrum of asthma in young children.

In conclusion, steroids have no effect on the isolated acute attack of wheeze during viral pneumonia in a previously healthy child (bronchiolitis). However, ICS are effective in viral-induced wheeze in young children with a history of persistent wheeze. ICS also have an effect, albeit small, on viral-induced mild episodic symptoms. The steroid response may be driven by subsets of patients. The data do not support the general use of steroids in children with episodic viral-induced asthmatic symptoms.

Side effects are of concern for any regular drug therapy. In particular, treating the young child with ICS requires the considered choice of a safe therapy (68). Some aspects of the assessment of safety are unique to preschool children, including rapid growth velocity and a somewhat different metabolism. These rapid changes may make the child more vulnerable to the adverse effects of drugs and/or disease and therefore the safety findings in school-children or adults cannot be extrapolated uncritically to

young children. There is evidence to suggest that a tailored daily dose of around 2–400 µg of budesonide or the equivalent of fluticasone propionate is without safety concerns in schoolchildren (69). However, most studies documenting the effects of inhaled steroids in young children have suggested the need for a dose of 400 µg of budesonide or the equivalent of fluticasone propionate. This would, by conventional wisdom, suggest a very high drug exposure in young children compared to older children (the same dose in a smaller body). However, we showed recently by a pharmacokinetic method that a fixed nominal dose delivered to young children, schoolchildren and adults provides similar systemic exposure, i.e. the dose reaching the lungs is reduced in proportion to body size. This is due probably to narrow upper airway geometry, as suggested in *in vitro* studies. Therefore, provided that efficient delivery devices are used, similar nominal doses prescribed to older and younger patients will result in similar relative lung doses and similar relative systemic drug exposure. This is probably the rationale behind the observation that young children apparently require similar doses to older children to benefit from inhaled steroids. Such proportionally reduced drug exposure in young children is reassuring from a safety perspective.

There is only one D-B RCT published on the safety of ICS in young children (70). Fourteen toddlers 1–2 years of age with mild recurrent wheezing were studied by knemometry in a three-way cross-over design. They received budesonide in daily doses of 200 and 800 µg and placebo inhaled from pressurized MDI via a large volume spacer. The high dose, but not the low dose, caused significant systemic activity in these toddlers. This is in good agreement with the findings in knemometry studies in schoolchildren which found a dose-related systemic activity in the dose-range of 200–800 µg; significant changes were found at a daily dose of 800 but not 400 µg (71, 72). Knemometry is a measure of the short-term growth of the lower leg, and bears no relation to long-term growth. However, it is probably the most sensitive measure of systemic steroid activity, and if a treatment has no effect on knemometry it is most unlikely that such treatment will be associated with any growth suppression during long-term treatment. Therefore, the above study suggests that a daily dose of 200 µg of

budesonide pMDI from a spacer is a safe treatment in 1–2-year-old toddlers.

Nevertheless, it is pertinent that long-term studies are conducted in young children to determine the effect of clinical doses of second-generation steroids on the growth of young children. Such studies should address separately the effect on rapid growth in the first 2–3 years of life, influenced mainly by factors similar to those controlling fetal growth, and the growth from age 3 attributed mainly to the endocrine system, particularly growth hormone (73).

Prenatal administration of steroids have been shown to impair normal alveolar development in animal models (74–76). Fears have sometimes been raised that inhaled corticosteroids may have similar effects in infants (77). However, there are no data to substantiate these fears and marked differences exist in lung development between species. Therefore, if inhaled corticosteroids have a definite positive clinical effect in a young child, concerns about possible adverse effects upon lung growth should not be a reason to withhold the treatment (78).

Conclusion

We have gained significant momentum in teasing out the particular aspects of asthma early in life. Evidence is emerging from epidemiological studies and also recent studies on immunopathology. This is furthered by new methods for objective assessments of airway patency, reactivity and inflammation applicable from an early age. Pharmacological intervention studies are providing important insight to the pathology of early asthma by scrutinizing the response to anti-asthmatics. Clearly, there is still a long way to go in the diagnosis and management of asthma in preschool children, but we have gained substantially increased knowledge and understanding which is likely to improve management even more during the coming years. Objective means of diagnosing and monitoring persistent asthma will be required in routine clinics. ICS is the mainstay for the treatment of young children with persistent asthma. Future research should study efficient environmental interventions to provide an evidence-based management complementary to pharmacotherapy. The possibility of preventing the development of asthma or for modifying its natural course is another key issue for future research.

References

1. CANE RS, RANGANATHAN SC, MCKENZIE SA. What do parents of wheezy children understand by 'wheeze'? Arch Dis Child 2000;**82**:327–332.
2. CANE RS, MCKENZIE SA. Parents' interpretations of children's respiratory symptoms on video. Arch Dis Child 2001;**84**:31–34.
3. TABACHNIK E, LEVISON H. Postgraduate course presentation. Infantile bronchial asthma. J Allergy Clin Immunol 1981;**67**:339–347.
4. MARTINEZ FD, WRIGHT AL, TAUSSIG LM, et al. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;**332**:133–138.

5. CASTRO-RODRIGUEZ JA, HOLBERG CJ, WRIGHT AL, MARTINEZ FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;**162**: 1403–1406.
6. BUCHVALD F, BISGAARD H. FeNO measured at fixed exhalation flow rate during controlled tidal breathing in children from the age of 2 yr. *Am J Respir Crit Care Med* 2001;**163**:699–704.
7. MARGUET C, JOUEN-BOEDES F, DEAN TP, WARNER JO. Bronchoalveolar cell profiles in children with asthma, infantile wheeze, chronic cough, or cystic fibrosis. *Am J Respir Crit Care Med* 1999;**159**:1533–1540.
8. STEVENSON EC, TURNER G, HEANEY LG, et al. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. *Clin Exp Allergy* 1997;**27**:1027–1035.
9. KRAWIEC ME, WESTCOTT JY, HONG WC, et al. Persistent wheezing in very young children is associated with lower respiratory inflammation. *Am J Respir Crit Care Med* 2001;**163**:1338–1343.
10. BENN CS, THORSEN P, JENSEN JS, et al. Maternal vaginal microflora during pregnancy and the risk of asthma hospitalization and use of antiasthma medication in early childhood. *J Allergy Clin Immunol* 2002;**110**:72–77.
11. KLUG B, BISGAARD H. Lung function and short-term outcome in young asthmatic children. *Eur Respir J* 1999;**14**:1185–1189.
12. STEIN RT, SHERRILL D, MORGAN WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;**354**:541–545.
13. BISGAARD H, GILLIES J, GROENEWALD M, MADEN C. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. *Am J Respir Crit Care Med* 1999;**160**:126–131.
14. WILSON NM, BRIDGE P, PHAGOO SB, SILVERMAN M. The measurement of methacholine responsiveness in 5 year old children: three methods compared. *Eur Respir J* 1995;**8**:364–370.
15. SPENCE DP, BENTLEY S, EVANS DH, MORGAN MD. Effect of methacholine induced bronchoconstriction on the spectral characteristics of breath sounds in asthma. *Thorax* 1992;**47**:680–683.
16. BISGAARD H, KLUG B. Lung function measurement in awake young children. *Eur Respir J* 1995;**8**:2067–2075.
17. KLUG B, BISGAARD H. Measurement of lung function in awake 2–4-year-old asthmatic children during methacholine challenge and acute asthma: a comparison of the impulse oscillation technique, the interrupter technique, and transcutaneous measurement of oxygen versus whole-body plethysmography. *Paediatr Pulmonol* 1996;**21**:290–300.
18. KLUG B, BISGAARD H. Measurement of the specific airway resistance by plethysmography in young children accompanied by an adult. *Eur Respir J* 1997;**10**:1599–1605.
19. KLUG B, BISGAARD H. Specific airway resistance, interrupter resistance, and respiratory impedance in healthy children aged 2–7 years. *Paediatr Pulmonol* 1998;**25**:322–331.
20. NIELSEN KG, BISGAARD H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med* 2000;**162**:1500–1506.
21. NIELSEN KG, BISGAARD H. Discriminative capacity of bronchodilator response measured with three different lung function techniques in asthmatic and healthy children aged 2–5 years. *Am J Respir Crit Care Med* 2001;**164**:554–559.
22. NIELSEN KG, BISGAARD H. Lung function response to cold air challenge in asthmatic and healthy children of 2–5 years of age. *Am J Respir Crit Care Med* 2000;**161**:1805–1809.
23. ZIMMERMAN B, ENANDER I, ZIMMERMAN R, AHLSTEDT S. Asthma in children less than 5 years of age: eosinophils and serum levels of the eosinophil proteins ECP and EPX in relation to atopy and symptoms. *Clin Exp Allergy* 1994;**24**:149–155.
24. WARNER JO ON BEHALF OF STUDY GROUP. Allergic factors associated with the development of asthma, the influence of cetirizine in a double-blind, randomised placebo-controlled trial: first results of ETAC. Early treatment of the atopic child. *Paediatr Allergy Immunol* 1998;**9**:116–124.
25. BRUNETTE MG, LANDS L, THIBODEAU LP. Childhood asthma. prevention of attacks with short-term corticosteroid treatment of upper respiratory tract infection. *Paediatrics* 1988;**81**: 624–629.
26. DAUGBERG P, BRENOE E, FORCHHAMMER H, et al. A comparison between nebulized terbutaline, nebulized corticosteroid and systemic corticosteroid for acute wheezing in children up to 18 months of age. *Acta Paediatr* 1993;**82**:547–551.
27. TAL A, BAVILSKI C, YOHAI D, et al. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Paediatrics* 1983;**71**:13–18.
28. TAL A, LEVY N, BEARMAN JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial [see comments]. *Paediatrics* 1990;**86**:350–356.
29. WEBB MS, HENRY RL, MILNER AD. Oral corticosteroids for wheezing attacks under 18 months. *Arch Dis Child* 1986;**61**:15–19.
30. FOX GF, MARSH MJ, MILNER AD. Treatment of recurrent acute wheezing episodes in infancy with oral salbutamol and prednisolone. *Eur J Paediatr* 1996;**155**:512–516.
31. BISGAARD H, MUNCK SL, NIELSEN JP, et al. Inhaled budesonide for treatment of recurrent wheezing in early childhood. *Lancet* 1990;**336**:649–651.
32. CONNETT GJ, WARDE C, WOOLER E, LENNEY W. Use of budesonide in severe asthmatics aged 1–3 years. *Arch Dis Child* 1993;**69**:351–355.
33. NOBLE V, RUGGINS NR, EVERARD ML, MILNER AD. Inhaled budesonide for chronic wheezing under 18 months of age. *Arch Dis Child* 1992;**67**:285–288.
34. DE BLIC J, DELACOURT C, LE BOURGEOIS M, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. *J Allergy Clin Immunol* 1996;**98**:14–20.
35. DE BENEDICTIS FM, MARTINATI LC, SOLINAS LF, et al. Nebulized flunisolide in infants and young children with asthma: a pilot study. *Paediatr Pulmonol* 1996;**21**:310–315.
36. KEMP JP, SKONER DP, SZEFLER SJ, et al. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. *Ann Allergy Asthma Immunol* 1999;**83**:231–239.
37. BAKER JW, MELLON M, WALD J, et al. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Paediatrics* 1999;**103**:414–421.
38. SHAPIRO G, MENDELSON L, KRAEMER MJ, et al. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma [see comments]. *J Allergy Clin Immunol* 1998;**102**:789–796.
39. GLEESON JG, PRICE JF. Controlled trial of budesonide given by the nebulizer in preschool children with asthma. *BMJ* 1988;**297**:163–166.
40. STORR J, LENNEY CA, LENNEY W. Nebulised beclomethasone dipropionate in preschool asthma. *Arch Dis Child* 1986;**61**:270–273.
41. WEBB MS, MILNER AD, HILLER EJ, HENRY RL. Nebulised beclomethasone dipropionate suspension. *Arch Dis Child* 1986;**61**:1108–1110.
42. O'CALLAGHAN C. Particle size of beclomethasone dipropionate produced by two nebulisers and two spacing devices. *Thorax* 1990;**45**:109–111.
43. CARLSEN KH, LEEGAARD J, LARSEN S, ORSTAVIK I. Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis. *Arch Dis Child* 1988;**63**:1428–1433.

44. ILANGOVAN P, PEDERSEN S, GODFREY S, et al. Treatment of severe steroid dependent preschool asthma with nebulised budesonide suspension. *Arch Dis Child* 1993;**68**:356–359.
45. VAN BEVER HP, SCHUDDINCK L, WOJCIECHOWSKI M, STEVENS WJ. Aerosolized budesonide in asthmatic infants: a double blind study. *Paediatr Pulmonol* 1990;**9**:177–180.
46. ALLEN ED, WHITAKER ER, RYU G. Six-week trial of nebulized flunisolide nasal spray: efficacy in young children with moderately severe asthma. *Paediatr Pulmonol* 1997;**24**:397–405.
47. WENNERGREN G, NORDVALL SL, HEDLIN G, et al. Nebulized budesonide for the treatment of moderate to severe asthma in infants and toddlers. *Acta Paediatr* 1996;**85**:183–189.
48. VIKRE-JORGENSEN J, AGERTOFT L, PEDERSEN S. Dose titration of nebulized budesonide in young children. *Paediatr Pulmonol* 1997;**23**:270–277.
49. MAAYAN C, ITZHAKI T, BAR-YISHAY E, et al. The functional response of infants with persistent wheezing to nebulized beclomethasone dipropionate. *Paediatr Pulmonol* 1986;**2**:9–14.
50. DE BAETS F, VAN DAELE S, FRANCKX H, VINAIMONT F. Inhaled steroids compared with disodium cromoglycate in preschool children with episodic viral wheeze. *Paediatr Pulmonol* 1998;**25**: 361–366.
51. STICK SM, BURTON PR, CLOUGH JB, et al. The effects of inhaled beclomethasone dipropionate on lung function and histamine responsiveness in recurrently wheezy infants. *Arch Dis Child* 1995;**73**:327–332.
52. KRAEMER R, GRAF BU, CASALTA AC, et al. Clinical and physiological improvement after inhalation of low-dose beclomethasone dipropionate and salbutamol in wheezy infants. *Respiration* 1997;**64**:342–349.
53. GREENOUGH A, POOL J, GLEESON JG, PRICE JF. Effect of budesonide on pulmonary hyperinflation in young asthmatic children. *Thorax* 1988;**43**:937–938.
54. ROOSEVELT G, SHEEHAN K, GRUPP-PHELAN J, et al. Dexamethasone in bronchiolitis: a randomised controlled trial [see comments]. *Lancet* 1996;**348**: 292–295.
55. KLASSEN TP, SUTCLIFFE T, WATTERS LK, et al. Dexamethasone in salbutamol-treated inpatients with acute bronchiolitis: a randomized, controlled trial [see comments]. *J Paediatr* 1997;**130**:191–196.
56. DE BOECK KAN, VAN LIERDE S, CORBEEL L, ECKELS R. Respiratory syncytial virus bronchiolitis: a double-blind dexamethasone efficacy study. *J Paediatr* 1997;**131**:919–921.
57. BULOW SM, NIR M, LEVIN E, et al. Prednisolone treatment of respiratory syncytial virus infection: a randomized controlled trial of 147 infants. *Paediatrics* 1999;**104**: e77.
58. SPRINGER C, BAR-YISHAY E, UWAYYED K, et al. Corticosteroids do not affect the clinical or physiological status of infants with bronchiolitis. *Paediatr Pulmonol* 1990;**9**:181–185.
59. RICHTER H, SEDDON P. Early nebulized budesonide in the treatment of bronchiolitis and the prevention of post-bronchiolitic wheezing. *J Paediatr* 1998;**132**:849–853.
60. WONG JY, MOON S, BEARDSMORE C, et al. No objective benefit from steroids inhaled via a spacer in infants recovering from bronchiolitis. *Eur Respir J* 2000;**15**:388–394.
61. FOX GF, EVERARD ML, MARSH MJ, MILNER AD. Randomised controlled trial of budesonide for the prevention of post-bronchiolitis wheezing. *Arch Dis Child* 1999;**80**:343–347.
62. CADE A, BROWNLEE KG, CONWAY SP, et al. Randomised placebo controlled trial of nebulised corticosteroids in acute respiratory syncytial viral bronchiolitis. *Arch Dis Child* 2000;**82**:126–130.
63. VAN WOENSEL JB, WOLFS TF, VAN AALDEREN WM, et al. Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis [see comments]. *Thorax* 1997;**52**:634–637.
64. WILSON NM, SILVERMAN M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child* 1990;**65**:407–410.
65. CONNETT G, LENNEY W. Prevention of viral induced asthma attacks using inhaled budesonide. *Arch Dis Child* 1993;**68**:85–87.
66. SVEDMYR J, NYBERG E, ASBRINK-NILSSON E, HEDLIN G. Intermittent treatment with inhaled steroids for deterioration of asthma due to upper respiratory tract infections. *Acta Paediatr* 1995;**84**:884–888.
67. WILSON N, SLOPER K, SILVERMAN M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. *Arch Dis Child* 1995;**72**:317–320.
68. BISGAARD H, PEDERSEN S. Safety of treatment. *Eur Respir J Suppl* 1996;**21**:28s–34s.
69. PEDERSEN S. Long-term outcomes in paediatric asthma. *Allergy* 2002;**57**(Suppl. 74):58–74.
70. BISGAARD H. Systemic activity of inhaled topical steroid in toddlers studied by knemometry. *Acta Paediatr* 1993;**82**:1066–1071.
71. WOLTERS OD, PEDERSEN S. Growth of asthmatic children during treatment with budesonide: a double-blind trial. *BMJ* 1991;**303**:163–165.
72. WOLTERS OD, PEDERSEN S. Controlled study of linear growth in asthmatic children during treatment with inhaled glucocorticosteroids. *Paediatrics* 1992;**89**:839–842.
73. KARLBERG J, ENGSTROM I, KARLBERG P, FRYER JG. Analysis of linear growth using a mathematical model. I. From birth to three years. *Acta Paediatr Scand* 1987;**76**:478–488.
74. WILLET KE, JOBE AH, IKEGAMI M, et al. Lung morphometry after repetitive antenatal glucocorticoid treatment in preterm sheep. *Am J Respir Crit Care Med* 2001;**163**:1437–1443.
75. WILLET KE, JOBE AH, IKEGAMI M, et al. Antenatal endotoxin and glucocorticoid effects on lung morphometry in preterm lambs. *Paediatr Res* 2000;**48**:782–788.
76. JOBE AH, NEWNHAM J, WILLET K, et al. Fetal versus maternal and gestational age effects of repetitive antenatal glucocorticoids. *Paediatrics* 1998;**102**: 1116–1125.
77. WARNER JO. The down-side of early intervention with inhaled corticosteroids [see comments]. *Clin Exp Allergy* 1997;**27**:999–1001.
78. PEDERSEN S. Early use of inhaled steroids in children with asthma [see comments]. *Clin Exp Allergy* 1997;**27**:995–999.