

## Issues at the interface between primary and secondary care in the management of common respiratory disease • 2

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### Are we too ready to diagnose asthma in children?

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Recurrent respiratory symptoms in children are extremely common. A proportion of those children who experience recurrent respiratory symptoms have asthma—reversible airways obstruction associated with bronchial hyperactivity, allergic inflammation of the airways, and a response to treatment with bronchodilators and regular prophylactic inhaled anti-inflammatory agents. Since we cannot easily measure bronchial hyperresponsiveness or inflammation and clinical correlates are not specific, diagnosis often depends on response to treatment. But how big is the proportion with asthma, how does that proportion vary with age, and are we successful in applying the asthma label and giving the asthma treatments to the right group of children?

The prevalence of asthma has undoubtedly increased in industrialised countries over the last few decades. Increases in rates of physician diagnosis of asthma are partially accounted for by changes in diagnostic preference, but there is consistent survey evidence for the increasing prevalence of symptomatic wheezing. Parent reported prevalence of attacks of wheezing in Oslo children aged 6–16 increased from 3.7% to 6.8% between 1981 and 1994.<sup>1</sup> Exercise induced bronchospasm is closely related to asthma, and the proportion of 12 year old children in Wales whose peak flow dropped by more than 25% after running doubled between 1973 and 1988.<sup>2</sup>

It was equally clear in the 1980s that childhood asthma was underdiagnosed and undertreated. Eleven out of 31 Tyneside schoolchildren experiencing more than 12 episodes of wheezing per year and three out of 56 with 4–12 episodes per year had been offered a diagnosis of asthma by their general practitioner.<sup>3</sup> Since then, growing awareness of the existence of childhood asthma and of the effectiveness and relative safety of regular inhaled prophylactic agents has led to considerably higher rates of diagnosis and treatment. Has the pendulum swung too far the other way? Are we now making false diagnoses of asthma and subjecting a large number of children with self-limiting respiratory symptoms to unnecessary or unnecessarily prolonged drug treatment?

#### Recent data on rates of diagnosis and treatment

The general practice records of 10 685 Tayside children aged 1–15 were carefully reviewed in 1991.<sup>4</sup> A history of “persistent cough” was documented in the records of 23% of children. Two or more episodes of wheeze were recorded in 11% of children, half of whom had received a diagnosis of asthma. Treatment with anti-asthma therapy at any point in the past was found in 20% of records. Of the total population 8.4% had a formal diagnosis of asthma and 5.4% had received a prescription for asthma treatment in the previous three months (4.8% a bronchodilator, 1.2% an inhaled steroid, and 1% sodium cromoglycate). The authors of this study imply that their figures represent continuing underdiagnosis and undertreatment of asthma.

The recently published ISAAC study of asthma symptoms in 12–14 year old British children was a school based questionnaire survey with an 86% response rate.<sup>5</sup> A 12 month prevalence of four or more attacks of wheeze of 9.6% and of frequent night waking with wheeze of 3.7% was reported. A diagnosis of asthma had been given at some point in the past to 21% of children and 20% reported treatment with anti-asthma drugs in the previous year. Nevertheless, one third of the children reporting frequent nocturnal wheeze had no diagnosis of asthma and denied receiving inhaled therapy. Four percent of the total sample continued to experience asthma symptoms with a moderate or greater interference with their lives despite having received diagnosis and treatment. The overall picture is one of high rates of asthma diagnosis and treatment but with evidence of continuing underdiagnosis and undertreatment of the most severely affected children. It is not possible to identify the extent of overdiagnosis of asthma from surveys of this kind. It is possible that children with significant asthma symptoms are being missed while children with minor symptoms of respiratory tract infection are being unnecessarily labelled and treated as having asthma.

The United Kingdom General Practice Research data base collects data on diagnoses and prescriptions from 288 general practices in England and Wales (total list size 2.1 million). A recent analysis found average rates of treatment for asthma of 96 per 1000 boys

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under five and 120 per 1000 boys age 5–15.<sup>6</sup> Of boys under five receiving treatment for asthma, 61% were receiving treatment with inhaled steroids or cromoglycate; in boys aged 5–15 that proportion was 71%. There were very wide inter-practice variations in the prevalence of diagnosed asthma (1.9–13.5%). The percentage of patients with asthma receiving treatment with inhaled steroids in 1996 varied from 39% to 95%.

What insights can be gained from cohort studies of respiratory symptoms in childhood? The Tucson Children's Respiratory Study enrolled newborn infants between 1980 and 1984.<sup>7</sup> One or more episodes of wheezing illness before the age of three years were reported in 33.6% of children, but at six years of age only a third of these children were still subject to wheezing (the criterion here being "at least one episode of wheezing during the previous year"). Children with transient early wheezing had diminished airway function on physiological testing both before the age of one and at six years of age, but did not have increased IgE levels or skin test reactivity. The Child Health and Education Study followed a cohort of 11 000 British children born in April 1970.<sup>8</sup> A history of wheezing episodes was taken by parental interview when the children were aged five and 10 years. Asthma at 10 years of age was defined as a history of one or more wheezing episodes in the preceding 12 months. Of 446 children who had a single attack of wheeze in the first year of life, 14% had asthma at the age of 10 years. Of those with four or more attacks of wheeze in the first year the figure was 23%. Of those with four or more attacks of wheeze between the ages of one and four years 33% were asthmatic at 10 years of age. Only a minority of children with episodic wheezing under the age of five continued to have wheezing episodes in later childhood.

#### **Not all cough and wheeze is asthma**

For pre-school children, especially those under the age of three, it is now clear that recurrent wheezing disorders fall into different phenotypes, though these may not be recognisable at the time and only become apparent in retrospect.<sup>9</sup> Episodic viral wheeze on a non-atopic basis probably has little in common with atopic asthma and its underlying chronic eosinophilic inflammation. Episodic viral wheeze has a better prognosis and responds less well to anti-asthma therapy.<sup>10 11</sup>

#### **Do regular inhaled steroids help recurrently wheezing pre-school children?**

Evidence of the effectiveness of inhaled steroids drawn from different studies appears inconsistent. This might be explained by different phenotypes of wheezing illness in early childhood, for the proportion of children with true asthma may differ in the groups recruited. Wilson *et al* found no benefit from four months of treatment with 400 µg budesonide daily in 41 children aged 0.7–6.0 years with episodic wheezing,<sup>10</sup> whereas Bisgaard *et al* found clear evidence of a reduction in acute

symptoms in 77 children aged 11–36 months following treatment with 800 µg daily for three months.<sup>12</sup> The first study entered children with at least two wheezing episodes in the previous three months but with "no or minimal symptoms between episodes". The second study entered children when "a physician had confirmed wheezing on at least three separate occasions during the previous year". However, in the discussion section we learn that "all (had) required nebulised beta agonist on most days during autumn and winter . . .". The second study which showed effectiveness therefore not only used a higher dose of budesonide, but was also conducted on a group of children whose need for daily bronchodilator therapy suggests they were more likely to have had true asthma rather than episodic viral wheeze.

Recurrent cough is an extremely common childhood symptom. While children with asthma may present with cough as the most prominent symptom, these children will almost always have evidence of wheezing on closer questioning or on examination. Pre-school children with chronic cough but no wheeze are no more likely to develop wheeze or asthma later in childhood than are symptom free pre-school children.<sup>13 14</sup> Healthy children may get numerous upper respiratory infections each year, and dry cough may sometimes continue for several weeks afterwards in the absence of any other pathology. Studies showing the effectiveness of asthma treatments in children with persistent cough have tended to include children who also had clinical or physiological evidence of airways obstruction, while a placebo controlled trial of salbutamol and inhaled steroid in children with cough alone showed no benefit.<sup>15</sup> An excessive readiness to apply the label of cough-variant asthma leads to the prescription (and often the apparent success) of asthma treatments for children with self-limiting post viral cough. In some cases steadily increasing doses of steroid are given to such children without effect. It may be safer practice to dispense with the spurious diagnosis of "cough-variant asthma".<sup>16</sup>

#### **Getting the diagnosis right**

Asthma is not an "all or none" diagnosis, nor is it a homogeneous disease. It is common and may therefore independently coincide with other disorders. What mistakes can be made in making a diagnosis of asthma in childhood? Firstly, more serious conditions, rare but important, can be missed. Lower respiratory illness originating in the neonatal period or early infancy may be due to congenital abnormality of the heart or lungs or to recurrent aspiration. A persistent moist or productive cough, particularly in the presence of failure to thrive or marked systemic upset in acute episodes, should raise the possibility of chronic infective or host defence disorders such as cystic fibrosis, bronchiectasis, ciliary dyskinesia, tuberculosis, HIV disease, or a congenital immune deficiency. The possibility of an inhaled foreign body should also be remembered. A combination of upper and lower respiratory tract symptoms can occur both in

asthma and in these more serious conditions. Onset of symptoms in the neonatal period, failure to thrive, and constant symptoms or chest signs warrant a chest radiograph and referral to a specialist. Secondly, the asthma label can be applied prematurely to pre-school children after a few episodes of self-limiting viral induced wheeze, and the resolution of symptoms mistakenly attributed to treatment rather than to the natural history of this wheezing phenotype. Thirdly, particularly in older and teenage children, the diagnosis of asthma may be correct but its severity seriously overestimated. Every paediatric asthma clinic receives referrals of children with severe continuing symptoms despite multiple high dose anti-asthma treatments. A proportion of such children prove to have symptoms based on hyperventilation, anxiety, and laryngeal dysfunction (glottic wheeze)—usually on a background of important emotional and family problems—and to need far less intensive anti-asthma treatment than when they presented. Fourthly, the old problem, appropriate diagnosis of asthma can be missed or made late in children who keep coming back with chest trouble. Repeated antibiotic courses should not be prescribed for “bronchitis” in children without considering a diagnosis of asthma or of other more serious conditions.

How do we get it right? Correct diagnosis involves the integration of different types of information and evidence acquired over a period of time. The process is one of pattern recognition, maintaining a continuing awareness of the potential pitfalls in the interpretation of history, examination and physiological data, and in the assessment of response or non-response to treatment. When seeing a new child with “asthma” diagnosed by someone else, we should always ask ourselves whether the diagnosis was soundly based. This becomes increasingly important as primary care teams grow and continuity of care decreases.

A good history is crucial, looking for pointers to more serious diagnoses and carefully establishing the presence or absence of respiratory symptoms between acute episodes, especially night time cough and exercise induced cough, wheeze or undue “shortness of breath”. Let parents use their own words. Do not offer the word “wheeze” but wait to see if parents use it. If they do, clarify what they mean. Allowance has to be made for the fact that anxious parents may be unduly aware of the symptoms of minor respiratory infection while other parents, suspecting but keen to avoid the diagnosis of asthma, may make light of quite marked symptoms. Examination of the cardiovascular and respiratory systems, the shape of the chest, and the child’s growth chart is important but all of these may be normal in children with asthma.

Physiological measurements may be of some help in school age children—peak flow charting, exercise challenge tests, bronchodilator responsiveness assessed by peak flow measurement or preferably by spirometric testing can all help. Clear and repeated demonstration of significant variability in peak flow or forced expiratory volume in one second (FEV<sub>1</sub>) over

time or with treatment strongly supports the diagnosis of asthma, although the criteria for a significant response are imprecise and highly dependent on the care and skill with which measurements are made. A gentle trot around the car park on a sunny day does not constitute a rigorous exercise challenge. Two peak flow readings with a 20% difference do not on their own sustain a diagnosis of asthma. Concurrent therapy may further complicate interpretation. Where symptoms are intermittent the parents can be asked to bring the child for clinical assessment, peak flow measurement, or spirometric testing during an episode of symptoms.

Respiratory function testing in infants and pre-school children is possible but requires specialised equipment and expertise which is not widely available; its difficulties confine application to research studies rather than to routine clinical assessment. A major research effort is under way to identify reliable markers of airway inflammation in blood or expired air but none are as yet usable in practice.

The final arbiter of the diagnostic process is often a therapeutic trial of anti-asthma therapy though the nature of such a trial and the outcomes to be measured are both ill defined. In infants with frequent or persistent wheeze in whom it has been decided to attempt treatment, Cochran has proposed an eight week trial of a moderately high dose inhaled steroid (800 µg daily of beclomethasone or equivalent) rather than “12–18 months of escalating and often erratic prescribing of asthma medication”.<sup>17</sup> The generous dosage increases the likelihood of a clear response if there is going to be one. Older children may not require the initial high dosage since the reliability of administration is greater. A clear response with less cough, wheeze and night time disturbance, and improvement in exercise tolerance should lead to continuation of treatment with reduction to the usual age appropriate dosage and subsequent stepping down, symptoms permitting, as outlined in the BTS guidelines.<sup>18</sup> Prompt and total resolution of symptoms should raise the suspicion that this would have happened without treatment and consideration of a more rapid stepping down. Scepticism should help to prevent overdiagnosis and overtreatment. Growth in height should be monitored at least twice yearly in children remaining on inhaled steroids. Failure of response to treatment should prompt consideration of the most common explanations—namely, inadequate dosage, faulty inhaler technique, non-adherence, or wrong diagnosis.

### Conclusions

We must remind ourselves, and our patients’ parents, that a certain amount of recurrent minor respiratory illness is a normal feature of childhood, is necessary for the acquisition of immunity, and does not require medical treatment. In children who we believe to have asthma the aim of totally eliminating symptoms can lead to overdiagnosis and overtreatment. We may need to accept occasional symptoms (and need for β<sub>2</sub> agonist use) as reassurance that diagnosis is correct and the prophylactic

therapy genuinely required. A parent's natural tendency to stop giving medicines when their child gets better is the main factor operating to minimise unnecessary persistence with prophylactic asthma therapy. However, if we conscientiously encourage parents of children who do not have asthma to continue regular treatment even when the child is well, then there is a risk that some of them will do as we say.

The diagnosis and management of asthma will continue to take place predominantly in primary care, but there must be a drive for continued improvement in standards in the soundness of diagnosis, in the supervision of the appropriateness of repeat prescribing, and in the monitoring of treated children, including the measurement of growth in children maintained on inhaled corticosteroids. Ways need to be found to include such issues in the agenda for clinical governance, but this is no small challenge. The routinely available data from current general practice computer systems are virtually useless for purposes of this kind, since no one knows the "correct" rates for diagnosis or treatment of asthma in children, and crude data on rates of diagnosis and prescription do not tell us whether the right patients are being diagnosed and treated. Rates of referral to specialists will continue to attract scrutiny, but again there is no method of determining correct rates. It tends to be assumed that wide variation in referral rates is inappropriate, but this assumption is questionable. Variation between general practitioners in their rates of referral of asthma patients to hospital may be entirely appropriate and in the best interests of patients. Neither general practitioners' pride in their own skills and interests nor budgetary considerations should inhibit the appropriate use of specialist opinion. Standards of specialist care in paediatric asthma need improving in some areas, and each district hospital should have at least one paediatrician with an interest in respiratory disease.

We need to identify children with asthma and offer effective treatment, but we should also avoid the indiscriminate use of the asthma label and the prescription of asthma medicines for self-limiting childhood respiratory illness. We should not substitute the overuse of bronchodilators and inhaled steroids for what we now recognise to have been the overuse of antibiotics for coughing children. Repeated and objective clinical and physiological evidence of significant variation in airway obstruction should, as far as possible, be sought and documented to sustain a diagnosis of asthma.

The following important research questions need to be addressed:

- How reliable are clinical descriptors such as "wheeze", "bronchitis", and "night cough"?
- How reliable is the reporting of symptoms by parents or children in epidemiological surveys?
- What proportion of children treated for asthma in primary care fulfil rigorous diagnostic criteria?

- Has increased public awareness of asthma increased the reporting of symptoms and the willingness of practitioners to initiate anti-asthma therapy?
- Does the definition of clinical phenotypes in early childhood wheezing disorders, largely derived from studies in the USA, apply in the UK context?
- When is it appropriate to use the label "asthma" for wheezy pre-school children?
- Is it possible to define clinical and physiological features which will reliably predict responsiveness to anti-asthma therapy?
- Is it necessary to differentiate between effects on day to day symptoms and on acute episodes in controlled trials of anti-asthma therapy in pre-school children?
- What are the mechanisms and appropriate treatment of chronic cough? How should we distinguish asthma from other causes of chronic cough?
- How does the timing and intensity of treatment of asthma influence long term clinical and physiological outcomes?
- What are the adverse effects of long term prophylactic asthma treatments, especially when introduced early in life?

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