OCCASIONAL REVIEW

Difficult asthma in children

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Asthmatic children on high dose corticosteroids need to be fully assessed to ensure that such dosages are really necessary. Further work needs to be undertaken to find the best approach to poor treatment adherence and false claims for financial support. The benefits of particular components of specialist assessment need to be evaluated prospectively and multicentre collaboration is needed to evaluate phenotype specific treatment and new treatments for truly difficult asthma.

The European Respiratory Society defines difficult asthma in children as asthma that is not controlled despite treatment with ⩾800 µg budesonide or equivalent.[1] Poor control is defined as the need for bronchodilators more than three times a week, school absence of more than five days a term, or one episode or more of wheezing each month. The dosage of inhaled corticosteroid (ICS) chosen for this definition was empirical, but there is now evidence to support it. Asthmatic children needing ⩾500 µg fluticasone/day is very unusual[2]; 90% of the benefit at this dose is achieved with 100–250 µg/day. A Cochrane review of the effect of ICS on height has suggested that height velocity is affected with doses of over 400 µg/day beclomethasone. Adrenal suppression in eight children on ⩾400 µg/day has recently been reported.[3] This dramatic side effect with an apparently modest dose of ICS could be because the dose was too high for the severity of the asthma. Absorption seems to be greater in patients with mild asthma than in those in whom the asthma is severe.[4]

These observations suggest that the need for ⩾800 µg/day budesonide or equivalent requires careful evaluation. The 1995 British Thoracic Society's guidelines recommended that children who need such dosages should be referred to a respiratory specialist.[5] The current draft of the new guidelines, shortly to be made available, is not so explicit. Is referral to a specialist worthwhile? The role of the specialist is to determine what is different about these children from the majority of children who are easy to manage. Thus, specialist evaluation should include a thorough review of the diagnosis, the child's environment, psychological factors in both child and family that could affect symptom reporting, and adherence to treatment. If, after a full evaluation of these issues, the child's asthma remains poorly controlled, a detailed evaluation of airway function and pathology including bronchoscopy and bronchial biopsy is justified.

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IS THE DIAGNOSIS CORRECT?

The first task is to ensure the child has asthma and not another wheezing disorder.[6] Some children often treated with large dosages of ICS do not have asthma at all, or have mild asthma, but have other respiratory symptoms such as functional breathing problems.[7] Evaluating respiratory sounds is not necessarily easy for the non-specialist, and it is not uncommon to confuse stridor, especially when it is biphasic, with wheeze. Persistent isolated cough, previously considered an asthma variant, is now regarded as a different disorder[8] and responds poorly, if at all, to very high doses of ICS.[9] Infants with prolonged wheezing following bronchiolitis can be difficult to manage. A few of these children will turn out to have asthma. ICS do not prevent post-bronchiolitis wheezing,[10] but they do help persistently wheezy infants who have an atopic family history.[11]

TREATMENT ADHERENCE AND SYMPTOM REPORTING

Probably the most common reason for the escalation of children's prescribed ICS dosage is that parents do not supervise treatment and then report poor control. One study of computerised prescribing databases showed that fewer than one in six parents were collecting sufficient prescriptions to cover regular prophylactic asthma medication for their children.[12] One can only speculate how many fewer were actually being administered the prescribed medication. There is ample proof of poor adherence to treatment, even in studies where parents know that adherence will be measured.[13] Unless parents own up, it is virtually impossible in the normal clinical setting to prove that they are not giving the treatment to their children. Perhaps other approaches to the problem are needed. First, it would be helpful to know how frequently prescriptions were collected and then filled by the pharmacist. Secondly, if children are not controlled on reasonable dosages of treatment, and if there is enough to suggest poor adherence, then the giving of medication by teachers at school could solve the problem. Once a day dosage appears nearly as efficacious as twice a day.[14] Since the washout time for ICS is about 4 weeks,[15] even if no drug were given there would be some benefit during school holidays, except perhaps during the summer. However, it might be difficult to get parents to agree to this approach. Personal practice suggests that some teachers are quite positive about giving medication. Thirdly, an approach that may differentiate the rare cases of true steroid resistant asthma from persistent wheezing due to non-adherence is the short term use of depot injections of triamcinolone. A marked response would suggest that non-adherence is the problem.

Another problem, often discussed but never studied, is the manipulation of children's asthma for secondary gain.[16] Children who have genuine asthma may deliberately not be given treatment so that control appears poor, or symptoms consistent with asthma are reported and exaggerated, either deliberately or because of anxiety. Such children can then be considered "disabled" and parents can claim financial support. This is very difficult to assess and child protection issues could be difficult to tackle. Sometimes a short period of admission and observation by experienced paediatric nurses and psychologists may help.

ADVERSE ENVIRONMENT

The role of an adverse environment still needs to be clarified. Poorly controlled asthmatics on a similar high dosage of ICS to well controlled subjects are probably in a worse environment with respect to aeroallergens and passive smoking.[17] Persistent allergen exposure in the sensitised patient causes eosinophilic airway inflammation, bronchial hyperresponsiveness,[18] and secondary steroid resistance.[19] Skin prick testing and a home visit from a children's respiratory nurse should be part of the specialist assessment. In sensitised patients the level of allergen exposure correlates with more severe disease, including hospital admissions, acute visits, and school days missed.[20 21] In an inner city population only asthmatic children with specific mite allergy on skin prick testing benefited from indoor allergen avoidance.[22] In this study, comparison of active and placebo avoidance groups who had home visits and a control group who did not showed significant benefit in those who had had the home visits.

PATHOPHYSIOLOGICAL ASSESSMENT

Symptoms of genuine asthma, which persist in spite of high dose ICS with additional long acting β agonists, a leukotriene receptor antagonist, and/or oral theophylline, may reflect a heterogeneous group of conditions.[23] These children should be fully investigated.[17] The concept of phenotype specific treatment needs developing. Determining the relative contributions of inflammation and bronchial reactivity might be beneficial in guiding treatment. Not all inflammation is eosinophilic; the role of the neutrophil in severe asthma is becoming better understood. The best possible lung function should be determined following optimal treatment. There is no point in increasing the doses of medication because of fixed airflow obstruction. If there is no functional improvement to prednisolone 40 mg/day for 2 weeks with adherence checked by measuring serum prednisolone and cortisol levels, a fibreoptic bronchoscopic examination with bronchoalveolar lavage and large airway biopsy is justified. Bronchial biopsy is safe in children in experienced hands.[24]

Corticosteroid resistant eosinophilic inflammation identified on the biopsy material in a child who has documented adherence to prednisolone therapy reflects a phenotype where alternative anti-inflammatory treatments such as cyclosporin could be considered.[25] Corticosteroid resistance, defined by low numbers or poor function of corticosteroid receptors, is quite rare and steroid receptor binding studies are difficult to interpret.[26] True congenital corticosteroid resistance is characterised by very low numbers of normally functioning steroid receptors. Much more common is secondary steroid resistance in which receptor numbers are normal or increased, but binding affinity reduced. This is usually seen in persistent inflammation, possibly mediated by interleukin (IL)-2 and IL-4.[19] For children with marked reversible bronchoconstriction and no evidence of inflammation on the biopsy material, subcutaneous β agonist infusion seems more logical than ever more potent treatments for non-existent inflammation. Neutrophilic phenotypes might be treated with macrolide antibiotics to downregulate IL-8 production, 5-lipogenase inhibitors to reduce leukotriene B_4, or theophyllines to accelerate neutrophil apoptosis. Trials of truly novel treatments such as anti-immunoglobulin E or some of the newer cytokine specific treatments need consideration. The number of truly difficult asthmatic children is small, so multicentre studies of interventions would be essential and should take place in centres where full assessments, including biopsies, could be undertaken.

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