Difficult asthma: beyond the guidelines

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PERSONAL PRACTICE

Difficult asthma: beyond the guidelines

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The current guidelines for prophylactic treatment of paediatric asthma culminate in the addition of regular oral corticosteroids after a stepwise increase in treatment.[1–3] However, there are still a few patients whose asthma is not controlled despite such maximal conventional treatment and these children are often referred to a tertiary paediatric respiratory centre. Childhood asthma has several manifestations and different approaches may be required for different patterns of asthma. Unfortunately, some of these children are difficult to treat. These include infants with severe recurrent viral wheezing who respond poorly to medication but generally have a good prognosis. There are those said to have "brittle asthma"; this has been classified into those with a wide peak flow variation despite maximal treatment (type 1), and those who are well controlled in between attacks, which when they occur are often sudden and severe (type 2).[4] This article concentrates on another group—children who have severe chronic background symptoms with acute exacerbations superimposed.

Confirming the diagnosis

The first question when confronted by a child with severe symptoms despite conventional treatment is: does the child really have asthma? There are several alternative diagnoses that should be considered, some more rare than others. Relevant investigations should be carried out when the history or examination suggests one of these other diagnoses (table 1). In particular, the presence of finger clubbing is incompatible with the lone diagnosis of asthma. An asthmatic child may be affected by another condition that contributes to or worsens the asthma symptoms. In particular, gastro-oesophageal reflux should be looked for and treated although its significance is not always clear.[5] Immunodeficiencies should also be excluded; an initial screen should include serum immunoglobulins and IgG subclasses, complement concentrations, and antibody responses to common antigens (diphtheria, tetanus, *Haemophilus influenzae* type b, and pneumococcus) (Jones A, personal communication, 1998).

Table 1 Some of the alternative and concomitant diagnoses with relevant investigations for children presenting with difficult asthma

Diagnosis	*Investigations*
Cystic fibrosis	Sweat test, DNA analysis
Primary ciliary dyskinesia	Ciliary brushings for structure and function, nasal nitric oxide
Congenital lung abnormalities	Chest *x* ray, CT chest scan
Tracheobronchomalacia	Flexible bronchoscopy
Vascular ring	Barium swallow
Bronchiectasis	Chest *x* ray, CT chest scan
Obliterative bronchiolitis	CT chest scan, viral titres
Inhaled foreign body	Chest *x* ray, inspiratory and expiratory chest imaging (older children), rigid bronchoscopy
Recurrent aspiration	Chest *x* ray, bronchoalveolar lavage for fat laden macrophages, radiolabelled milk scan
Congenital heart disease	Echocardiography, electrocardiography
Vocal cord dysfunction	Laryngoscopy
Gastro-oesophageal reflux	24 hour pH study or radiolabelled milk scan
Immune problems	Immune function testing

CT, computed tomography.

VOCAL CORD DYSFUNCTION

Vocal cord dysfunction frequently mimics or complicates asthma, and is characterised by a paradoxical adduction of the vocal cords on inspiration.[6] The resultant airflow obstruction produces wheezing or stridor (usually loudest over the larynx), chest tightness, breathlessness, and cough. Symptoms can be produced throughout the respiratory cycle, so they may be inspiratory, expiratory or both[7] but they are never present during sleep. Although patients with vocal cord dysfunction are usually women aged 20–40 years, the condition is well recognised in children and adolescents.[8] There are often underlying psychological stresses but it is not factitious as patients do not consciously control the process.[6] Patients with vocal cord dysfunction have often been misdiagnosed with asthma (subsequently found to be unresponsive to bronchodilators and corticosteroids), but the condition may coexist with asthma.[9] Spirometry is poorly reproducible, but the flow–volume loop may show evidence of variable extrathoracic obstruction or be normal.[7] Diagnosis is confirmed by laryngoscopy, which shows adducted cords relieved by sedation.[7] Treatment evolves around a clear explanation of the syndrome, stopping unnecessary medication, speech therapy, and psychological support.

Confirming the severity

In many cases, severity can be gauged from the history and physical examination. Simple

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spirometry, which can be performed in the outpatient clinic, will provide measures of airflow limitation, and a look at the flow–volume loop can be helpful. Day to day peak flow variability is a useful measure assuming that the home diaries are accurate. Unfortunately, experience shows that these diaries can rarely be relied on, compliance is poor, and measurements are often fabricated.[10] Formal lung function testing in a laboratory may also be necessary for full evaluation, and would include measures of airway resistance, lung volumes and air trapping, bronchodilator responsiveness, and the effects of exercise. A directly observed exercise test may be useful to help differentiate whether it is the patient's perception of breathlessness, general muscle fitness, or true exercise induced asthma that is causing problems with exercise. Patients often start to complain of breathing difficulties the minute they start exercising, in which case it is unlikely this is caused by asthma itself. Measurement of exhaled nitric oxide may also be used to monitor the effects of corticosteroids on the underlying inflammation, although the usefulness of this measure is uncertain.[11 12] It has been suggested that assessment of bronchial hyperresponsiveness (methacholine or histamine challenge) is the single most useful test of asthma severity,[13] but in practice it is rarely useful in children.

Inconsistencies with the clinical picture should raise suspicions that the asthma severity is not as great as the child and his or her family (and perhaps the referring doctors) perceive. The history should then be treated with caution, and while reliable measures in the examination include chest hyperinflation and Harrison sulci, added sounds on auscultation may not be genuine. Spirometry becomes harder to interpret as measures are so effort dependent, although the shape of the flow–volume curve may give clues to poor effort. Other measures that may be useful when the situation is in doubt include a straight and lateral chest *x* ray for hyperinflation, and in extreme cases a ventilation–perfusion scan. During a prolonged exacerbation the latter is likely to show patchy areas of ventilation–perfusion mismatch and a normal scan should raise suspicions. Doubts will also arise when a severely "symptomatic" child has a normal bronchial challenge. These children are often being overtreated, and as the perceived symptoms inevitably fail to resolve, the treatment regimen is increased further still resulting in potentially serious side effects.

Another problem is poor perception and underestimation of symptom severity in a child who truly has severe asthma. A significant number of patients with asthma (and their parents) fail to recognise how serious the symptoms are, in both the acute and chronic situation. This increases the risks of noncompliance and severe exacerbations. Reasons for this lack of insight range from psychological denial to a blunted perception of breathlessness and airway obstruction intrinsic to some patients.[14]

PSYCHOSOCIAL ASPECTS

It is not uncommon for psychosocial aspects to play a large role in the wellbeing of a child and particularly an adolescent with asthma. Difficult home circumstances may lead to a worsening of symptoms and sometimes the illness is used as a weapon or a cry for help. It may even be the mechanism for school refusal. Admission to hospital is often needed to assess the true functional status of the child and to gain an impression of family interactions, albeit in unfamiliar surroundings. As well as simple observations from the nursing staff on the ward, help can be enlisted from the clinical psychologist, teachers and play leaders, and sometimes social workers. Psychosocial problems do not mean the child does not have asthma (a point that must be emphasised to the child), but the severity of symptoms are often out of keeping with the actual disease severity. The asthma and psychological disturbance must both be treated on their own merits without necessarily deciding which is primary and which secondary.

Reasons for treatment failure

Assuming the patient genuinely has severe asthma responding poorly to treatment, it may be possible to improve matters by simple means.

ALLERGENS AND OTHER AVOIDABLE FACTORS

There may be allergens in the home that are providing a constant source of immunological stress to the airways. While house dust mites are almost impossible to eradicate, their effect may be reduced by various methods, including regular ventilation of the bedroom, mite proof allergen covers on bedding, and the use of an efficient vacuum cleaner with an adequate filter.[15] It is surprising how many asthmatic children live in homes with a multitude of furry pets, and horse riding seems to be a favourite pastime of teenage girls with severe asthma. Rather than being dictatorial, it is best for the families to come to decisions about removing pets themselves. This may be helped by providing objective evidence, and if the history suggests worsening symptoms after exposure to a particular animal, skin prick testing or RAST (radioallergosorbent) testing for specific IgE may be useful. Families should be warned that it may take up to six months for symptom improvement to be seen after the pet has been removed.[16]

Exposure to cigarette smoke at home and in the car may be a contributory factor, and a child with a serious disease does not always provide enough motivation for some parents to stop smoking. It is worth considering whether the adolescent asthmatic has started smoking themselves. The issue of poor housing and damp in the home is controversial but may contribute to symptoms.[17]

INAPPROPRIATE DEVICES

It is surprising how often asthma control can be improved by changing the device used to administer inhaled drugs. Watching the child's technique with their medicines is essential, and

time spent in retraining is well spent. Drug deposition in the lungs varies significantly according to the device; spacers are very effective[18] so these are recommended for taking twice daily prophylaxis. However, owing to their size, spacers are inconvenient to carry around during the day, so dry powder inhalers are recommended as the next best thing, with Turbohalers (Astra Pharmaceuticals, Kings Langley, UK) being the most efficient.[18] I never prescribe metered dose inhalers without a spacer device. In fact the choice of device is probably more important than the choice of drug, with the child's age and coordination being the most critical factors. In addition, devices that are "uncool" will not be used at school, and compliance can be improved by giving the child a degree of choice.

INADEQUATE DOSES

Use of regular systemic steroids may sometimes be avoided with high enough doses of inhaled corticosteroids. There is no room for being timid, and fears of adverse effects, particularly poor growth, should not lead to inadequate treatment. Professor Charles Brook, with his expertise on growth, is the first to say, "asthmatics do not die of short stature". However, equally there is no need to be cavalier; safety can be enhanced by delivery through a spacer device combined with rinsing the mouth afterwards, which will reduce oral absorption of the drug. Regular monitoring of growth and examination for cataracts[19] is recommended when using very high doses. Deciding whether one inhaled corticosteroid is truly safer or more efficacious than another is difficult to determine as, despite many claims, it is almost impossible for clinicians to judge whether such claims are correct.[20] Anecdotally, switching to high dose fluticasone propionate has sometimes resulted in improved control. In terms of other drugs, there is little evidence that giving doses of salmeterol above those generally recommended leads to additional benefit, although there are some anecdotal cases in which this has proved useful.

NON-ADHERENCE TO TREATMENT

There is little doubt that patients do not take their medication as we think or hope. One study using electronic monitors attached to inhaler devices has shown that more than 90% of children exaggerated their use of inhaled steroids, with a median use reported in diaries of 95% compared to actual electronically recorded use of 58%.[21] Compliance was worse in those who experienced an exacerbation requiring oral steroids. Furthermore, compliance does not improve with increasing disease severity and, worryingly, non-compliance often occurs with tacit approval from parents.[21] Reasons for non-adherence to long term medication are multiple, including poor understanding, fear of steroid side effects, adolescence, and a wish to be just like everyone else. A patient approach from a multidisciplinary team, which the child and family must feel a part of, is the way forwards, although there are no guarantees of success.

STEROID RESISTANCE

Steroid resistant asthma occurs in a small subset of patients with genuine asthma that fails to show a clinical response to high dose systemic corticosteroids that are genuinely taken. Despite adequate treatment, they have persistent airway obstruction and immune activation. Steroid resistant asthma has been recognised for a while in adults and there are now reports of a few children with the condition.[22 23] The clinical definition for adults is failure to improve morning FEV_1 (forced expiratory volume in one second) by more than 15% predicted after 14 days of 40 mg/day prednisolone.[24] In children, there is no set definition but 10 days of at least 15 mg twice a day has been suggested as an adequate trial.[25] However, symptoms and persisting evidence of airway inflammation can occur in children with relatively well preserved lung function.

The steroid resistance is not necessarily generalised; the patients are often Cushingoid despite lack of a local response in the lungs, so they suffer the adverse effects of corticosteroids while receiving little clinical benefit.[25] There are several mechanisms behind steroid resistance, both primary and secondary (acquired), which have recently been reviewed.[24 26] If a child does not respond to a controlled therapeutic trial, bronchial mucosal biopsy is recommended to determine the cellular and inflammatory cytokine profiles.[23] Less invasive methods such as induced sputum for inflammatory markers and exhaled nitric oxide levels can also be used. If this confirms unrestrained inflammation despite high dose systemic steroids, then alternative treatments should be considered as there is little point in continuing with steroids. Complete steroid resistance is fortunately rare, but there is a group of patients with reduced responsiveness to steroids (corticosteroid insensitive asthma) in which high doses of inhaled or systemic steroids are needed to maintain adequate control. Finally, there is a group of patients requiring constant systemic corticosteroids for control (steroid dependent asthma). This last group is thought to have severe disease with profound airway inflammation.[24]

Therapeutic options

It may not be possible to reduce or stop systemic steroids, in which case they should be given in a way to enhance safety. Suppression of the hypothalamo–pituitary–adrenal axis is lessened by taking the steroids in the morning, and if possible on alternate days. Prednisolone tends to be used and recent claims that deflazacort has a lower incidence of steroid induced side effects compared to prednisolone have been revised at the request of the Medicines Control Agency.[27] However, the following are alternative forms of treatment that may allow reduction of steroids or at least lead to improved control. The assumption is that the child is already taking high dose inhaled steroids and oral steroids, a long acting β_2 agonist (salmeterol or eformoterol) and perhaps theophylline.

NEBULISED BUDESONIDE

In a double blind, placebo controlled study, 36 children aged 10 months to 5 years who were dependent on oral steroids were given 2 mg/day nebulised budesonide or placebo.[28] There was a significant reduction in oral steroids and an improvement in subjective symptom scores in the active treatment group. However, the patients had not been taking inhaled steroids by other means and it is not clear whether budesonide administered by a spacer device would have been equally effective. With an optimal nebuliser setup budesonide delivered by spacer is equipotent to that delivered by nebuliser[29] and, in practice, nebulisers are less efficient at drug deposition compared to spacers.[18] No study of nebulised budesonide has been carried out in steroid dependent older children, but an open study in 42 adults given 2 mg/day found that 55% were able to reduce their oral steroid intake by a mean of 59%.[30] It is best to use a mouthpiece, but if a mask must be used it should be tight fitting and children should be advised to wash their faces and rinse their mouths afterwards. The holes in the mask facing upwards towards the eyes should be covered and children should be reminded to breathe through their mouths and not their noses.

SUBCUTANEOUS TERBUTALINE

Continuous subcutaneous terbutaline and salbutamol have been shown to be useful in some adults with severe chronic or brittle asthma.[31 32] This form of treatment has been used in acute severe infantile asthma[33] and can be quite effective in the chronic phase in children who are prepared to tolerate a subcutaneous needle. The intravenous preparation (0.5 mg/ml) is administered by Graseby pump (Graseby Medical Ltd, Watford, UK) at a starting dose of 5 mg/day. Systemic side effects include tremor, hyperactivity, sinus tachycardia, palpitations, headache, and muscle cramps, although generally it is well tolerated. Serum potassium should be monitored owing to the theoretical possibility of developing hypokalaemia, although this is in fact rare.[4] Local problems are more common and include tender subcutaneous nodules and haematomas at the site of injection. It is advisable to start this treatment in hospital for safety reasons, and to allow adequate time for educating the patient and family. It is often useful to start with saline for 48–72 hours and essentially perform an n = 1 single blind therapeutic trial; this ensures any symptom improvement is not simply a placebo effect.[34]

ORAL ANTI-LEUKOTRIENES

Since the discovery of the leukotrienes and their role in asthma, there has been intense activity to produce drugs that counteract their effects. This has been achieved by blocking leukotriene synthesis with enzyme inhibitors (5-lipoxygenase inhibitors, such as zileuton) or interfering with binding of leukotrienes to their receptors (receptor antagonists, such as montelukast, zafirlukast) recently reviewed by Horwitz *et al*.[35] Montelukast (Singulair; Merck, Sharp & Dohme Ltd, Hoddesdon, UK) is available for children over 6 years and has the advantage of being a once daily chewable tablet. The only published paediatric study was multicentre and involved 336 children aged 6–14 years.[36] A significant improvement in morning FEV_1 was shown after eight weeks of treatment with benefit seen after one day's treatment. There were no differences in adverse events between the drug and placebo groups, in particular there were no problems with liver enzymes. Further studies are needed to assess the long term safety profile of montelukast. Zafirlukast (Accolate; Zeneca Pharma, Wilmslow, UK), a twice daily tablet, is also available and licensed for children over 12 years.[37] These drugs are an exciting development as they represent the first mediator specific treatments for asthma. They have not yet been proved as steroid sparing agents in children, but inevitably if better control is achieved, steroid doses will be reduced. Within the next year, their therapeutic role in mild asthma may become clearer, but for now it is likely that their use will be restricted to the stage before oral steroids are introduced—even though there is no evidence of their benefit in this situation.

ORAL CYCLOSPORIN

Cyclosporin is an immunosuppressant used after organ transplantation that works by inhibiting T helper lymphocytes. The prominent role of T lymphocytes in asthma has led to trials of cyclosporin in adults which showed improved lung function[38 39] and a steroid sparing effect.[39] No trials have been carried out on children although its successful use in three of five children on regular oral steroids has been recently reported using 5 mg/kg daily.[40] The side effects in adults include hirsutism, paraesthesia, mild hypertension, headaches, and tremor.[38 39] The only concern in the paediatric report was hirsutism, which led to one girl stopping its use even though her steroid dose had been profoundly reduced. There is obviously a concern about renal impairment with long term use, so renal function must be carefully monitored, and cyclosporin blood concentrations maintained at 80–150 mg/l. A proper randomised trial is urgently needed as this drug has real potential in severe asthma. Furthermore, nebulised cyclosporin is being tried in some post-transplant patients, and this may offer an improved risk–benefit ratio over systemic cyclosporin in asthma.

INTRAVENOUS IMMUNOGLOBULIN

Two small, open label studies found that infusions of intravenous immunoglobulin (IVIG) led to a reduction of oral steroids in children aged over 6 years.[41 42] It was thought the IVIG had an immunomodulatory role and, interestingly, serum IgE and skin test reactivity were reduced in one study.[41] A recent case report showed a reduction in markers of disease activity in peripheral blood as well as a decrease in numbers of all cell types (especially CD3+, CD4+, and activated CD25+ T lymphocytes) on bronchial biopsy.[43] A recent randomised

placebo controlled trial in 31 children and adolescents was disappointing in that no benefit was seen in lung function, bronchial hyperreactivity, or symptom scores.[44] There was however a trend towards fewer total days of upper respiratory tract infections, and the effect of IVIG may simply be to reduce viral exacerbations. For this reason, it may be most useful in severe infant wheezing, although evidence for this will be required. The main side effects reported have been fever and headaches, but it is a blood product and regular intravenous cannulation is required.

ORAL METHOTREXATE

Methotrexate is an immunosuppressive and anti-inflammatory agent. It has been shown in many studies to reduce steroid use in adults with asthma; these studies have recently been subjected to meta-analysis.[45] To date, there have been two small open label studies on children. Both showed steroid doses could be reduced in some of the children while lung function was maintained or improved.[46 47] Reported side effects in the children were gastrointestinal upset and transiently raised liver transaminases.[47] However, there are numerous potentially serious adverse effects associated with the drug (pulmonary fibrosis, pneumonitis, hepatic cirrhosis, myelosuppression), particularly when given in high doses. Low doses are relatively safe, and its use may be considered in some children.

Conclusions

The mainstay of managing the small group of children with severe asthma failing to respond to conventional treatment is to check that there are no alternative or concomitant diagnoses. External factors that are aggravating symptoms should also be excluded. Non-adherence to treatment must be considered and correct use of inhaler devices checked. Once this is done, some of the alternative treatments outlined should be tried. In future, it is likely that new forms of treatment will be available, and most likely these will target more specifically the immunological and inflammatory cascade of asthma.

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