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REVIEW ARTICLE

Children with Difficult Asthma: A Practical Approach

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INTRODUCTION

The National Heart, Lung, and Blood Institute (NHLBI) and British Thoracic Society (BTS) guidelines for the diagnosis and management of asthma recommend a stepwise approach to therapy (1,2). The majority of children with asthma have symptoms that are readily controlled by a short-acting bronchodilator and regular inhaled corticosteroids, with or without the addition of a regular long-acting β_2-agonist. A small proportion, however, continues to experience frequent symptoms despite such treatment. A recent European Respiratory Society task force on difficult or therapy-resistant asthma has suggested that children treated with $\geq$800 μg/day of inhaled beclomethasone or equivalent (step 3 of the NHLBI or BTS guidelines) who continue to experience frequent symptoms requiring rescue bronchodilator should be classified as having "difficult asthma" (3). Our own experience is that these children are often prescribed doses of inhaled steroids in the range of 1000–2000 μg/day.

Although the number of patients is small (probably $<$5% of all children with asthma), their impact on asthma morbidity and the use of health service resources is disproportionately large (4). This review focuses on this group of patients and outlines a practical approach to their management (Fig. 1). This involves confirmation of the diagnosis with possible alternatives, identification of associated conditions, and assessment of asthma severity and the degree of control. Possible reasons for treatment failure, such as poor treatment adherence or the persistence of avoidable precipitating factors, are then discussed. Finally, for patients with genuinely difficult asthma that is resistant to conventional therapy, other therapeutic options are explored.

THE DIAGNOSIS

Is It Truly Asthma?

The first step in the management of a child with difficult asthma involves confirming the diagnosis and identifying other conditions that may either mimic or coexist with asthma. An attempt must be made to document objective findings that verify the history. Clinical findings such as

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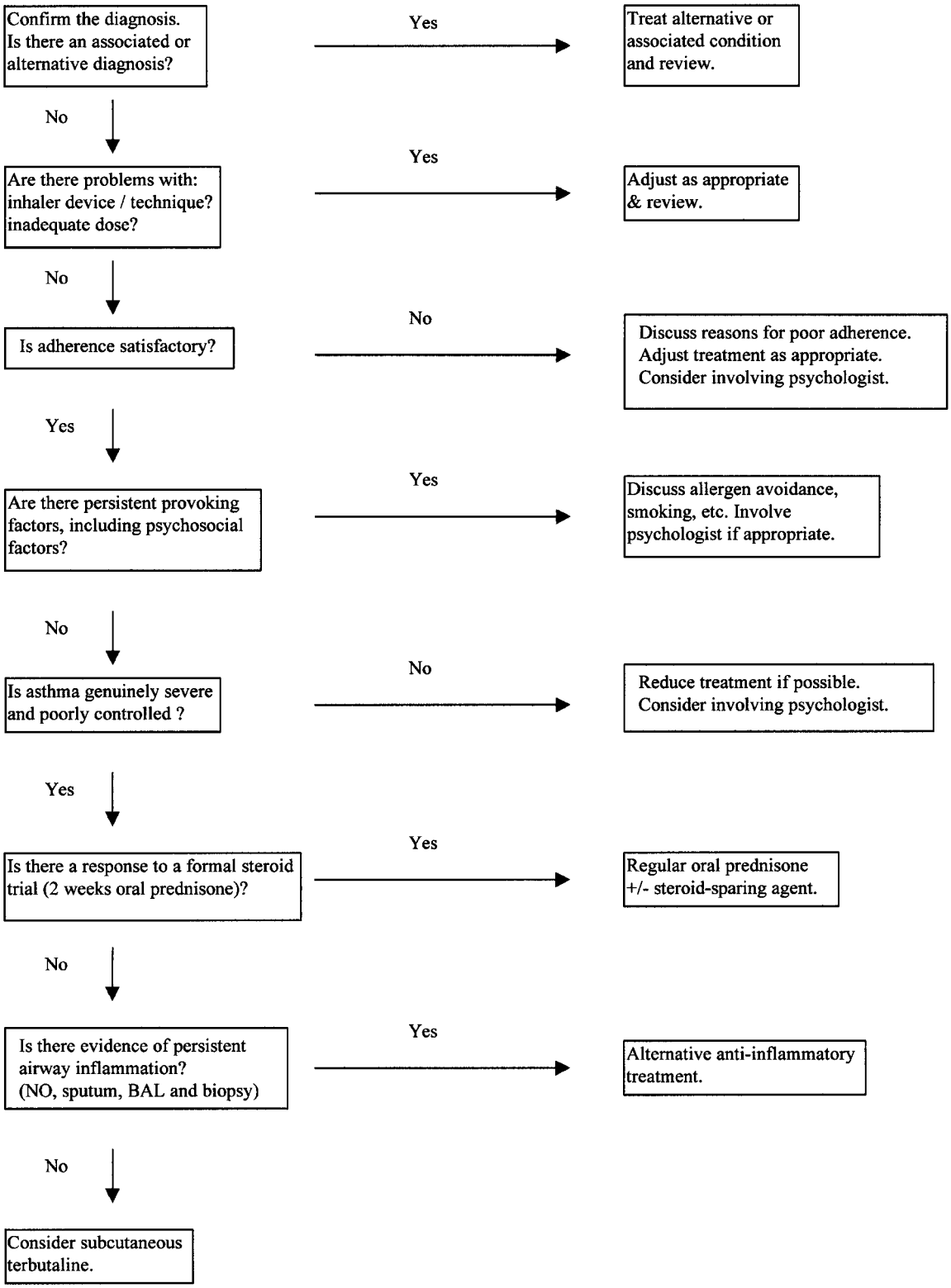

Figure 1. Algorithm for the management of a child with difficult asthma.

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hyperinflation of the chest and Harrison's sulci demonstrate evidence of chronic respiratory disease but do not point exclusively to a diagnosis of asthma. The presence of finger clubbing always indicates that asthma is not the principal diagnosis.

Assessment of dynamic lung function is essential in the diagnosis of asthma. However, the performance of spirometry is effort dependent, and patients must be supervised by a suitably trained person, who should be able to ensure that the child's technique is satisfactory. The expiratory flow-volume curve of patients with persistent airways obstruction will have a scooped-out concave appearance. Although suggestive, this is not diagnostic of asthma, and evidence of airway reversibility should be sought. Bronchodilators should ideally be withheld for 4 hours before assessment of reversibility. Baseline forced expiratory volume in 1 second (FEV_1) should be measured, followed by the administration of a short-acting bronchodilator. In an effort to demonstrate reversibility, a large dose should be used, such as 1000 μg of salbutamol via a metered dose inhaler with a spacer device or 5 mg via a nebulizer (5). FEV_1 should then be measured 15 minutes later. Bronchodilator reversibility is commonly expressed as a calculated increase in $FEV_1 > 15\%$ of the baseline value, but this is in fact statistically inappropriate. Change in FEV_1 should be expressed in absolute terms (6,7). In adults an increase of >190 mL indicates reversibility and is independent of the baseline value of FEV_1. In children it has been suggested that an absolute increase of $>9\%$ of the predicted value (e.g., from 60% predicted to $>69\%$) is the most appropriate way of defining reversibility (8). Lack of a bronchodilator response in a child with marked airflow obstruction may indicate the presence of fixed airway obstruction. However, if a large proportion of the obstruction is due to mucosal swelling and edema, treatment with corticosteroids may reduce this and unmask any hidden bronchodilator responsiveness.

In some children with genuine asthma it may not be possible to document reversibility because they have near normal lung function at the time of testing. In this situation some form of challenge test such as a methacholine challenge or an exercise test may provide evidence of airway hyperresponsiveness. Absence of both reversibility and hyperresponsiveness in a child with persistent symptoms should lead to a careful reevaluation, with emphasis on issues of overreporting or a diagnosis other than asthma.

What Else Could It Be?

Children will respond poorly to asthma therapy if they do not have asthma. A list of alternative diagnoses is given in Table 1. Some of these may be suggested by the history (inhaled foreign body) or clinical examination (finger clubbing in cystic fibrosis or bronchiectasis). Clues may also be provided by simple investigations performed as part of the initial evaluation of the patient. The side of the aortic arch should be noted on a plain chest X-ray, as a right-sided arch may indicate the presence of a vascular ring (9). When spirometry is performed, the shape of the flow-volume loop gives important diagnostic information. Flattening of the inspiratory and expiratory flow-volume loops indicates large airways obstruction (vascular ring, tracheomalacia), and poorly reproducible curves may suggest vocal cord dysfunction.

Table 1

Diagnoses That May Mimic or Coexist with Asthma

Diagnosis	Investigations
Gastroesophageal reflux	pH study, isotope milk scan
Vascular ring	Chest X-ray, spirometry, barium swallow, flexible bronchoscopy
Vocal cord dysfunction	Spirometry, laryngoscopy
Cystic fibrosis	Sweat test, DNA analysis
Inhaled foreign body	Rigid bronchoscopy
Obliterative bronchiolitis	CT scan, respiratory viral titers in serum
Bronchiectasis	CT scan
Primary ciliary dyskinesia	Ciliary brushing, nasal nitric oxide
Tracheobronchomalacia	Flexible bronchoscopy, bronchography
Recurrent aspiration	Bronchoalveolar lavage for lipid-laden macrophages, chest X-ray, CT scan, videofluoroscopy
Immune deficiency	Immune function testing

Is There Something in Addition to the Asthma?

Asthma may coexist with other diagnoses, such as gastroesophageal reflux disease, vocal cord dysfunction, and immune deficiency. Recognition of these associated conditions will allow targeted treatment, rather than an escalation in asthma therapy.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) may coexist with asthma, but whether one is primary and the other secondary remains a question of debate (10–13). If there is any suggestion that GERD may be contributing to symptoms,

a 24-hour pH study should be performed. A positive pH study indicates acid reflux, which should be treated with antacids and a prokinetic agent. Non-acid reflux, in which the stomach acid is buffered by food, is a feature of infants receiving frequent milk feeding (14) but may occasionally be seen in older children as well (15). If present, it will result in a negative pH study, but it may be diagnosed with a reflux scintigram (isotope milk scan). Treatment with prokinetic agents, and probably antacids as well, should be given. If the respiratory symptoms fail to improve despite maximal medical antireflux therapy, the next step in the management is not clear. A logical approach would be to repeat any previously abnormal GERD investigations. If these have become normal, it should then be assumed that other remaining factors are predominantly responsible for the respiratory symptoms. If evidence of reflux persists, then antireflux surgery may need to be considered. However, a recent review has suggested that the effects of anti-reflux surgery on asthma are no better than those of conventional medical antireflux therapy (16).

Vocal Cord Dysfunction

Vocal cord dysfunction (VCD) frequently mimics or complicates asthma and is characterized by a paradoxical adduction of the vocal cords on inspiration (17). 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, but they are never present during sleep (18). Although patients with VCD are usually women aged 20–40 years, the condition is well recognized in children and adolescents (19). There are often underlying psychological stresses, but it is not factitious, as patients do not consciously control the process (17). Patients with VCD have often been misdiagnosed with asthma (subsequently found to be unresponsive to bronchodilators and corticosteroids), but in some patients the condition may coexist with asthma (20). Spirometry is poorly reproducible, and although the flow-volume loop may show evidence of variable extrathoracic obstruction, it is often normal (18). Diagnosis is confirmed by laryngoscopy while the patient is breathing spontaneously; this may show adducted cords that are relieved by sedation. Treatment evolves around a clear explanation of the syndrome, speech therapy, and psychological support, while stopping unnecessary medication.

Immune Deficiency

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) (21). Treatment depends on the underlying deficiency but may involve antibiotics for exacerbations, regular prophylactic antibiotics, or, in severe cases, regular infusions of replacement immunoglobulin.

Is the Asthma Genuinely Severe?

In addition to establishing the diagnosis of asthma, attempts must be made to confirm the severity of the disease and the degree of control. Different methods have been used to define disease severity (3,22), and severe asthma is not the same as poorly controlled asthma. The latter implies the persistence of symptoms on a regular basis, and treatment with low-dose inhaled steroids may bring symptoms under control. Conversely, patients on high-dose inhaled steroids, that is, those with severe asthma, may be well controlled with few symptoms. Children with difficult asthma would appear to have severe asthma that is poorly controlled or that is well controlled but at the expense of steroid side effects. Before deciding whether such high doses of medication are required, there is a need to demonstrate that the child's symptoms are as frequent and troublesome as described.

The simplest way to achieve this, albeit an expensive one, is to admit the child to hospital for several days. Repeated clinical examination can be performed along with objective measurements, such as spirometry. The child's need for rescue bronchodilator can be monitored and, with it, the objective and subjective effects of bronchodilator therapy. The family dynamics can also be observed. This type of admission can provide useful information, allowing for the fact that a hospital ward is an artificial environment. Some families will attribute a marked improvement in symptoms and a reduction in medication use to this change in environment or the lack of activity that occurs in hospital. An improvement in symptoms may, however, allow an opportunity for discussing with the family whether changes can be made at home to produce a similar type of environment, for example, by stopping parental smoking.

An alternative to hospital admission is intensive home monitoring of symptoms and lung function. This will be worthwhile only if electronic monitors are used, as diary records are unreliable (23,24). Portable instruments are now available to record peak flow and FEV_1 (Medtrac, Colorado, USA; Ferraris, Enfield, UK). These can record the timing of the spirometry and the patient's effort, which will go some way to overcoming the potential problem

of performing lung function tests unsupervised. Whether these monitors will be of practical benefit remains to be proven.

More detailed lung function testing can provide information about lung volumes, air trapping, and airway resistance, although the latter measure does show considerable variability. 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 that this is caused by asthma alone. 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 doctor) perceive. The history should then be treated with caution, and while reliable measures in the examination include chest hyperinflation and Harrison's sulci, added respiratory sounds are easy to produce voluntarily. Spirometry may be hard 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 a 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.

Another problem, which can be life threatening, is poor perception and underestimation of symptom severity in a child who truly has severe asthma (25). A significant number of patients with asthma (and their parents) fail to recognize how serious the symptoms are, in both the acute and the chronic situation. This increases the risks of nonadherence 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 (26).

REASONS FOR TREATMENT FAILURE

Inappropriate Devices

If inhaled medications are prescribed, it is essential that the child is able to take them effectively. An inhaler device should be chosen that is appropriate for the child's age and coordination. Both the child and parents should be trained in the use of the device and should be able to demonstrate how to use it. They should also be able to tell when the inhaler is empty. Metered dose inhalers (MDIs) without spacers are difficult to use, and it is our practice never to prescribe them to children of any age. MDIs with a spacer device are simple to use and effective (27). Taking inhaled steroids via a spacer results in decreased systemic absorption compared to dry powder devices, with almost comparable lung deposition (27,28). Some older children will prefer to use a dry powder device rather than a spacer, and if it increases the chance of the drug being taken regularly, then it should be considered.

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. However, equally, there is no need to be cavalier. The dose-response curve for inhaled steroids indicates that increasing the dose beyond a certain level has little additional benefit while resulting in a large increase in adverse effects (Fig. 2). Safety can be enhanced by delivery through a spacer device combined with rinsing the mouth afterward, which will reduce oral absorption of the drug.

Regular monitoring of growth and examination for cataracts is recommended when using very high doses (29). 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 (28). Anecdotally, switching to high-dose fluticasone propionate has sometimes resulted in improved control, which may be due to the systemic potency of the proportion absorbed from the lungs. A recent study demonstrated that 2000 μg/day of inhaled fluticasone was more effective than 30 mg/day of oral prednisolone in reducing airway hyperresponsiveness in adult asthmatics (30). 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.

Steroid Insensitivity

For the purposes of research, steroid-insensitive (or steroid-resistant) asthma has been defined as a failure to improve morning prebronchodilator FEV_1 by more than 15% of the baseline value, following 2 weeks of treatment with 30–40 mg/day of oral prednisone (31). Patients who have been included in these studies must have a baseline $FEV_1 < 70\%$ predicted and show a $>15\%$ increase from baseline following bronchodilator use. In clinical practice

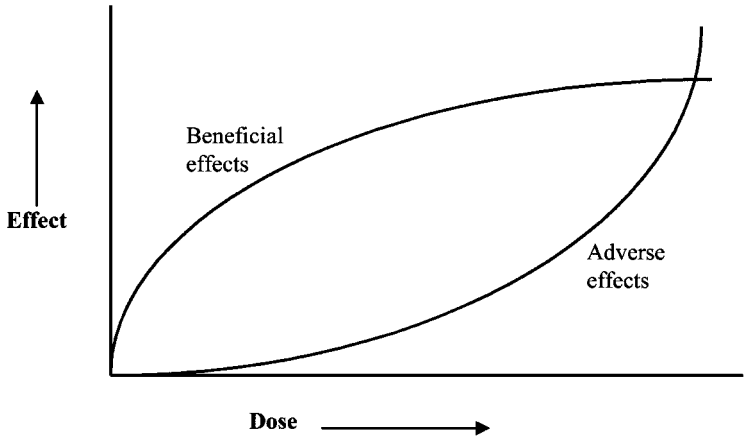

Figure 2. Balance between benefits and adverse effects of inhaled corticosteroid treatment.

there is a range of steroid responsiveness, and this research definition is purely arbitrary, using an artificial cutoff to define a group of patients at one end of the spectrum of steroid responsiveness. Some of these "insensitive" patients will show an increase in FEV_1 if prednisone is given for longer than 2 weeks or in a dose greater than 40 mg/day. In the clinical context most children on high-dose oral steroids will respond to some degree. There will come a point at which increasing the dose leads to a minimal increase in benefit while disproportionately increasing the risks of adverse effects. At this stage the benefits of increasing the dose are outweighed by the side effects. In these situations other treatment strategies need to be tried while continuing the steroids at an optimum dose or attempting to reduce the dose.

Very rarely, a patient will appear to derive no benefit from steroids (32). If this is suspected, then steroids should be gradually withdrawn and the response carefully documented. If there is no deterioration in the clinical condition (and the asthma is genuine), then the patient can be said to be steroid-resistant. This may be a primary or acquired phenomenon, and ideally, any such patient should be included in a research study investigating the mechanisms of steroid resistance, as this is such a rare condition in children (31). Early identification of these patients will prevent the unnecessary use of long-term steroids.

Avoidable Precipitating Factors

Management of difficult asthma should also include reducing avoidable factors that provoke or worsen symptoms.

Allergens

There may be allergens in the home that are providing a constant source of immunological stress to the airways. Although 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 (33). Residual cockroach allergen may also prove difficult to eradicate, even with intensive cleaning and use of pest control teams (34). It is surprising how many asthmatic children live in homes with a multitude of furry pets. 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 tests or radioallergosorbent tests (RAST) for specific IgE may be useful. Families should be warned that it may take up to 6 months for symptom improvement to be seen after the pet has been removed (35). Unfortunately, in the UK at least, having a cat often takes precedence over the health of an asthmatic child.

Smoking

Either the patient or the parents may smoke, leading to worsening of asthma control. Environmental tobacco smoke appears to be an important trigger of acute episodes of asthma. Mechanisms include nonspecific airway irritant activity, nonspecific IgE stimulation, enhanced sensitization to common allergens, or a specific immune response to substances in tobacco smoke (36,37). Studies have documented increased symptoms, poorer lung function, and increased bronchial responsiveness in children

whose parents smoke (38,39). Exposure to tobacco smoke can usually be ascertained from history and examination. If necessary, urinary cotinine is a useful marker. Patients or parents who continue to smoke must be encouraged to give up and may need professional help. However, there is some evidence that advising parents to stop smoking for the sake of their child's health is counterproductive (40). Surprisingly, it would appear that for some parents, having a chronically ill child on high-dose steroids does not provide sufficient motivation to give up the habit.

Nonadherence to Treatment

Assessing whether patients are taking the amount of medication that is prescribed is extremely difficult. Typically, doctors overestimate the degree to which patients adhere to treatment. If children and their parents are unable to describe their treatment regimen, then it is unlikely that full adherence is being achieved. Other methods of evaluation include weighing drug canisters or counting remaining doses of dry powder inhalers (41), contacting primary care physicians to see how often prescriptions are collected, and the use of electronic monitors that record the timing and number of actuations from an MDI (Medtrac, Colorado, USA) (42,43). Assays are also available for patients taking oral prednisone that measure serum prednisone levels. Demonstrating a problem with adherence is one thing; determining the multiple reasons behind it another. Reasons for nonadherence have been classified as follows (44).

Inadequate Knowledge

Parents and children may not understand the reasons for the treatment or may have unfounded concerns about the side effects of the treatment, particularly those related to use of steroids. Careful and repeated explanation of the treatment is therefore needed. Language barriers are also a potential problem, and every effort should be made to involve an interpreter when appropriate.

Complexity of the Treatment

Patients with difficult asthma will often be treated with three or more different medications, each with separate indications and timings. In addition, they may be using different inhaler devices. In the effort to control symptoms, drug regimens are often changed, with new treatments added, others discontinued, and doses altered. Physicians need to do their best to simplify the treatment by keeping the number of drugs, devices, and daily doses to a minimum. Giving the family a written record of their drugs would seem to be a sensible approach for most patients. An understanding of the family's lifestyle and organizational ability is also necessary in planning treatment, and the amount of time needed to administer medication should be as short as possible (e.g., by using spacers rather than nebulizers).

Psychosocial Issues

For adolescents, major issues include power struggles within the family or at school, cultural/peer group pressure, and denial of the disease due to a desire to be normal. Some children dislike having to use their inhaler at school; therefore, treatment should be targeted to maximize the benefits of regular therapy that can be taken at home. In younger children, for whom the major responsibility for adherence lies with the parents, nonadherence may result in financial gain through sickness benefit. These issues require careful handling by an experienced professional, and involving a clinical psychologist or even a psychiatrist may be very helpful.

Educated Nonadherence

Some patients and families will choose nonadherence on the basis of a full understanding of the risks and benefits of treatment. Others may choose to use alternative therapies such as chiropractic manipulation, homeopathy, and the Buteyko method (45–47). Management of this situation will inevitably involve long periods of discussion and a degree of compromise, but it is usually very hard to alter people's entrenched beliefs.

Psychosocial Problems

Attention needs to be paid to the psychosocial aspects of asthma, and a psychologist should be an integral part of the management team. Reference has been made above to psychosocial issues when discussing VCD and treatment adherence. Emotional arousal and asthmatic symptoms are closely linked, and either one may precipitate or aggravate the other. In particular, anger or excitement can provoke asthma attacks in some children (48). Anxiety may lead to hyperventilation, and it may be difficult to tease out the relative contributions of hyperventilation and airway obstruction during an attack. Teaching relaxation and breathing techniques may be helpful in this situation.

A psychosocial referral or intervention should be considered if there is an obvious psychological trigger, clear evidence of behavioral or emotional problems, family

dysfunction or inappropriate handling of the illness by the family, concern at school, or significant nonadherence (49). The most useful interventions include parental counseling, family therapy, behavioral techniques, individual counseling, and environmental change. This latter approach involves separating the child from their parents, in the form of either short-term hospitalization or long-term residential schooling. This may have the added bonus of removing the child from any provoking allergens in the home.

GENUINE ASTHMA: TREATMENT OPTIONS

For children with genuinely severe asthma who continue to experience frequent symptoms despite regular treatment with high-dose inhaled steroids and long-acting bronchodilators, regular oral prednisone is recommended as the next and final step (1,2). A number of other treatment options are available for patients whose symptoms are not controlled by prednisone or who cannot tolerate the side effects. The majority of these can be classed as anti-inflammatory or immunosuppressive treatments. Before considering one of the other treatments, many of which have a low benefit-to-risk ratio, it is worth trying to document the presence of ongoing airway inflammation, as this would support the choice of further anti-inflammatory therapy. Measurement of exhaled nitric oxide (NO) and inflammatory markers in induced sputum are two ways in which airway inflammation can be monitored noninvasively in children (50,51). Typically, exhaled NO is elevated in steroid-naive asthmatics and falls after treatment with inhaled steroids (52–54). Elevated levels of NO have been detected in adults with difficult asthma, despite treatment with regular oral prednisolone (55), and NO may reflect the presence of eosinophils in induced sputum (50). A more direct assessment of airway inflammation can be obtained from bronchoalveolar lavage and bronchial mucosal biopsy (56,57). The question as to whether the typical inflammatory infiltrate of eosinophils, T-cells, and mast cells is present in patients with difficult asthma is yet to be answered. There is some evidence that two distinct subgroups of patients may exist, distinguished by the presence or absence of airway eosinophilia (58,59). Further attempts to describe the pathological basis of difficult asthma need to be encouraged, as little scientific evidence is currently available to guide the choice of other therapies. The following section discusses the use of oral prednisone and nebulized steroids and then focuses on the other available treatments.

Oral Prednisone

Increasing the dose of steroids may be helpful for some patients. Both the NHLBI (step 4) and BTS (step 5) guidelines recommend the addition of regular oral steroids for the most severe patients (1,2). A survey in the United Kingdom of almost 4000 asthmatic children under 16 years of age found only 27 children who were taking regular oral steroids (60). Assays of serum prednisone are available and can help with the assessment of treatment adherence. The use of regular prednisone involves a balance between the benefits and the side effects of treatment. Side effects include growth failure, weight gain, adrenal suppression, hypertension, glucose intolerance, cataracts, and mood disturbances. Both excessive doses of prednisone and poorly controlled asthma may suppress growth in childhood. The use of prednisone to control asthma may therefore actually improve growth rather than suppress it. However, it is extremely important that growth be monitored regularly (i.e., at least every 6 months) in these children. Oral prednisone undoubtedly causes suppression of the hypothalamo-pituitary-adrenal axis, but this may be lessened by taking the dose in the morning and, if possible, on alternate days. The drug should never be stopped suddenly, and additional doses may be required for patients undergoing surgery. In addition, children on regular oral steroids should not have live vaccines and are at increased risk of severe chickenpox.

Nebulized Steroids

In a randomized, double-blind, placebo-controlled study, 36 children aged 10 months to 5 years who were dependent on oral steroids, were given 2 mg/day nebulized budesonide or placebo for 8 weeks (61). There was a significant reduction in oral steroid use 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 nebulizer setup, budesonide delivered by spacer is equipotent to that delivered by nebulizer (62), and in practice, nebulizers are less efficient at drug deposition than spacers (27). No study of nebulized budesonide has been carried out in steroid-dependent older children, but an open study in 42 adults who were given 2 mg/day found that 55% were able to reduce their oral steroid intake by a mean of 59% (63). A recent trial of nebulized fluticasone in oral steroid-dependent adult asthmatics showed a small reduction in mean daily prednisolone dosage, using a dose of fluticasone of 4 mg/day

(64). In using a nebulizer, it is best to use a mouthpiece, but if a mask is needed, it should be tight fitting, and children should be advised to wash their faces and rinse their mouths afterward. The holes in the mask facing upward toward the eyes should be covered, and children should be reminded to breathe through their mouths and not their noses. The main role for nebulized therapy is probably in very young children only. In older children the adherence to nebulized treatment is likely to be poor, and it is unlikely that children on high doses of inhaled steroids via a spacer who are able to use the device effectively will benefit from switching to a nebulizer.

Oral Antileukotrienes

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 and zafirlukast) (65,66). Montelukast is available for children over 6 years and has the advantage of being a once-daily chewable tablet. The principal published pediatric study was multicenter and involved 336 children aged 6–14 years (67). Significant improvement in morning FEV_1 was shown after 8 weeks of treatment, with benefit seen after 1 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. Another study has demonstrated an effect of montelukast on exercise-induced asthma in children (68). Further studies are needed to assess the long-term safety profile of montelukast and its role in severe asthma. Zafirlukast, a twice-daily tablet, is also available and licensed for children over 12 years (69). Like montelukast, it has been shown to be effective in exercise-induced asthma in children (70). Zileuton is licensed for use in children over the age of 12 in the United States, but not in the United Kingdom. There are no published clinical trials evaluating its use in children, and the need to give it four times a day is unlikely to make it popular for pediatric patients.

These drugs are an exciting development, as they represent the first mediator-specific treatments for asthma. However, they have not yet been proven as steroid-sparing agents in children, although, inevitably, if better control is achieved, steroid doses will be reduced. A randomized placebo-controlled study in adults with moderate asthma recently demonstrated that montelukast was superior to placebo in allowing a reduction in inhaled steroids over 12 weeks (71). With time, the therapeutic role of these drugs in severe asthma may become clearer, but for now it is likely that their use will be restricted to the stage before oral steroids are introduced. In some difficult cases it may be worthwhile trying an antileukotriene, probably montelukast. Ideally, this would be done as an $n = 1$ single-blind therapeutic trial to ensure that any placebo effect is excluded.

Oral Cyclosporin

Cyclosporin is an immunosuppressant used after organ transplantation that works by inhibiting T-lymphocyte activation. The prominent role of T-lymphocytes in asthma has led to trials of cyclosporin in adults. Treatment of 33 adults for 12 weeks produced an improvement in lung function and a reduction in the frequency of exacerbations requiring rescue courses of prednisolone (72). In a later study, treatment of 16 adults with cyclosporin for 36 weeks resulted in a significant reduction in prednisolone usage compared to placebo, as well as an improvement in lung function (73). No trials have been carried out on children, although there is a case report of its use in five children on regular oral steroids, three of whom experienced a definite benefit (74). The side effects in adults include hirsutism, paresthesia, mildhypertension, headaches, and tremor (72,73). The only concern in the pediatric reports was hirsutism, which led to one girl stopping its use even though her steroid dose had been profoundly reduced (74). There is obviously a concern about renal impairment with long-term use, so renal function must be carefully monitored, and cyclosporin blood concentrations must be maintained at 80–150 mg/L. A proper randomized trial in children is urgently needed, as this drug has real potential in severe asthma. Unfortunately, nebulized cyclosporin, which has been used in some adults after heart-lung transplant, causes marked bronchospasm and therefore has no place in asthma (Professor Margaret Hodson, personal communication).

Subcutaneous Bronchodilator

Continuous subcutaneous terbutaline and salbutamol have been shown to be useful in some adults with severe chronic or brittle asthma (75,76). This form of treatment has been used in acute severe infantile asthma (77), but 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 a pump (Graseby Medical Ltd., Watford, UK; MiniMed

Inc., Sylmar, California, USA) at a starting dose of 2.5–5 mg/day. Systemic side effects include tremor, hyperactivity, sinus tachycardia, palpitations, headache, and muscle cramps, although generally the treatment is well tolerated. Hypokalemia is a theoretical possibility, although this is in fact rare (78). Local problems are more common and include tender subcutaneous nodules and hematomas at the site of injection. It is advisable to start this treatment in the 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 that any symptom improvement is not simply a placebo effect (78). In the last 5 years, we have treated seven children (age 8–14 years) in our department with subcutaneous terbutaline, with a good response seen in five.

Intravenous Immunoglobulin

Three small open label studies have found that infusions of intravenous immunoglobulin (IVIG) led to a reduction in oral steroid use in children aged over 6 years (79–81). A number of studies have investigated the mechanism of action, with evidence of in vitro inhibition of IgE production from human B-cells and, acting synergistically with dexamethasone, suppression of lymphocyte proliferation (81,82). Following trials of therapy there have also been reports of improvement in glucocorticoid receptor binding affinity in peripheral blood mononuclear cells and a reduction in numbers of all cell types (especially CD3+, CD4+, and activated CD25+ T-lymphocytes) in bronchial biopsy (81,83). The results of randomized, placebo-controlled trials are conflicting. One study of 31 children and adolescents who were given 4 g/kg over 8 weeks was disappointing in that no benefit was seen in lung function, bronchial hyperreactivity, or symptom scores (84). There was, however, a trend toward fewer total days of upper respiratory tract infections, and the effect of IVIG may simply be to reduce viral exacerbations. A more recent trial involving 28 children and adults who were given 2 g/kg at the start of treatment, followed by 400 mg/kg every 3 weeks for 9 months, demonstrated a significant steroid-sparing effect in a subgroup of patients taking more than 5.5 mg/day of prednisolone (85). Another trial demonstrated no difference between two different doses of immunoglobulin (2 g/kg and 1 g/kg) and placebo, given monthly for 7 months (86). This study reported three cases of aseptic meningitis in the high-dose treatment group (86), and other reported side effects of IVIG include rash and hypertension. Given that it is a blood product, there is also the theoretical risk of transmission of viral infections. Although the open studies offer some encouragement, the controlled trials have failed to provide conclusive evidence to support the use of IVIG. Significant drawbacks include the expense, the need for inpatient administration, and regular intravenous cannulation.

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 two meta-analyses (87,88). Both concluded that methotrexate allowed a modest reduction in daily prednisone dosage (4.3 mg and 3.3 mg) compared to placebo. Three small open label studies on children have shown steroid doses could be reduced in some of the children while lung function was maintained or improved (89–91). Doses of methotrexate used were between 7.5 and 17 mg/week for up to 2 years (89,90), and 0.6 mg/kg per week for 3 months (91). Reported side effects in the children were gastrointestinal upset and transiently raised liver transaminases (90). Numerous potentially serious adverse effects are associated with the drug (pulmonary fibrosis, pneumonitis, hepatic cirrhosis, myelosuppression), particularly when it is given in high doses. However, low doses seem to be relatively safe, and use of methotrexate may be considered for some children.

Immunotherapy

The role of immunotherapy in the treatment of asthma remains controversial (92,93). It is seldom used in the United Kingdom but more widely practiced in continental Europe and the United States. A meta-analysis of 20 double-blind controlled studies of allergen immunotherapy showed a small but significant improvement in asthma control (94). Patient selection is essential, with the best results seen in patients with single allergies and mild asthma (95,96). A controlled trial of multiple-allergen immunotherapy for over 2 years in children with moderate-to-severe perennial asthma failed to demonstrate any discernible benefit (97). By definition, children with difficult asthma have symptoms all year round, and in practice the majority have multiple allergies. Consequently, there is currently insufficient evidence to advocate the use of immunotherapy for this group of children.

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Miscellaneous Drugs

Parenteral gold salts have been used to treat asthma for some time in Japan (98,99). Two randomized, double-blind, placebo-controlled trials of oral gold (auranofin, 3 mg twice a day), in steroid-dependent adult asthmatics demonstrated steroid-sparing effects (100,101). The major adverse event in the treatment group was diarrhea, which improved following a temporary reduction in the dose. Although oral gold has been used to treat children with difficult asthma, there are no published reports.

Troleandomycin is a macrolide antibiotic that also appears to have steroid-sparing effects (102,103). Its mechanism of action is thought to be through inhibition of prednisone metabolism, thereby allowing lower doses to be prescribed, although it does not alter the side effect profile. An open study of 16 patients, which included three teenagers, reported improvements in lung function and patient well-being within 2 weeks of starting therapy. After 4–18 months of follow-up, 15 of 16 patients remained well controlled on a combination of troleandomycin and methylprednisolone. The main side effect of hepatic dysfunction appears to be dose related and reverses when therapy is discontinued. Macrolides have also been shown to have an anti-inflammatory effect. Low-dose erythromycin is used to treat patients with diffuse panbronchiolitis, and the successful use of long-term macrolide treatment has been reported in three steroid-dependent asthmatics with serological evidence of recent *Chlamydia pneumoniae* infection (104). All three managed to discontinue oral steroids following treatment with either clarithromycin or azithromycin.

Steroid-sparing effects have also been reported with both dapsone and hydroxychloroquine in open studies involving adult steroid-dependent asthmatics (105,106). A double-blind, placebo-controlled, crossover trial of hydroxychloroquine in nine adult patients over 8 weeks did not demonstrate any benefit, however (107).

Future Therapies

As a result of the greater understanding of the mechanisms involved in the initiation and progression of asthma, new therapies are being developed (108). Some of these drugs are antibodies directed against specific components of the inflammatory cascade, such as T-cells, IgE, interleukin-5, and adhesion molecules. A recent trial of monoclonal anti-IgE antibody demonstrated a steroid-sparing effect in a subgroup of patients taking regular oral prednisolone (109). There is also renewed interest in the use of theophylline, a nonselective phosphodiesterase inhibitor, because of its anti-inflammatory effects (110,111). Selective phosphodiesterase inhibitors targeting the isoenzymes III and IV have been developed that should maximize the anti-inflammatory effects, with potentially fewer side effects than their predecessors. As the mechanisms of steroid action are better understood, new corticosteroids may also be produced that have fewer adverse effects and greater anti-inflammatory activity (112).

SUMMARY

Many open studies investigating the effects of innovative treatments for steroid-dependent asthma demonstrate some benefit. This is also true of the majority of placebo arms in placebo-controlled trials. This suggests that children with difficult asthma benefit from the high level of input that is typically provided in clinical trials, with or without additional medication (113). Such intensive management of patients, with the emphasis on establishing the diagnosis, improving adherence, and identifying provoking factors, is the key to optimizing asthma control for these children. For patients with genuinely severe asthma, despite high doses of conventional treatment, a greater understanding of the pathological basis of persistent symptoms is needed. Identification of different pathological subtypes of severe asthma should allow for more rational prescribing of asthma therapy, as well as the design of further trials of potential steroid-sparing treatments.

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