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HOW I MANAGE THE DIFFICULT ASTHMATIC*

G. K. Crompton, Respiratory Unit, Western General Hospital, Edinburgh

The vast majority of patients suffering from asthma respond to the treatment prescribed and supervised by their General Practitioners. Early intervention with inhaled steroids has revolutionised treatment of this disease and nowadays most asthmatics are able to lead normal active lives. The small proportion of patients referred to specialist units are a minute fraction of the total asthmatic population. Within this group is an even smaller group of patients who can be labelled 'difficult asthmatics' and this specific group will be discussed.

In the clinical management of these patients, the physician should consider carefully a number of important possible causes as to why their control of symptoms is difficult to achieve. The questions which must be explored in this context include:

- Do these patients have 'genuine' bronchial asthma?
- Are they complying with the treatment recommended?
- Are they acting on advice given about avoidance of allergens?
- Do they have corticosteroid-resistant (or hyporesponsive) asthma?
- Is their condition less responsive because of delayed treatment with an inhaled corticosteroid?
- Is the treatment they are being prescribed aggravating their symptoms?

If all of these reasons are excluded one can be reasonably certain that the individual being investigated has a genuinely difficult variety of asthma to control, and it is then that alternative toxic treatments such as cyclosporin must be considered.

Are all the patients asthmatic symptoms genuine?

A high proportion of asthmatics requiring treatment with oral prednisolone either suffer from asthma complicated by hyperventilation or have become 'dependent' on prednisolone therapy for the systemic and psychological properties of this drug, rather than for its direct effect on the pathological changes of the asthmatic bronchial wall. Many of these patients feel generally and non-specifically better when they are taking large doses of prednisolone, but it is rarely possible to get objective confirmation of improvement in airways function. Some are admitted to hospital on numerous occasions in spite of being treated with long-term, often high-dose, prednisolone. Usually it is obvious to the clinician that oral corticosteroids are being taken, because of the moon face, obesity and other dermal side-effects, but doubt often lingers about compliance with other treatments, especially inhaled corticosteroids.

When asthmatic patients have numerous admissions to hospital, arterial blood gas results and chest X-rays should be carefully scrutinised and evaluated. If the blood gases on admission to hospital show respiratory alkalosis without hypoxaemia, and chest X-rays do not have evidence of pulmonary hyperinflation, one must consider seriously the possibility that the patient does not have asthma! I have now come across a number of patients who have had numerous hospital admissions and had

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been taking oral prednisolone in high doses, and who record consistently and reproducibly low peak expiratory flows (PEF). They seem to be able to manufacture and generate numerous expiratory rhonchi without an intrinsic underlying pathological bronchial problem; there is almost invariably an audible laryngeal element to their apparent expiratory airflow limitation.

These individuals are able to create this 'simulated acute asthma episode' by bending forwards in the sitting position and using forced expiratory efforts at low lung volumes against a partially closed glottis. To the inexperienced, the clinical picture created can be so similar to genuine severe acute asthma that some are treated by assisted ventilation, in spite of blood gases which show respiratory alkalosis and a high arterial oxygen tension. As soon as they are artificially ventilated, inflation pressures are found to be normal.

Whenever 'simulated' asthma is considered, the patient should be gently encouraged to change posture from the sitting crouched forward position to the upright position, initially by sitting up and then by standing with the heels and back of the head against a wall. In the upright standing position, it is not physiologically possible to produce 'low lung volume' rhonchi. If rhonchi are still present in the upright standing position, genuine asthma is confirmed.

Some patients with 'simulated' asthma will continue to produce a laryngeal noise. Laboratory assessment of ventilatory function should then be made using different techniques. A Vitalograph type of spirometer should then be used initially to record ventilatory function, and the patients allowed to bend forwards, if they wish. Other pulmonary function testing equipment should be used, so that eventually measurements of airways function are made in the upright position. In our experience the body plethysmograph is ideal for these recordings, since the patient has to be sitting upright in order to obtain the measurements necessary for this testing. In 'simulated' asthma the ventilatory function tests are normal when measured in the upright position in the body plethysmograph.

These patients are not usually consciously aware that they are feigning asthma; an explanation to them of the changes in the breathing tests brought about by changes in body position are often helpful in their management, although all require further expert psychological help. Unfortunately only a few respond to this management.

The most difficult of this group of patients to treat are those who can have 'simulated asthma attacks' as well as genuine severe acute asthma episodes. Very few patients have pure 'simulated asthma', since most have had genuine disease; they may have had mild asthma many years previously.

'Simulated' asthma is a variety of hyperventilation; in most of these patients respiratory alkalosis is present and can be quite extreme during exacerbations. The combination of asthma with hyperventilation, which is not associated with breathing in a posture that creates low lung volumes allowing a wheeze to be generated, is another problem which can render asthmatics more difficult to manage. The hyperventilation element is often not recognised by clinicians and does not, of course, respond to the increases in specific anti-asthma therapy which are very often made in these patients.

The development of superimposed hyperventilation should be considered in all patients with asthma whose disease has become more troublesome, apparently without reason. Hyperventilation usually causes worsening of respiratory symptoms during the day more than at night, whereas a gradual deterioration of genuine asthma causes an increase in nocturnal symptoms, before there is any diurnal deterioration of

cough, wheeze, chest tightness and breathlessness. When hyperventilation complicates asthma, the complaint is of increased shortness of breath but without an increase in wheeze, cough and chest tightness.

When hyperventilation is suspected the question which must be asked is whether the shortness of breath currently experienced is different from the breathlessness noted in the past. Patients can usually differentiate 'asthma breathlessness' from 'exertional breathlessness', even if one has to inquire specifically about the respiratory effects of exertion prior to the development of asthma. Hyperventilation frequently creates a subjective sensation that the lungs are not 'big enough' and this leads to extra deep breaths having to be taken. Quite often the complaint of the patient will be that 'not enough air or oxygen is getting into the lungs', and this leads to the taking of extra deep breaths, often superimposed on a normal respiratory excursion.

If the patient can recognise that the breathlessness of hyperventilation is different from normal exertional shortness of breath and previous respiratory distress associated with asthma symptoms such as wheeze and chest tightness, the prognosis is usually very much better. These patients require breathing retraining programmes to overcome the hyperventilation element.

Unfortunately many patients with the combination of asthma and hyperventilation do not respond to treatment and remain patients with 'difficult asthma'. The most problematic members of this group are those who have suffered from genuine severe asthmatic episodes which were understandably treated with frequent courses of high-dose prednisolone, and as a consequence many end up being re-prescribed long-term prednisolone, often in high doses when this deterioration takes place.

Compliance

Poor adherence to medical advice is a major problem in the management of asthma and in many patients with 'difficult to control asthma' the reason for a poor response to therapy is poor compliance with treatment. The impression of most physicians who have a special interest in the management of this condition is that compliance with inhaled corticosteroid preparations is much worse than with bronchodilator therapy. However, although one study has confirmed this, compliance is often found to be patient dependent rather than drug dependent.[1] Many patients with asthma take prophylactic therapy only when they have symptoms, and because these individuals have little inconvenience from their disease, it is assumed that compliance is good.

There are now ways of objectively assessing compliance with inhaled therapy. Weighing of pressurised aerosol canisters and counting the doses remaining, when dry powder delivery systems are used, are inaccurate assessments of actual drug use, because more sophisticated surveillance of therapy reveals deliberate 'dumping' by these patients when they become aware that drug compliance is being checked.[2,3] Inhalers with built-in electronic recording devices have been developed which record actuation, times of actuation and even whether the drug has been inhaled.[4-6] These devices have revealed unexpectedly poor compliance in the 'clinical trial' situation, in which one would expect to be very much better than that in routine clinical practice. The study by Spector *et al*[5] revealed less than 50 per cent compliance with a four times daily regimen, and Bosley *et al*[6] found that only 15 per cent of their patients took the drugs as prescribed for more than 80 per cent of the study days.

Asthmatic patients are considered to be non-compliant, if they are taking less than 70 per cent of prescribed therapy or who had not taken any treatment for more than one week. These specific patients were found to have higher mental depression scores than compliant patients. When asthmatic patients are studied as a group, they tend to have a higher mean anxiety score than a non-asthmatic population, but there is no significant difference in anxiety between the compliant and non-compliant asthmatic subjects. In a non-compliant group, there was a preponderance of females with a younger age at which the diagnosis of asthma was made, and this group also tended to rationalise harmful activities such as smoking and keeping pets.[7]

Poor compliance may be easy to define and detect, but difficult to improve. Educational programmes about the disease, particularly on aerosol technique and individual drugs help to improve compliance.[7] Simple drug regimens are important, and reassurance about real or feared drug adverse effects is also of benefit in some patients; poor compliance is often associated with anxiety about side-effects, particularly with inhaled corticosteroids.

Compliance with advice about avoidance allergens

The most important allergen source in children is the house dust mite. It is very difficult to significantly decrease the house dust mite population and any attempts to do this are often expensive and not very successful. Therefore, it is understandable and has to be taken for granted that little is, or can be, done in many households to eradicate this allergen.

Domestic pets, particularly the cat, are another major source of allergenic proteins which often perpetuate asthma and also induce severe acute episodes of the disease. Domestic pets are, of course, much easier to avoid than the house dust mite, but it is amazingly difficult to persuade asthmatic patients to part with their pets. In a study of two hundred adult asthmatic patients attending our asthma clinic compared with an age and sex matched control population of patients with diabetes, current pet ownership was as shown in Table 1.

TABLE 1

Pet ownership of adult asthmatic and diabetic patients

	Asthmatics	Diabetics
Dog	32.4%	25%
Cat	21.5%	14%
Bird	5%	7%
Pets of any kind	52%	42%

The fact that asthmatic patients had more pets than diabetic patients was of no surprise, but what was somewhat surprising and disconcerting was the number of patients who admitted to having allergic symptoms when in close contact with their pets. Of the 104 asthmatic pet owners, 94 had cats or dogs and some both. The number of patients admitting allergic symptoms was as in Table 2:

TABLE 2

'Allergic' symptoms in 104 pet-owning asthmatic patients

General symptoms such as itchy skin, nose and eye symptoms.	50 (48%)
Asthma made worse by own pet.	15 (14%)
Asthma made worse by other peoples' cats or dogs, but not their own.	10 (9.6%)

The fact that so many of these patients admitted to allergic problems because of their own pets but were not willing to part with their animals emphasises the problem that asthmatics have with animals. It was not in the least surprising to find that asthmatic symptoms of ten patients were made worse by other peoples' pets but not their own, since this type of denial reaction is common in an asthmatic population.

The final part of this study was to compare the treatments being taken by the cat owners and non-cat owning asthmatics, excluding those who kept both cats and dogs. There were 23 cat owners and 70 per cent were taking high-dose inhaled corticosteroid therapy (1 mg per day or more) but only 42 per cent of the 66 non-cat owners required high-dose therapy. This difference in inhaled corticosteroid therapy is statistically significant ($p>0.05$) and supports the general clinical impression that domestic cats have a greater allergenic potential than dogs. The results of this small study must be viewed with some caution, since if the patients' compliance with drug therapy was as bad as their compliance with the advice given to them about their pets, the conclusions from this study are not easy to interpret.

The fact that allergic patients do not comply with doctors' advice to cease owning pets, has been recently emphasised by Coren.[8] Out of 122 patients who did not take advice about 'ridding themselves' of their pets, 86 (70 per cent) actually went on to replace the animals after they had died!

Corticosteroid resistance or hypo-responsiveness

In a small proportion of asthmatic patients, ventilatory function is not improved by inhaled and/or systemic corticosteroids even when these are given in high doses.[9,10] Little or no scientific interest was expressed in the concept of corticosteroid resistance in asthma following the original publication on this subject by the Edinburgh group;[9,11] many clinicians and research workers did not believe that such patients existed. However, after the demonstration of defective skin blanching induced by beclomethasone dipropionate in patients defined as corticosteroid-resistant was described in these patients when compared with corticosteroid-sensitive asthmatic patients,[12] active research programmes into this issue were stimulated all over the world.

The concept that some asthmatic patients do not respond as well to corticosteroids as others, and that a small proportion are completely resistant to their use, is now accepted and the results of numerous confirmatory studies have been reported.[10,13] Patients with asthma, in whom all known aggravating factors have been excluded, and whose ventilatory function (mean PEF recorded at least twice daily) does not improve by 10 per cent or more during treatment with prednisolone, in a daily dose of at least 30 mg given for at least two weeks, can be assumed to have corticosteroid resistant asthma.

These patients are extremely difficult to manage and many end up being prescribed large doses of corticosteroids, even though they do not respond effectively to these drugs. Clinically it is difficult to deny this form of treatment to patients who are distressed and might have life-threatening acute episodes, even though it has not been established that there is any favourable response to corticosteroids during acute severe attacks.

Corticosteroid resistance in asthma is not common, and it is not yet known whether it is a permanent state. A corticosteroid trial should be performed in all asthmatic patients, and in all wheezy and breathless patients in whom the diagnosis is in doubt. Objective response to 30 mg of prednisolone given for 10 to 14 days, as demonstrated by a 15 per cent or greater improvement in mean PEF, does not necessarily establish a diagnosis of asthma, but a response of this magnitude in a patient whose respiratory problem was stable at the beginning of the treatment period, proves corticosteroid-reversible airflow obstruction which should be treated with anti-asthma remedies.

A diagnosis of corticosteroid-resistant asthma should be established as soon as possible and this cannot be done without a corticosteroid trial.

Delay of appropriate treatment of asthma

Delay in treatment of asthma with an inhaled corticosteroid is associated with a poorer response to treatment than when treatment is given soon after the diagnosis is established. One study showed that a delay of treatment of just two years is associated with a decreased objective response to budesonide, and this response did not 'catch up' after twelve months of therapy.[14] Convincing correlation has been identified in children and adults between delay in corticosteroid therapy and objective response to this treatment.[15,16] It is possible, therefore, that a prolonged delay in starting inhaled corticosteroid treatment could lead to asthma which is more difficult to control and because of this, early intervention with these drugs is recommended.[17]

Since the original publication of Sears *et al* in 1990, much debate has occurred about the possibility that regular use of beta-agonists increases bronchial reactivity or even makes asthma worse.[18] This question remains unresolved, but large clinical trials are in progress, and it is likely that it will soon be known whether or not the regular use of bronchodilators is in any way detrimental. Until these results are known, regular use of beta-agonists in asthma should be avoided, if at all possible. There are anecdotal reports that withdrawal of beta-agonists from patients taking huge doses of these drugs may result in clinical improvement, but controlled clinical trials are virtually impossible to design to prove this one way or the other.

Surfactants/lubricants in pressurised metered dose inhalers (pMDIs) can cause problems in some patients. All asthmatics whose disease is poorly controlled, and especially if they cough after using a pMDI, should have their inhaler changed to a dry powder device. This problem is much more common than is realised. In a survey of our patients, a third admitted to having cough after the use of their corticosteroid pMDI;[19] Shim and Williams[20] reported considerable decreases in ventilatory function in patients who coughed after inhaling beclomethasone dipropionate. It is also reported that some patients obtain little or no benefit from a bronchodilator delivered by pMDI, but have considerable improvement in ventilatory function when they inhale the same drug through a dry powder inhaler.[21] Because of these potential problems with pMDIs, all patients who cough after using one should be prescribed a

dry powder device instead of the pMDI, and in the patients who have poor disease control of unknown cause, a trial of dry powder delivery systems is reasonable.

Treatment of the patient with genuine asthma which is difficult to control

Most of the problem asthmatic patients in clinical practice have one or more of the problems discussed above. There however remains a small group of patients whose disease is difficult to control in spite of their complying with treatment and adhering to personalised management plans, etc. The majority of those with severe chronic symptoms have corticosteroid-hyporesponsive disease and in these, every attempt must be made to reduce treatment side-effects, as it is difficult to avoid prescribing them large doses of inhaled and systemic corticosteroids.

Only rarely should toxic immuno-suppressive drugs be considered; these have not been shown to have a dramatic effect in the control of asthmatic symptoms and, as an alternative treatment, are likely to have more long-term adverse effects than conventional asthma therapies, including low-dose prednisolone. Less toxic treatments may in the future become available; these may include inhaled cyclosporin or its derivatives. These therapeutic developments are still awaited.

REFERENCES

[1] Dompelling E, Vangrunsven PM, Van Schayckn CP, Folgering H, Molema J, Van Weel C. Treatment with inhaled steroids in asthma and chronic bronchitis. Long-term compliance with inhaler technique, *Fam Pract* 1992; **912:** 161-6.

[2] Rand CS, Wise RA, Nides M *et al*. Metered dose inhaler adherence in a clinical trial *Am Rev Respir Dis* 1992; **146:** 1559-64.

[3] Spector SL. Is your asthmatic really complying? *Ann Allergy* 1985; **55:** 552-6.

[4] Yeung M, O'Connor SA, Parry DT, Cochrane GM. Compliance with drug therapy and the management of asthma. *Respir Med* 1994; **88:** 31-5.

[5] Spector SL, Kinsman RA, Mawhinney M *et al*. Compliance of patients with asthma with an experimental aerosolised medication. Implications for controlled trials. *J Allergy Clin Immunol* 1986; **77:** 65-70.

[6] Bosley CM, Parry DT, Cochrane GM. Patient compliance with inhaler medication. Does combining beta-agonists with corticosteroids improve compliance? *Eur Respir J* 1994; **7:** 504-9.

[7] Cochrane GM. Assessment of compliance. In: Manual of asthma management. Eds O'Byrne P, Thomson NC. 1995, WB Saunders Company Ltd, London.

[8] Coren S. Allergic patients do not comply with doctors' advice to stop owning pets. *Br Med J* 1997; **314:** 517.

[9] Carmichael J, Paterson IC, Diaz P, Crompton GK, Kay AB, Grant IWB. Corticosteroid resistance in chronic asthma. *Br Med J* 1981, **282:** 1419-22.

[10] Barnes PJ, Greening AP, Crompton GK. Glucocorticold resistance in asthma. *Am J Respir Crit Care Med* 1995; **152:** S125-42.

[11] Poznansky MC, Gordon ACH, Krajewski AS, Wyllie AH, Grant IWB. Resistance to methylprednisolone in cultures of blood mononuclear cells from glucocorticoid-resistant asthmatic patients. *Clin Sci* 1984. **67:** 639-45.

[12] Brown PH, Teelucksingh S, Matusiewiez S, Greening AP, Crompton GK, Edwards CRW. Cutaneous vasoconstriction responses to glucocorticoids in asthma. *Lancet* 1991; **337:** 576-80.

[13] Lee T, Brattsand R, Leung D. Corticosteroid action and resistance in asthma. *Am J Respir Crit Care Med* 1996; **154:** S2-S6.

[14] Haahtela T, Järvinen M, Kava T *et al.* Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Eng J Med* 1994. **331:** 700-5.
[15] Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994, **88:** 373-81.
[16] Selroos O, Backman R, Forsén K-O *et al.* The effect of inhaled corticosteroids in asthma is related to the duration of pretreatment symptoms. *AM J Crit Care Med* 1994; **149 (Suppl):** A211.
[17] Jackson B. Early intervention in asthma. 1994. Clinical Vision Ltd, Harwell.UK.
[18] Sears MR, Taylor DR, Print CG *et al.* Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990; **336:** 1391-6.
[19] Williamson I, Matusievicz S, Brown PH, Crompton GK, Greening AP. Frequency of voice problems and cough in patients using aerosol steroid preparations. *Eur Respir J* 1995; **8:** 590-2.
[20] Shim CS, Williams MH. Cough and wheezing from beclomethasone dipropionate aerosol are absent after triamcinolone acetonide. *Ann Intern Med* 1987; **106:** 700-3.
[21] Selroos O, Löfroos AB, Pletinalho A, Riska H. Comparison of terbutaline and placebo from a pressurised metered dose inhaler and a dry powder inhaler in a subgroup of patients with asthma. *Thorax* 1994; **49:** 1228-30.

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Boats on the Padma, Bangladesh
(Photograph by David H. A. Boyd)