"CF asthma": what is it and what do we do about it?

I M Balfour-Lynn, J S Elborn

Thorax 2002;**57**:742–748

The diagnosis of "CF asthma" is problematic and it is difficult to determine which patients have a combination of CF and asthma and which have asthma like symptoms caused by inflammation of the CF lung. This may not matter, however; the relevance lies in the possible approaches to treatment.

There is no dispute that many patients with cystic fibrosis (CF) wheeze, but it is difficult to determine which have concomitant asthma and which wheeze as a result of their underlying CF lung disease. The pathogenesis of airways obstruction and wheezing in CF involves several overlapping mechanisms, including airway mucosal oedema secondary to chronic infection and inflammation, mechanical obstruction by abnormal viscid secretions, stimulation of autonomic nerve fibres caused by damage to respiratory epithelium, airway smooth muscle contraction due to stimulation by a host of inflammatory mediators, and dynamic collapse of airways rendered more compliant because of the destruction of their walls.¹ Bronchial hyperresponsiveness (BHR) is also common in CF patients of all ages, although the underlying mechanism is not known.² Finally, it is likely that an underlying tendency to atopic asthma contributes to some of these pathological mechanisms.

DEFINING "CF ASTHMA"

Defining and diagnosing CF is usually straightforward, and only occasionally problematic.^{3–4} For the purposes of this review, we have assumed that the diagnosis of CF is not an issue. The diagnosis of asthma can be difficult, especially in preschool children. Asthma has been given a multitude of definitions, including that of the International Paediatric Asthma Consensus Group who defined it as "episodic wheeze and/or cough in a clinical setting where asthma was likely and other rarer conditions have been excluded".⁵ This definition is particularly unhelpful, however, in patients with CF.

It is even harder to define "CF asthma", but an attempt has been made by the US and Canadian Epidemiologic Study of Cystic Fibrosis (ESCF). The patient is reported as having concomitant asthma if "in the treating physician's opinion, asthma contributes significantly to the patient's lung disease. The diagnosis of asthma is suggested by the following: episodes of acute airway obstruction reversed by bronchodilators (especially if seasonal), a strong family history of asthma and/or evidence of atopy (such as eczema or hay fever), or laboratory evidence of allergy

such as eosinophilia or elevated IgE".⁶ This definition is a useful guide and is pragmatic, although the use of serum IgE and eosinophilia is only of value if allergic bronchopulmonary aspergillosis (ABPA) has definitely been excluded. The European Epidemiologic Registry of Cystic Fibrosis (ERCF) recorded the presence of complicating "asthma like symptoms" if the patient had "bronchial hyperreactivity (with or without histamine challenge) or asthma like symptoms (prolonged exhalation with crepitations and wheezing)".⁷ This definition is too general to help in the diagnosis of individuals with CF and asthma.

HOW BIG IS THE PROBLEM?

Data from the International Study of Asthma and Allergies in Childhood (ISAAC) on teenage children around the world indicate a prevalence of asthma symptoms that ranges from 2% to 37%, depending on the country (with UK children having the higher reported prevalences).⁸ In UK adults the prevalence of asthma is estimated at around 5%.⁹ So, in theory, these proportions of CF patients would be expected to have concomitant asthma. However, this assumes that the CF gene defect has no influence on the development of asthma. This assumption cannot be made given the controversy over whether CF gene heterozygosity predisposes to the development of asthma.^{10–11}

Using the above definitions, the North American ESCF reported that 19% (of 18 411 patients) had asthma, with the same proportion found in children and adults.⁶ However, in their paper on the use of treatments, the same group quotes a reported asthma prevalence of 31.5% (of 12 622 patients).¹² The apparent discrepancy is due to the fact that the initial figures are derived from a single visit when the patients were enrolled on to the database, while the latter figures reflect several visits from a subset of the patients over a year. Multiple observations of the patients presumably led to an increased cumulative proportion thought to have asthma (personal communication, M Konstan). The European ERCF describes asthma like symptoms (prolonged exhalation with crepitations and wheezing) as occurring in 17% (of 6856 patients), and again the proportions were identical in children and adults.⁷ In the ERCF data an increase in asthma like symptoms was associated with worse lung function across all age groups (table 1). The ERCF data reported only 14% of those under 6 years as having asthma like symptoms, although undoubtedly a higher proportion of these children would have had recurrent wheezing. This may reflect the reluctance of many paediatricians to label wheezy infants less than 2 years of age as asthmatic. In a

See end of article for authors' affiliations

Correspondence to:
Dr I M Balfour-Lynn,
Department of Paediatric
Respiratory Medicine,
Royal Brompton &
Harefield NHS Trust,
Sydney Street, London
SW3 6NP, UK;
i.balfourlynn@ic.ac.uk

Table 1 Percentage of children and adults in European Epidemiologic Registry of Cystic Fibrosis reported as having asthma like symptoms by lung function. Adapted from Koch *et al.*⁷

Age (years)	FEV ₁ (% predicted)	Asthma like symptoms (%)
6–17	>71	15
	40–70	22
	<40	26
18 +	>71	15
	40–70	21
	<40	24

study that followed 229 CF patients diagnosed before 2 years of age, 25% had physician documented wheezing during the first 2 years of life.¹³ This was associated with a positive family history of asthma, eczema and allergic rhinitis. The wheezing had resolved by the age of 2 years in 50% of the patients and by 4 years in 75%. Lung function was significantly lower in the wheezing group than in the non-wheezing group at 13 years of age, but survival was unaffected. One consequence is that many of these wheezy CF infants are prescribed inhaled corticosteroids, which are continued for many years despite little evidence of continued benefit.

DIAGNOSING "CF ASTHMA"

One diagnostic approach is to consider the factors that lead to the diagnosis of asthma in non-CF patients and to see how applicable these are to the CF population. A history of wheezing is important but non-specific, and the timing of wheezing—for example, associated with exercise or night time—is not helpful. Recurrent cough applies to most CF patients regardless of whether they have asthma. A personal history of atopy (eczema or allergic rhinitis) and a family history of atopy (including asthma) in first degree relatives are probably the most useful guides to the likelihood of asthma in the patient. Examination is unhelpful; hyperinflation or Harrison sulci are found in many CF patients.

Investigations may provide some clues. These can be considered under the following categories.

Physiology

Spirometric tests

Standard spirometric tests give invaluable information on flow but do not help in differentiating obstruction due to concomitant asthma from that due to typical CF lung disease. Measurement of small airway function—for example, maximal expiratory flow at 25% vital capacity—tends to be the most reduced measure in patients with CF, but it is also one of the more variable measurements made, although variability does lessen with increasing age independent of severity of disease.¹⁴ Measurement of peak expiratory flow rate (and, particularly, its day to day variability) is often useful in assessing asthmatic patients.³ Unfortunately, it is a measure that is not useful (nor used) in CF where the obstruction mainly involves medium and small airways, hence reduction in peak flow is only a late sign of airway obstruction¹⁵; it is unlikely that it would help to differentiate a patient with CF who also has asthma, but studies have not been done.

Body plethysmography can give further information including the degree of hyperinflation and airways resistance, but again it is not specific to CF asthma.

Bronchodilator responsiveness

Bronchodilator responsiveness is widely recommended for the diagnosis of asthma³ but its role in patients with CF is less clear cut. The problem in CF is that, because the degree of

variability in lung function measures (forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC)) can vary by as much as 15–20% spontaneously, including same day testing,^{14, 16} defining the cut off for a significant change after inhaling a bronchodilator becomes arbitrary. It has been suggested that the variability for the individual patient needs to be assessed and that figure used to estimate the percentage change that is significant for that patient.¹⁶ Many patients with CF will show a degree of bronchodilator responsiveness regardless of whether they have CF asthma, and most studies have shown no relationship with atopy.¹⁷ Studies in infants and children as young as 1–41 months (mean age 16 months) showed that those with CF had an increased baseline airway tone manifest by a lower maximal flow at functional residual capacity (V'maxFRC). After an inhaled bronchodilator, this increased significantly so that there was no longer a difference between infants with CF and normal controls.¹⁸ In this study the bronchodilator responsiveness was unrelated to either a family history of asthma or the presence of acute respiratory symptoms. There have been numerous studies in older children and adolescents showing bronchodilator responsiveness in approximately 50–60% of patients with CF (reviewed by Brand¹), many of whom will not have CF asthma, so it is unlikely that this form of testing alone will be useful as a diagnostic aid. The situation in adults is similar.² However, regardless of testing in the respiratory laboratory, the actual response to anti-asthma treatment in the individual may be one of the more important guides to the diagnosis of asthma, as it is in asthmatic patients without CF.

Bronchial hyperreactivity

Bronchial hyperreactivity (BHR) is sometimes used interchangeably with bronchodilator responsiveness, but it is not the same. Tests of BHR are not routinely performed in paediatric practice but may have a place in adult care. BHR to directly acting smooth muscle constricting agents such as histamine or methacholine is found in at least 40% of patients with CF.¹ One study found it in 40% of young children (age 4–7 years) and 77% of older children (8–18 years).¹⁹ Interestingly, this same study showed that some of these children had significant airways obstruction but did not wheeze. The incidence of BHR in adults is similar.² A positive methacholine response has been shown to correlate with more severe lung disease and, on follow up to 2 years, with a greater number of pulmonary exacerbations and a more rapid decline in lung function.²⁰ However, the response to indirect stimuli such as hypertonic saline or exercise is different in CF from that in asthma, as the patients with CF usually bronchodilate after such challenges.¹ This implies that the mechanisms underlying BHR in CF are not the same as in asthma, and makes the use of BHR testing for diagnosing CF asthma less useful. The situation is further complicated by the variability over time of BHR testing in children with CF.²¹ Furthermore, due to the frequency of paradoxical responses, conventional challenges are a poor way of determining the true incidence of BHR in patients with CF.²²

Exercise testing

Exercise testing has a valuable role in evaluating both CF and asthma.²³ There are important differences between the responses to exercise in the two conditions, however. In asthma, after the normal transient bronchodilation, progressive bronchoconstriction occurs. It is usually at its maximum 5–10 minutes after stopping exercise. Symptoms are usually gone within 15–30 minutes and lung function is back to normal within 30–60 minutes.²⁴ In CF there is a marked increase in peak expiratory flows during exercise which is most exaggerated in those with worst lung disease.²⁵ After exercise, the decrease in peak flow is seen to a much lesser extent than in asthma.²⁵ Similar findings are seen when measuring FEV₁ but

airflows are markedly variable and paradoxical changes may be seen.²⁶ Although bronchodilatation may account for some of these findings, it is thought that instability of the CF airway is the principal factor. Beneficial effects of bronchial tone reduction are countered by the effects of compression of damaged airways, which are easily distended and compliant.²⁶ Whether the different response to exercise seen in CF compared with asthma can be used to determine which patients with CF have concomitant asthma is unclear. Unfortunately, due to the wide variability of the responses²¹ and the many factors that affect exercise tolerance in patients with CF,²³ we suspect it will not be helpful.

Atopy

Serum total IgE

Serum total IgE can be a guide to atopic status but will also rise with ABPA so only indicates atopy if ABPA has been excluded.²⁷

Skin prick testing

Skin prick testing or serum radioallergosorbent tests (RASTs) will be a clue to atopic status if the common aeroallergens are tested (house dust mite, cat, dog, grass and tree pollens). There is little evidence that response to these allergens is greater than in the non-CF population,²⁸ so a positive result would support the diagnosis of CF asthma. A reaction to *Aspergillus* does not necessarily denote atopy, however, so it should not form part of the screening in CF. Positive *Aspergillus* skin prick testing (found in up to 75% adolescents and adults) was the reason why early publications exaggerated the presence of atopy in CF. The prevalence of atopy in CF is, in fact, similar to that in the non-CF population.²⁹ It has been stated that atopic CF patients have worse lung disease but, when the confounding variables of *Pseudomonas aeruginosa* chronic infection and age are taken into account, the effect of allergy has been shown to be small and non-significant.²⁹

Inflammation

Both the quantity and quality of lung inflammation can now be assessed in a number of ways. A variety of inflammatory markers can be studied in sputum (induced or spontaneous), bronchoalveolar and nasal lavage, exhaled gases and breath condensate, and airway mucosal brushing/biopsy specimens.^{30–33} The lung inflammation in CF is a predominantly neutrophil driven process,³⁴ while that in asthma depends mostly on eosinophils and lymphocytes, although more severe forms of asthma tend to be associated with neutrophils as well.³⁵

From the profile of predominant cytokine production, atopic asthma is characterised by a T helper cell (Th2) type immune response.³⁵ In CF it is interleukin (IL)-8, a neutrophil chemoattractant, that dominates the cytokine profile although, because of the wide variety of inflammatory mediators found in the CF lung, it has been described as a “cytokine soup”.³⁶ In general, CF does not fit neatly into the Th1/Th2 story, although it has been shown that Th2 is the predominant pattern in those with chronic *P. aeruginosa* infection³⁷ and ABPA.³⁸

Measurement of nitric oxide (NO) in exhaled and nasal air has been extensively studied. Exhaled NO is low or normal in CF but is usually raised in asthma (unless on corticosteroids), whereas nasal NO is low in CF and normal in asthma.^{39–42} The situation in CF asthma has not been studied. However, eliciting and differentiating markers of “asthma associated” inflammation from CF-derived inflammation is unlikely to be fruitful.

Whether any of these measures can be used for diagnosing CF asthma remains to be seen, but the problem will always remain of how to agree a gold standard definition of CF asthma.

DIFFERENTIAL DIAGNOSIS

In a patient with intractable wheezing, certain conditions need to be excluded and form part of the differential diagnosis of CF asthma. They can, of course, coexist.

Tracheo/bronchomalacia

Tracheo/bronchomalacia, in which soft compliant cartilage leads to dynamic airway narrowing, needs to be excluded by flexible bronchoscopy with the patient breathing spontaneously. This can be done under intravenous sedation or general anaesthesia via a face mask. A small bronchoscope of, for example, 2.7 mm external diameter should preferably be used to minimise the rise in positive end expiratory pressure caused by airway obstruction from the bronchoscope itself, which can potentially mask malacic airways. The particular importance of this diagnosis is that it can mimic asthma symptoms, but may be worsened by bronchodilators relaxing the smooth muscle and thus making the airways even more floppy.

Gastro-oesophageal reflux

Gastro-oesophageal reflux is particularly common in infants with CF, but the problem persists in many older children and adults.^{43–44} A 24 hour pH study needs to be performed to confirm the diagnosis. It is well established that reflux is associated with bronchospasm and wheezing but, unfortunately, in practice, treating the reflux is often disappointing in terms of the effect on respiratory symptoms.

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) must be excluded as well, although sometimes the diagnosis is difficult. Certain criteria are suggested for diagnostic confirmation, however, which are similar for both the European ERF and North American ESCF databases.⁴⁵ One of the minor criteria used by the ERF to suggest ABPA is “reversible bronchoconstriction or asthma”; using asthma as part of the definition is somewhat unhelpful and it does not form part of the North American criteria. In practice, a fourfold rise in serum total IgE (to >500 IU/ml) is strongly suggestive of the diagnosis.²⁷

Severe small airways disease

Severe small airways disease is difficult to define precisely and often it is not clear where this diagnosis merges into that of severe concomitant asthma. Essentially, the children have intractable wheezing with tight airways, and often sputum expectoration is minimal even though the lungs are full of thick secretions. High resolution CT scanning may be useful in patients who are not responding to standard treatments as, in some cases, it reveals extensive small airways disease manifest by distal air trapping due to fixed obliterative bronchiolitis.⁴⁶ It will not diagnose CF asthma but will highlight the need for a different therapeutic approach than that required for patients with bronchiectasis only.

HOW SHOULD WHEEZING IN CF BE MANAGED?

It could be argued that it makes little difference whether a patient with CF has the label of asthma, as long as the symptoms are treated. To an extent this is true but, from the North American ESCF figures on the use of treatments, it is clear that the label of asthma had a major effect on drug prescribing (table 2).¹² For example, inhaled corticosteroids were used over 2.5 times more often and oral corticosteroids almost 1.5 times more often if the patient was thought to have asthma. Although there is a current move towards the use of anti-inflammatory treatments—particularly inhaled steroids—for CF lung disease,^{47–48} it is clear that physicians are more inclined to focus on these forms of treatment if they believe that asthma is present as well.

Table 2 Use of pulmonary treatments reported to North American Epidemiologic Study of Cystic Fibrosis in 1995 (12 622 CF children and adults) related to the presence of concomitant asthma (reported in 31.5% of patients). Adapted from Konstan *et al*¹²

	Asthma (%) (n=3976)	No asthma (%) (n=8646)
Oral bronchodilators	27	12
Inhaled bronchodilators	95	76
Oral corticosteroids	31	21
Inhaled corticosteroids	45	17
Cromolyn/nedocromil	48	11

The treatment of wheezing in CF follows the standard step-wise progression used in asthma⁴⁹:

Step 1

Inhaled short acting bronchodilators

The mainstay of treatment for symptomatic bronchospasm remains inhaled short acting bronchodilators (β_2 adrenergic agonists) used on an as required basis. There is little point in routine regular bronchodilatation, however. In fact, there is little published evidence on the usefulness of bronchodilator treatment in CF¹ yet, despite this, they are prescribed to the majority of CF patients. More than half the patients in the European database were on regular inhaled bronchodilators, with greater proportions given to those with poorer lung function (80% of adults with FEV₁ <40%).⁷ According to the North American database, 76% who did not have asthma were on inhaled bronchodilators.¹² Brand has reviewed the published evidence (12 papers) and, interestingly, there were only two studies that continued for more than 2 weeks, both of which had methodological flaws.¹ Although in most studies 50–60% of patients with CF showed an improvement in FEV₁ after inhaling a bronchodilator, 30% showed no change and, importantly, 10–20% actually deteriorated.¹ The response is so variable for many individuals that a favourable response on one occasion does not necessarily predict future responses. Deterioration is likely to be due to collapse of damaged bronchiectatic airways or malacic airways that are reliant on smooth muscle tone to maintain their patency.^{50 51} It has been proposed that bronchodilators may reduce end expiratory flow rates and the effectiveness of cough by increasing large airway collapse.⁵²

The limited data on the use of ipratropium bromide have been reviewed by Cropp⁵¹ who concluded that it was as effective as β_2 agonists and that it was likely to be more effective in adults than in children. Although Cropp also concluded that combining them might be more beneficial,⁵¹ a more recent study found that adding ipratropium to salbutamol gave no additional benefit.⁵³ There are theoretical concerns, however, that anticholinergic agents may further thicken the airway mucus in CF.⁵⁴ There is little evidence for the common practice of routine bronchodilation before physiotherapy, and the improvement in mucociliary clearance that has been shown in healthy subjects after inhaled β_2 agonists is much less convincing in patients with CF.⁵⁵

The strongest reason to prescribe bronchodilators will therefore be if the patient feels symptomatic benefit, whatever the changes seen in their lung function. There is no place, however, for automatically prescribing bronchodilators in CF.

Step 2

Cromolyns/nedocromil (not recommended)

There is no evidence of benefit for this class of drugs in CF, with just one small negative study published on nebulised sodium cromoglycate.⁵⁶ This makes the widespread use in

North America somewhat surprising; it was prescribed to almost half of those with CF asthma and to 11% of patients without asthma.¹² These figures reflect 1995 practice and it may well be less now, particularly since the use of inhaled corticosteroids has been increasing.

Inhaled corticosteroids

Regular inhaled corticosteroids (ICS) are the mainstay of asthma prophylaxis. There has been an increase in their use in CF over the last decade. Wheezing that requires recurrent use of bronchodilators warrants prophylaxis with ICS. However, it is likely that they are often started and continued in patients in whom benefit has not been shown. In addition, they are often started in wheezy CF infants and continued for many years, even when unnecessary. Many parents stop giving them to their children if they do not think they are having an effect, and many are wary of using steroids. Regular use of ICS is common, nonetheless, but quite variable; the European database recorded that 10% in France, 12% in Germany, and 36% in the UK were prescribed them, with little correlation to age or disease severity.⁷ A survey of UK paediatric centres in 1998 showed that about 40% of children with CF were prescribed them, but there was a wide range between centres with a median use that ranged from 10% to 93%.⁴⁷ In the North American database, 45% with asthma were on ICS and 17% who had no asthma.¹² The latter figure is interesting as there has been a move towards using ICS as a form of treatment for lung inflammation, regardless of asthma like symptoms. Whether this is justified is unclear, as a Cochrane systematic review concluded that published trials have failed to prove benefit in CF.³⁷ A small study published since the Cochrane review has, however, shown that beclomethasone dipropionate given for 2 months led to a reduction in bronchoalveolar lavage markers of inflammation, with no adverse effect on adrenal function or infection rate.⁵⁸ We suggest that ICS should be tried in CF patients with wheezing, and the response should guide continuation of treatment. However, it is not appropriate, particularly in children, to give increasing doses if there is no clinical improvement. There are concerns over potential side effects, particularly on growth, and at high doses the dose-response curve flattens out while the side effect profile continues to increase in a linear manner.⁵⁹

Step 3

Long acting β_2 agonists

Long acting β_2 agonists are often given to patients with CF who are responding poorly to a combination of short acting β_2 agonists and ICS, in a similar fashion to standard asthma management. There have been two small trials of salmeterol in adolescents and adults with CF that have been encouraging in terms both of change in peak flow, symptoms and rescue short acting β_2 agonist use⁶⁰ as well as FEV₁.⁶¹ However, no data are available on long term use or factors to identify which patients would benefit the most. Nevertheless, we would recommend a trial of salmeterol or formoterol in patients with wheeze not responding to initial treatments, but treatment should only be continued if symptomatic or preferably objective benefit is seen.

Step 4

Theophyllines

The main action of theophyllines is as bronchodilators, but they may also have a direct effect on mucociliary clearance.⁶² Because this group of drugs has been used in asthma, efficacy has also been assessed in patients with CF. One study showed that oral theophylline did not alter lung function in most patients with CF, and no additional benefit was seen when they were added to β_2 agonists.⁵⁰ However, another small study showed a modest increase in FEV₁ in five of 12 children with CF treated for 10 days and the treated group desaturated less

during sleep (although slept worse).⁶³ The role of long term oral theophyllines in CF has not been fully evaluated, but it is doubtful that they would have a major clinical role. Apart from lack of proven benefit, problems remain with behavioural side effects and the need for repeated venepuncture to monitor drug levels. Intravenous aminophylline has been shown to have some benefit,⁶⁴ but clearly this is only useful for short term treatment of inpatients with severe bronchospasm.

Leukotriene antagonists

Leukotriene B₄ (LTB₄) is a potent neutrophil chemoattractant, inhibits neutrophil apoptosis, induces release of oxygen radicals and elastase, and is involved in CF lung pathophysiology.⁶⁵ It is also likely that the cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) are involved, and several studies have shown overproduction of both LTB₄ and the cysteinyl leukotrienes in CF.⁶⁵ In particular, the latter were higher in atopic than in non-atopic children with CF,⁶⁶ although this may simply be a manifestation of the atopy. Leukotriene receptor antagonists such as montelukast or zafirlukast have been shown to have a degree of benefit in asthma and a trial in patients with CF would be worthwhile, as long as subgroups of atopy and recurrent wheezing were studied. There has been a small open study on adults with CF which was encouraging,⁶⁷ but to date there is no convincing evidence of benefit. We believe that a proper randomised controlled trial is necessary before their use can be recommended. In theory, the 5-lipoxygenase inhibitor zileuton could have a beneficial role in CF, as it would act on LTB₄ production as well. However, currently the drug is not licensed in the UK and there are concerns about its effect on the liver which could potentially be compounded in the CF population.

Step 5

Oral corticosteroids

Short courses (<7 days) of oral corticosteroids, as used in acute asthma, may provide symptomatic relief in CF patients with bronchospasm. Providing the patient does not receive these courses too often, steroid side effects are rarely seen. The issue of whether short courses are useful for chest exacerbations in CF is not known. Long term administration of oral corticosteroids is a different matter, however. Although a degree of benefit has been demonstrated (in those chronically infected with *P aeruginosa*), the benefit was outweighed by the multitude of adverse effects seen, particularly on growth and glucose metabolism.⁶⁸ There are no data on the long term use of very low doses such as are sometimes used in severe asthma (5–10 mg/day). Despite the evidence,⁶⁹ use of long term oral corticosteroids is surprisingly high; according to the North American CF database 31% with asthma and even 21% of those without asthma were prescribed them.¹² In Europe their use is less common but increases with age and disease severity.⁷ The figures are certainly higher than the reported prevalence of ABPA (for which they are still the main treatment), so presumably they are being given as long term anti-inflammatory therapy, something that would seem ill advised. We would not advocate their routine long term use, although there will always be a few patients with intractable wheezing or severe small airways disease in whom their continued use is necessary. However, most patients with CF with milder bronchospasm and wheeze should not be taking them regularly.

Beyond the guidelines

Novel treatments

At the extreme end of the CF asthma spectrum are a group of patients with deteriorating lung function who have persistent wheeze and are non-productive of sputum, despite the fact that their airways are full of thick secretions. This group has severe small airways disease and is difficult to manage.

Although they sometimes respond to oral corticosteroids, as discussed above, adverse effects may make their long term use intolerable. For this reason, alternatives to corticosteroids are sought, and these have recently been reviewed.⁷⁰ Many of these treatments have been used in severe asthma with variable success.⁷¹ Monthly infusions of intravenous immunoglobulin given to 17 children at the Royal Brompton Hospital led to a reduction in the oral corticosteroid dose in most cases, often with improvement in symptoms.⁷² Although the mechanism of action may relate to immunomodulation, the most obvious effect is that the children developed fewer viral colds and hence fewer chest symptoms. We have also used continuous subcutaneous terbutaline infusions in a few children with intractable symptoms, in a similar way to its use in severe asthma.⁷¹ As well as bronchodilation, the patients may have an improvement in mucociliary clearance that has been shown with subcutaneous terbutaline.⁷³ Finally, regular oral cyclosporin was successfully used in four out of six children in whom oral corticosteroids were eventually stopped.⁷⁴

None of these treatments has undergone a proper randomised controlled trial in CF, and it is unlikely they ever will. The problem is that the number of patients with such severe symptoms is (fortunately) small and defining these patients is difficult. It is therefore necessary to try these novel treatments on an n=1 basis in individual patients, with careful monitoring of outcomes and side effects.

CONCLUSIONS

The diagnosis of asthma in a patient with CF is predominantly based on the patient's history. The presence of cough is irrelevant, but recurrent wheezing is a cardinal symptom. There may be bronchial hyperreactivity and there may be bronchodilator responsiveness, but both are common in patients with CF. The diagnosis is strengthened by a strong family and personal history of atopy. Response to anti-asthma medication may also help with the diagnosis. However, it will still be difficult—if not impossible—to determine who has CF and asthma, and who has asthma like symptoms due to CF lung inflammation. It could justifiably be asked whether it matters, and the relevance lies in the possible approaches to treatment. From the North American and European databases, it seems that labelling a CF patient with concomitant asthma influenced drug prescribing. Either way, the diagnosis will rely on the clinical judgement of the physician or paediatrician who should then try the relevant treatment, but only continue with it if benefit is objectively proven. The problems of defining and diagnosing CF asthma make research in this area difficult.

Authors' affiliations

I M Balfour-Lynn, Department of Paediatric Respiratory Medicine, Royal Brompton & Harefield NHS Trust, London SW3 6NP, UK
J S Elborn, Regional Respiratory Centre, Belfast City Hospital, Belfast BT9 7AB, UK

REFERENCES

- 1 **Brand PLP**. Bronchodilators in cystic fibrosis. *J R Soc Med* 2000;**93**(Suppl 38):37–9.
- 2 **Van Haren EHJ**, Lammers J-WJ, Festen J, *et al*. Bronchial vagal tone and responsiveness to histamine, exercise and bronchodilators in adult patients with cystic fibrosis. *Eur Respir J* 1992;**5**:1083–8.
- 3 **Wallis C**. Diagnosing cystic fibrosis: blood, sweat, and tears. *Arch Dis Child* 1997;**76**:85–91.
- 4 **Bush A**, Wallis C. Time to think again: cystic fibrosis is not an "all or none" disease. *Pediatr Pulmonol* 2000;**30**:139–44.
- 5 **Warner JO**, Götz M, Landau LI, *et al*. Management of asthma: a consensus statement. *Arch Dis Child* 1989;**64**:1065–79.
- 6 **Morgan WJ**, Butler SM, Johnson CA, *et al* for the Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Epidemiologic study of cystic fibrosis: design and implementation of a prospective, multicenter, observational study of patients with cystic fibrosis in the US and Canada. *Pediatr Pulmonol* 1999;**28**:231–41.

- 7 Koch C, McKenzie SG, Kaplowitz H, *et al.* International practice patterns by age and severity of lung disease in cystic fibrosis: Data from the Epidemiologic Registry of Cystic Fibrosis (ERCF). *Pediatr Pulmonol* 1997;**24**:147-54.
- 8 International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;**351**:1225-32.
- 9 McCormick A, Fleming D, Charlton J. *Morbidity statistics from general practice. 4th national study 1991-2.* Series MB5, No 3. Study carried out by the Royal College of General Practitioners, the Office of Population Censuses and Surveys, and the Department of Health. London: HMSO, 1995.
- 10 Schroeder SA, Gaughan DM, Swift M. Protection against bronchial asthma by CFTR $\Delta F508$ mutation: a heterozygote advantage in cystic fibrosis. *Nature Med* 1995;**1**:703-5.
- 11 Dahl M, Tybjaerg-Hansen A, Lange P, *et al.* $\Delta F508$ heterozygosity in cystic fibrosis and susceptibility to asthma. *Lancet* 1998;**351**:1911-3.
- 12 Konstan MW, Butler SM, Schildow DV, *et al.* for the Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Patterns of medical practice in cystic fibrosis: Part II. Use of therapies. *Pediatr Pulmonol* 1999;**28**:248-54.
- 13 Kerem E, Reisman J, Corey M, *et al.* Wheezing in infants with cystic fibrosis: clinical course, pulmonary function, and survival analysis. *Pediatrics* 1992;**90**:703-6.
- 14 Cooper PJ, Robertson CF, Hudson IL, *et al.* Variability of pulmonary function tests in cystic fibrosis. *Pediatr Pulmonol* 1990;**8**:16-22.
- 15 Brand PLP, van der Ent CK. The practical application and interpretation of simple lung function tests in cystic fibrosis. *J R Soc Med* 1999;**92**(Suppl 37):2-12.
- 16 Nickerson BG, Lemen RJ, Gerdes CB, *et al.* Within-subject variability and per cent change for significance for spirometry in normal subjects and in patients with cystic fibrosis. *Am Rev Respir Dis* 1980;**122**:859-68.
- 17 Conway SP, Watson A. Nebulised bronchodilators, corticosteroids, and rhDNase in adult patients with cystic fibrosis. *Thorax* 1997;**52**(Suppl 2):S64-8.
- 18 Hiatt P, Eigen H, Yu P, *et al.* Bronchodilator responsiveness in infants and young children with cystic fibrosis. *Am Rev Respir Dis* 1988;**137**:119-22.
- 19 Sanchez I, Powell RE, Pasterkamp H. Wheezing and airflow obstruction during methacholine challenge in children with cystic fibrosis and in normal children. *Am Rev Respir Dis* 1993;**147**:705-9.
- 20 Eggleston PA, Rosenstein BJ, Stackhouse CM, *et al.* Airway hyperreactivity in cystic fibrosis. Clinical correlates and possible effects on the course of the disease. *Chest* 1988;**94**:360-5.
- 21 Holzer FJ, Olinsky A, Phelan PD. Variability of airways hyper-reactivity and allergy in cystic fibrosis. *Arch Dis Child* 1981;**56**:455-9.
- 22 Darga LL, Eason LA, Zach DMS, *et al.* Cold air provocation of airway hyperreactivity in patients with cystic fibrosis. *Pediatr Pulmonol* 1986;**2**:82-8.
- 23 Balfour-Lynn IM. Cardiopulmonary function testing. Paediatrics. In: Pryor JA, Prasad SA, eds. *Physiotherapy for respiratory and cardiac problems. Children and adults.* 3rd ed. Edinburgh: Harcourt Sciences, 2002: 102-26.
- 24 Cypcar D, Lemanske Jr RF. Asthma and exercise. *Clin Chest Med* 1994;**15**:351-68.
- 25 Day G, Mearns MB. Bronchial lability in cystic fibrosis. *Arch Dis Child* 1973;**48**:355-9.
- 26 Macfarlane PI, Heaf D. Changes in airflow obstruction and oxygen saturation in response to exercise and bronchodilators in cystic fibrosis. *Pediatr Pulmonol* 1990;**8**:4-11.
- 27 Marchant JL, Warner JO, Bush A. Rise in total IgE as an indicator of allergic bronchopulmonary aspergillosis in cystic fibrosis. *Thorax* 1994;**49**:1002-5.
- 28 Warner JO, Kilburn SA. Cystic fibrosis and allergy. *Pediatr Allergy Immunol* 1996;**7**(Suppl 9):67-9.
- 29 Wilmott RW. The relationship between atopy and cystic fibrosis. *Clin Rev Allergy* 1991;**9**:29-46.
- 30 Shields MD, Riedler J. Bronchoalveolar lavage and tracheal aspirate for assessing inflammation in children. *Am J Respir Crit Care Med* 2000;**162**:S15-7.
- 31 Bush A, Pohunek P. Brush biopsy and mucosal biopsy. *Am J Respir Crit Care Med* 2000;**162**:S18-22.
- 32 De Jongste JC, Alving K. Gas analysis. *Am J Respir Crit Care Med* 2000;**162**:S23-7.
- 33 Frischer T, Baraldi E. Upper airway sampling. *Am J Respir Crit Care Med* 2000;**162**:S28-30.
- 34 Konstan MW, Berger M. Current understanding of the inflammatory process in cystic fibrosis: onset and etiology. *Pediatr Pulmonol* 1997;**24**:137-42.
- 35 Bousquet J, Jeffrey PK, Busse WW, *et al.* Asthma. From bronchoconstriction to airways inflammation and remodelling. *Am J Respir Crit Care Med* 2000;**161**:1720-45.
- 36 Richman-Eisenstat J. Cytokine soup: making sense of inflammation in cystic fibrosis. *Pediatr Pulmonol* 1996;**21**:3-5.
- 37 Moser C, Kjaergaard S, Pressler T, *et al.* The immune response to chronic *Pseudomonas aeruginosa* lung infection in cystic fibrosis patients is predominantly of the Th2 type. *Acta Pathol Microbiol Immunol Scand* 2000;**108**:329-35.
- 38 Skov M, Poulsen LK, Koch C. Increased antigen-specific Th-2 response in allergic bronchopulmonary aspergillosis (ABPA) in patients with cystic fibrosis. *Pediatr Pulmonol* 1999;**27**:74-9.
- 39 Balfour-Lynn IM, Lavery A, Dinwiddie R. Reduced upper airway nitric oxide in cystic fibrosis. *Arch Dis Child* 1996;**75**:319-22.
- 40 Thomas SR, Kharitonov SA, Scott SF, *et al.* Nasal and exhaled nitric oxide is reduced in adult patients with cystic fibrosis and does not correlate with cystic fibrosis genotype. *Chest* 2000;**117**:1085-9.
- 41 Kharitonov SA, Yates D, Robbins RA, *et al.* Increased nitric oxide in exhaled air of asthmatic patients. *Lancet* 1994;**343**:133-5.
- 42 Lundberg JO, Nordvall SL, Weitzberg E, *et al.* Exhaled nitric oxide in paediatric asthma and cystic fibrosis. *Arch Dis Child* 1996;**75**:323-6.
- 43 Heine RG, Button BM, Olinsky A, *et al.* Gastro-oesophageal reflux in infants under 6 months with cystic fibrosis. *Arch Dis Child* 1998;**78**:44-8.
- 44 Ledson MJ, Tran J, Walshaw MJ. Prevalence and mechanisms of gastro-oesophageal reflux in adult cystic fibrosis patients. *J R Soc Med* 1998;**91**:7-9.
- 45 Mastella G, Rainisio M, Harms HK, *et al.* on behalf of the investigators of the Epidemiologic Registry of Cystic Fibrosis. Allergic bronchopulmonary aspergillosis in cystic fibrosis. A European epidemiological study. *Eur Respir J* 2000;**16**:464-71.
- 46 Coren ME, Ng V, Rubens M, *et al.* The value of ultrafast computed tomography in the investigation of pediatric chest disease. *Pediatr Pulmonol* 1998;**26**:389-95.
- 47 Balfour-Lynn IM, Dezateux C. Corticosteroids and ibuprofen in cystic fibrosis. *Thorax* 1999;**54**:657.
- 48 Oermann CM, Sockrider MM, Konstan MW. The use of anti-inflammatory medications in cystic fibrosis: trends and physician attitudes. *Chest* 1999;**115**:1053-8.
- 49 British Thoracic Society, National Asthma Campaign, Royal College of Physicians of London, *et al.* The British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997;**52**(Suppl 1):S1-21.
- 50 Eber E, Oberwaldner B, Zach MS. Airway obstruction and airway wall instability in cystic fibrosis: the isolated and combined effect of theophylline and sympathomimetics. *Pediatr Pulmonol* 1988;**4**:205-12.
- 51 Cropp GJ. Effectiveness of bronchodilators in cystic fibrosis. *Am J Med* 1996;**100**(Suppl 1A):19-29S.
- 52 Zach MS, Oberwaldner B, Forche G, *et al.* Bronchodilators increase airway instability in cystic fibrosis. *Am Rev Respir Dis* 1985;**131**:537-43.
- 53 Ziebach R, Pietsch-Breitfeld B, Bichler M, *et al.* Bronchodilatory effects of salbutamol, ipratropium bromide and their combination: double-blind, placebo-controlled crossover study in cystic fibrosis. *Pediatr Pulmonol* 2001;**31**:431-5.
- 54 Spencer DA. Nebulised bronchodilators, antibiotics and rhDNase for children with cystic fibrosis. *Thorax* 1997;**52**(Suppl 2):S89-91.
- 55 Mortensen J, Hansen A, Falk M, *et al.* Reduced effect of inhaled β_2 -adrenergic agonists on lung mucociliary clearance in patients with cystic fibrosis. *Chest* 1993;**103**:805-11.
- 56 Sivan Y, Arce P, Eigen H, *et al.* A double-blind, randomized study of sodium cromoglycate versus placebo in patients with cystic fibrosis and bronchial hyperreactivity. *J Allergy Clin Immunol* 1990;**85**:649-54.
- 57 Dezateux C, Walters S, Balfour-Lynn IM. Inhaled corticosteroids for cystic fibrosis. (Cochrane Review). In: *The Cochrane Library.* Issue 2. Oxford: Update Software, 2002.
- 58 Wojtack HA, Kerby GS, Wagener JS, *et al.* Beclomethasone dipropionate reduced airway inflammation without adrenal suppression in young children with cystic fibrosis: a pilot study. *Pediatr Pulmonol* 2001;**32**:293-302.
- 59 Holt S, Suder A, Weatherall M, *et al.* Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001;**323**:253-6.
- 60 Bargon J, Viel K, Dauletbaev N, *et al.* Short-term effects of regular salmeterol treatment on adult cystic fibrosis patients. *Eur Respir J* 1997;**10**:2307-11.
- 61 Hordvik NL, Sammut PH, Judy CG, *et al.* Effects of standard and high doses of salmeterol on lung function of hospitalized patients with cystic fibrosis. *Pediatr Pulmonol* 1999;**27**:43-53.
- 62 Wanner A. Effects of methylxanthines on airway mucociliary function. *Am J Med* 1985;**79**:16-21.
- 63 Avital A, Sanchez I, Holbrow J, *et al.* Effect of theophylline on lung function tests, sleep quality, and nighttime SaO_2 in children with cystic fibrosis. *Am Rev Respir Dis* 1991;**144**:1245-9.
- 64 Larsen GL, Barron RJ, Landay RA, *et al.* Intravenous aminophylline in patients with cystic fibrosis. Pharmacokinetics and effect on pulmonary function. *Am J Dis Child* 1980;**134**:1143-8.
- 65 Lammers J-W. Leukotrienes and cystic fibrosis. *Clin Exp Allergy Rev* 2001;**1**:175-7.
- 66 Greally P, Cook AJ, Sampson AP, *et al.* Atopic children with cystic fibrosis have increased urinary leukotriene E_4 concentrations and more severe pulmonary disease. *J Allergy Clin Immunol* 1994;**93**:100-7.
- 67 Morice AH, Kastelik JA, Aziz I. Montelukast sodium in cystic fibrosis. *Thorax* 2001;**56**:244-5.
- 68 Eigen H, Rosenstein BJ, FitzSimmons S, *et al.* Cystic Fibrosis Foundation Prednisone Trial Group. A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. *J Pediatr* 1995;**126**:515-23.
- 69 Cheng K, Ashby D, Smyth R. Oral steroids for cystic fibrosis (Cochrane Review). In: *The Cochrane Library.* Issue 2. Oxford: Update Software, 2002.
- 70 Jaffe A, Balfour-Lynn IM. Treatment of severe small airways disease in children with cystic fibrosis: alternatives to corticosteroids. *Paediatric Drugs* 2002;**4**:381-9.

- 71 **Payne DNR**, Balfour-Lynn IM. Difficult asthma in children: a practical approach. *J Asthma* 2001;**38**:189–203.
- 72 **Balfour-Lynn IM**, Mohan U, Bush A, *et al*. Intravenous immunoglobulin (IVIg) for severe lung disease in children with CF (abstract). *Pediatr Pulmonol* 2001;Suppl 22:306.
- 73 **Wood RE**, Wanner A, Hirsch J, *et al*. Tracheal mucociliary transport in patients with cystic fibrosis and its stimulation by terbutaline. *Am Rev Respir Dis* 1975;**111**:733–8.
- 74 **Bhal GK**, Maguire SA, Bowler IM. Use of cyclosporin A as a steroid sparing agent in cystic fibrosis (letter). *Arch Dis Child* 2001;**84**:89.

Call for peer reviewers

Clinical Evidence is a regularly updated evidence based journal available world wide both as a paper version and on the internet. *Clinical Evidence* urgently needs to recruit a number of new contributors. Contributors are health care professionals or epidemiologists with experience in evidence based medicine and the ability to write in a concise and structured way.

Clinical Evidence needs to recruit a number of new peer reviewers. Peer reviewers are health care professionals or epidemiologists with experience in evidence based medicine. As a peer reviewer you would be asked for your views on the clinical relevance, validity and accessibility of specific topics within the journal, and their usefulness to the intended audience (international generalists and health care professionals, possibly with limited statistical knowledge). Topics are usually 2000–3000 words in length and we would ask you to review between 2–5 topics per year. The peer review process takes place throughout the year, and our turnaround time for each review is ideally 10–14 days.

If you are interested in becoming a peer reviewer for *Clinical Evidence*, please complete the peer review questionnaire at www.clinicalevidence.com or contact Polly Brown (pbrown@bmjgroup.com).