OCCASIONAL REVIEW

“CF asthma”: what is it and what do we do about it?

I M Balfour-Lynn, J S Elborn

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. Bronchial hyperresponsiveness (BHR) is also common in CF patients of all ages, although the underlying mechanism is not known. 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. 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”. 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”. 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)”. 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). In UK adults the prevalence of asthma is estimated at around 5%. 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.

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. However, in their paper on the use of treatments, the same group quotes a reported asthma prevalence of 31.5% (of 12 622 patients). 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. 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
study that followed 229 CF patients diagnosed before 2 years of age, 25% had physician documented wheezing during the first 2 years of life. 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 atopy (eczema or allergic rhinitis) and 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 Brand), 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. 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. One study found it in 40% of young children (age 4–7 years) and 77% of older children (8–18 years). Interestingly, this study showed that some of these children had significant airways obstruction but did not wheeze. The incidence of BHR in adults is similar. 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. 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. 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. 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.

Exercise testing

Exercise testing has a valuable role in evaluating both CF and asthma. There are important differences between the responses to exercise in the two conditions, however. In asthma, after the normal transient bronchodilatation, 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. In CF there is a marked increase in peak expiratory flows during exercise which is most exaggerated in those with worse lung disease. After exercise, the decrease in peak flow is seen to a much lesser extent than in asthma. Similar findings are seen when measuring FEV1, but

<table>
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<tr>
<th>Age (years)</th>
<th>FEV1 (% predicted)</th>
<th>Asthma like symptoms (%)</th>
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<tr>
<td>6–17</td>
<td>&gt;71</td>
<td>15</td>
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<tr>
<td></td>
<td>40–70</td>
<td>22</td>
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<td>&lt;40</td>
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<tr>
<td>18+</td>
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<td>40–70</td>
<td>21</td>
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<td></td>
<td>&lt;40</td>
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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.42 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 ERCF and North American ESCF databases.43 One of the minor criteria used by the ERCF 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.42

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 obliteratorive bronchiolitis.43 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).42 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,44 it is clear that physicians are more inclined to focus on these forms of treatment if they believe that asthma is present as well.

Allergy has been shown to be small and non-significant. 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 responses and the many factors that affect exercise tolerance in patients with CF,21 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.29

Skin prick testing

Skin prick testing or serum radioallergosorbet 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,29 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.21 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,40 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.41 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".42 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 infection1 and ABPA.19

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.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.

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The treatment of wheezing in CF follows the standard stepwise progression used in asthma):

**Step 1**

**Inhaled short acting bronchodilators**

The mainstay of treatment for symptomatic bronchospasm remains inhaled short acting bronchodilators (β₂ 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 CF 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%). According to the North American database, 76% who did not have asthma were on inhaled bronchodilators.  

<table>
<thead>
<tr>
<th>Asthma (%)</th>
<th>No asthma (%)</th>
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<tbody>
<tr>
<td>Oral bronchodilators</td>
<td>27</td>
</tr>
<tr>
<td>Inhaled bronchodilators</td>
<td>95</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>31</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>45</td>
</tr>
<tr>
<td>Cromlyn/nedocromil</td>
<td>48</td>
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The limited data on the use of ipratropium bromide have been reviewed by Cropp who concluded that it was as effective as β₂ 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, a more recent study found that adding ipratropium to salbutamol gave no additional benefit. There are theoretical concerns, however, that anticholinergic agents may further thicken the airway mucus in CF. There is little evidence for the common practice of routine bronchodilatation before physiotherapy, and the improvement in mucociliary clearance that has been shown in healthy subjects after inhaled β₂ agonists is much less convincing in patients with CF.

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**

**Cromolyn/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. 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. 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. 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%. In the North American database, 45% with asthma were on ICS and 17% who had no asthma. 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. 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. 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.

**Step 3**

**Long acting β₂ agonists**

Long acting β₂ agonists are often given to patients with CF who are responding poorly to a combination of short acting β₂ 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 β₂ agonist use as well as FEV₁. 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. 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 β₂ agonists. 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). 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, but clearly this is only useful for short term treatment of inpatients with severe bronchospasm.

Leukotriene antagonists
Leukotriene B_{4} (LTB_{4}) is a potent neutrophil chemoattractant, inhibits neutrophil apoptosis, induces release of oxygen radicals and elastase, and is involved in CF lung pathophysiology. It is also likely that the cysteinyl leukotrienes (LTC_{4}, LTD_{4}, LTE_{4}) are involved, and several studies have shown overproduction of both LTC_{4} and the cysteinyl leukotrienes in CF. In particular, the latter were higher in atopic than in non-atopic children with CF, 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, 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 LTB_{4} 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. 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, 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. In Europe their use is less common but increases with age and disease severity. 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. Many of these treatments have been used in severe asthma with variable success. 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. 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. As well as bronchodilation, the patients may have an improvement in mucociliary clearance that has been shown with subcutaneous terbutaline. Finally, regular oral cyclosporin was successfully used in four out of six children in whom oral corticosteroids were eventually stopped.

None of these treatments has undergone a proper randomised controlled trial in CF, and it is unlikely they 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.

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REFERENCES
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