Asthma in cystic fibrosis

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INTRODUCTION

Wheeze is a common symptom in cystic fibrosis (CF) and, whilst in many patients this is due to their underlying lung disease, in some cases the wheeze is due to the presence of concomitant asthma. It is not easy to differentiate the cause of wheezing and there is a view that it does not matter anyway—i.e. symptoms should be treated in their own rights. However, it is clear from the North American Epidemiologic Study of Cystic Fibrosis (ESCF) that the diagnosis of asthma in CF does influence prescribing practice (Table 1).[1,2] Inhaled corticosteroids were used over 2½ times more often and oral corticosteroids almost 1½ times more often if the patient was thought to have asthma. The topic of CF asthma has been the subject of a recent review and this article summarizes much of this review.[2]

Table 1 **Use of pulmonary therapies 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 the patients)**. (From Ref 2, adapted from Ref. 1. with permission)

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

WHAT IS CF ASTHMA?

There is no consensus on how to define CF asthma. The North American ESCF stated that a patient has 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'.[3] This definition is reasonable although the use of serum IgE and eosinophilia is only of value if allergic bronchopulmonary aspergillosis (ABPA) has been excluded. The European Epidemiologic Registry of Cystic Fibrosis (ERCF) gave a briefer definition, and patients were recorded as having the presence of complicating 'asthma-like symptoms' if the patient had 'bronchial hyper-reactivity (with or without histamine challenge) or asthma-like symptoms (prolonged exhalation with crepitations and wheezing)'.[4] Unfortunately, this definition is not particularly helpful.

HOW MAY CF ASTHMA BE DIAGNOSED?

Although it may be useful to look at how asthma is diagnosed in those who do not have CF and see how they apply to those who do, some symptoms are of less relevance to CF patients.[2] For example, a history of wheeze though important is non-specific, and most patients with CF have recurrent coughs whether or not they have asthma. Probably the most appropriate indicators are a family history of atopy in first-degree relatives and a personal history of eczema and allergic rhinitis. As many CF patients suffer from hyperinflation or Harrison sulci, physical examination is not very productive either. However, the following may produce some very useful indicators.

Lung function

Standard clinic spirometry may indicate the presence of airway obstruction (particularly from the shape of the flow-volume curve), however, it does not differentiate obstruction due to concomitant asthma from that due to typical CF lung disease. Even measurements of small airway function (such as maximal expiratory flow at 25% vital capacity) will not help for they tend to be reduced in most CF patients, and are quite variable.[5] Measuring peak expiratory flow rate are often useful,[6] except in CF where the obstruction mainly involves medium and small airways—so reduction in peak flow is only a late sign.[7] Body plethysmography is not specific to CF asthma although it may provide useful information such as the degree of hyperinflation and airways resistance.

Bronchodilator responsiveness is recommended for the diagnosis of asthma,[6] however its usefulness in CF asthma diagnosis is less obvious. The reason for this is that due to the degree of variability in lung function measures (forced

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expiratory volume in one second and forced vital capacity can vary by as much as 15–20% spontaneously, including same day testing[5,8]) defining the cut-off for a significant change after inhaling a bronchodilator becomes arbitrary.[2] CF patients often show a degree of bronchodilator responsiveness whether or not they have CF asthma—most studies show no relationship with atopy.[9] Studies in older children and adolescents have shown bronchodilator responsiveness in approximately 50–60% of CF patients,[10] many of whom will not have CF asthma. It is therefore unlikely that this form of testing on its own will be a useful diagnostic aid.

Bronchial hyperresponsiveness (BHR) is common in CF patients of all ages, the underlying mechanism, however, is unknown.[11] Although BHR tests are not routinely performed in paediatrics they may be useful in adults. BHR to histamine or methacholine is found in at least 40% CF patients.[10,11] One study found it in 40% of those aged 4–7 years and 77% 8–18 years old.[12] The response to indirect stimuli such as hypertonic saline or exercise, however, is different in CF from that in asthma. Patients with CF usually bronchodilate after such challenges[10] which implies the mechanisms underlying BHR in CF are not the same as in asthma. This then weakens the case for BHR testing, especially given the variability over time in CF children.[13] Because of the frequency of paradoxical responses, normal conventional challenges are poor and do not give an accurate account of the incidence of BHR in CF patients.[14]

Exercise testing plays an important part in the evaluation of both asthma and CF.[15] However, the differences between the responses in the two conditions are important. In asthma progressive bronchoconstriction occurs and reaches its maximum 5–10 minutes after exercise. The symptoms cease within 15–30 minutes, and after 30–60 minutes lung function returns to normal. In CF patients with extensive lung disease there is a marked increase in the peak expiratory flow during exercise. The decrease after exercise is markedly less than in non-CF asthma.[17] These are similar to the FEV_1 findings except that the airflow is more variable and paradoxical changes will be noted.[18] It is probable that the main cause of these results is the instability of the CF airway. It is unlikely that exercise testing will prove to be a very useful diagnostic tool because of the variable responses[13] and the many different factors affecting exercise tolerance in CF patients.[15]

Atopy

Assuming ABPA has been excluded, serum total IgE can be a guide to atopic status.[19] Positive skin prick testing or serum radioallergosorbent tests (RASTs) will indicate atopic status when the common aeroallergens such as house dust mite, cat, dog, grass and tree pollens, are tested. A reaction to *Aspergillus* does not necessarily denote atopy. It should not therefore form part of atopic screening in CF. Early studies exaggerated the presence of atopy in CF when positive *Aspergillus* skin prick testing was found in up to 75% of CF patients. There is little evidence that response to these allergens is greater than in the non-CF population.[20] A positive result would therefore support the diagnosis of CF asthma.[21]

Measures of airway inflammation

Lung inflammation has been extensively investigated in both CF and asthma. In CF it is predominantly neutrophil-driven,[22] whilst in asthma it depends mostly on eosinophils and lymphocytes—more severe forms of asthma however do also tend to be associated with neutrophils.[23]

Atopic asthma is characterized by a (T helper cell) Th2 type immune response.[23] In general, CF does not quite fit into the Th1/Th2 pattern although Th2 has been shown to be the predominant pattern in those with chronic *Pseudomonas aeruginosa* infection[24] and ABPA.[25] It may prove to be pointless to try to elicit and differentiate markers of 'asthma-associated' inflammation from CF-drived inflammation.

DIFFERENTIAL DIAGNOSIS (TABLE 2)

The importance of diagnosing malacic airways is that although the resultant symptoms can mimic asthma they may be made worse by bronchodilators. Gastro-oesophageal reflux is particularly common in infants with CF, but may persist in older children and adults.[26,27] Reflux is associated with bronchospasm and wheezing.

ABPA is not always easy to diagnose although there are certain criteria used for diagnostic confirmation.[28] In practice, a fourfold rise in serum total IgE (to above 500 IU/mL) indicates the presence of ABPA.[19]

The line between severe small airways disease and severe concomitant asthma is not always clearly defined. The children have intractable wheezing with tight airways, and sputum expectoration may be minimal even when the

Table 2 **Differential diagnosis of cystic fibrosis asthma with some key investigations**

Condition	*Investigation*
Tracheo/bronchomalacia	Flexible bronchoscopy
Gastro-oesophageal reflux	24-hour pH study
Allergic bronchopulmonary aspergillosis	Serum total IgE, aspergillus RAST, aspergillus precipitins, eosinophil count, sputum microbiology, chest X-ray
Severe small airways disease/ obliterative bronchiolitis	High resolution computerized tomography scan of chest

lungs are full of thick secretions. Extensive small airways disease, manifest by distal air trapping that is due to fixed obliterative bronchiolitis may be diagnosed on high resolution computerized tomography scanning.[29]

HOW COMMON IS CF ASTHMA?

The International Study of Asthma and Allergies in Childhood (ISAAC) indicates a worldwide prevalence of asthma symptoms in teenagers that ranges from 2–37%.[30] In UK adults it is estimated at around 5%.[31] One would therefore expect that the same proportion of CF patients would have concomitant asthma. The North American ESCF initially reported that 19% (of 18 411 patients) had asthma.[3] However with cumulative data the same group quotes a reported asthma prevalence of 31.5% (of 12 622 patients).[1] The European ERCF reports asthma-like symptoms in 17% of 6856 patients with the same proportions in children and adults.[4] Kerem *et al.* followed 229 CF patients diagnosed before 2 years of age—25% had physician-documented wheezing during the first 2 years of life, which was associated with a positive family history of atopy.[32]

By the time they were 2-years-old the wheezing had resolved in 50% of the patients, and by 4 years in 75%. Later follow-up at 13 years showed lung function was significantly lower in the wheezing group compared to the non-wheezing children.

MANAGEMENT OF WHEEZING IN CF

Whether wheezing is due to concomitant asthma or not, the treatment follows the standard step-wise progression used in asthma.[33] The response to anti-asthma therapy in an individual may be as helpful in the diagnosis of CF asthma as it is in asthmatic patients without CF.

Inhaled short-acting bronchodilators

Despite the lack of evidence of the usefulness of bronchodilator therapy in CF,[10] β_2-adrenergic agonists are prescribed to the majority of CF patients. In his review of the published evidence (a dozen papers) Brand found only two studies that went beyond 2 weeks and both had methodological flaws.[10] Although in most studies 50–60% CF patients showed an improvement in FEV_1 after inhaling a bronchodilator, 30% showed no change, and importantly 10–20% actually deteriorated.[10]

Cropp reviewed the data on the use of ipratropium bromide. He concluded that it was as effective as the β_2-agonists, and likely to be more so in adults than children.[34] Although Cropp believed that adding ipratropium to salbutamol would prove beneficial a report by Ziebach *et al.* indicated no such benefits.[35] In his report Spencer voiced theoretical concerns that in CF patients anticholinergic agents may thicken the airway mucus.[36] So it seems sensible to suggest that the best reason for prescribing bronchodilators is that the patient finds some relief whatever the changes seen in their lung function.

Cromolyns/nedocromil

These are not recommended as there is no published evidence of benefit. There is, however one small negative study published on nebulized sodium cromoglycate.[37]

Inhaled corticosteroids

Without doubt, regular inhaled corticosteroids (ICS) are widely used for asthma prophylaxis. It seems that wheezing in CF that requires recurrent use of bronchodilators also warrants prophylaxis with ICS. However, they are often started and continued in patients who show no benefit from their use. Often they are prescribed for wheezy CF infants and continued unnecessarily for many years. A Cochrane systematic review concluded that published trials have failed to prove benefit (or harm) in CF.[38] Despite this there has been an increase in their use in CF over the last decade. It is inappropriate to give ever increasing doses when no clinical improvement is shown. There are concerns over potential side effects—at high doses the dose–response curve flattens out whilst the side effect profile continues to increase.[39]

Long-acting β_2-agonists

These are often prescribed for CF patients who are responding poorly to a combination of short-acting β_2-agonists and inhaled corticosteroids. Bargon *et al.*[40] and Hordvik *et al.*[41] published the results of their trials of salmeterol in adolescents and adults with CF. Both were small trials but both were encouraging in terms of change in peak flow, symptoms, rescue short-acting β_2-agonist use,[40] and FEV_1.[41] A more recent trial studied patients >13 years (none of whom were taking ICS), using high dose dry powder salmeterol (100 μg twice daily) for 24 weeks.[42] When compared with twice daily nebulized albuterol, there was better lung function, less need for rescue bronchodilators, and fewer respiratory symptoms. There was also a trend to less antibiotic use which was well tolerated. However, there was no difference in lung function after 4 weeks. Unfortunately it is not yet known which factors identify those patients who would benefit the most. A therapeutic trial of salmeterol or eformoterol in patients with wheeze not responding to initial therapies is warranted, but treatment should only be continued if symptomatic or objective benefit is seen.

Theophyllines

It is believed that, in addition to acting as bronchodilators, theophyllines have a direct effect on mucociliary clearance.[43]

Eber *et al.* reported that in the majority of CF patients oral theophyllines did not alter lung function and that adding them to β_2-agonists was not beneficial either.[44] Avital *et al.* found that of the 12 CF children in their study who had been treated for 10 days, five had a small increase in FEV_1. They also found that although the treated group had a more disturbed sleep pattern they desaturated less during sleep.[45] There are still problems with the behavioural side effects of long-term oral theophyllines and the need to repeatedly monitor drug levels. More research is needed in order to see what, if any, are the benefits of their use.

Leukotriene antagonists

Leukotriene B_4 (LTB_4) and the cysteinyl-leukotrienes (LTC_4, LTD_4, LTE_4) are involved in CF lung pathophysiology, and several studies have demonstrated their overproduction in CF.[46] Greally *et al.*[47] found that the latter were raised in atopic CF children but that may simply be a manifestation of the atopy. As leukotriene receptor antagonists such as montelukast or zafirlukast appear to be beneficial perhaps a clinical trial should be run which included subgroups of atropy and recurrent wheezing. Except for a small, encouraging study of CF adults, there has so far been no real evidence of benefit. Because it may also act on LTB_4 production, the 5-lipoxygenase-inhibitor zileuton is thought to play a positive role. The drug is not at present licensed in the UK and there are concerns about its effect on the liver. It will therefore be interesting to see the results of the phase 2 trial of a newer LTB_4 receptor antagonist, BIIL284 BS.[49]

Oral corticosteroids

Given as short courses (<7 days) oral corticosteroids may provide symptomatic relief to CF patients with bronchospasm. Steroid side effects are rarely seen except when the patient receives too many courses. Whether or not short courses are useful for chest exacerbations is unclear but long-term use is not recommended. The benefits do not outweigh the adverse effects reported, although some benefit is seen in those with *Pseudomonas aeruginosa* infection.[50] Of course, some of those suffering intractable wheezing or severe small airways disease may need to use them but most CF patients should not be using them regularly. At present there are no data on the long-term use in CF of very low doses (i.e. 5–10 mg/day) used in severe asthma.

Novel therapies

CF asthma patients with deteriorating lung function, who have persistent wheeze but do not produce sputum even though their airways are full of thick secretions, are difficult to manage. Although they do sometimes respond to oral corticosteroids, the adverse side effects may make their long-term use unacceptable. Alternative treatments such as monthly infusions of intravenous immunoglobulin, continuous subcutaneous terbutaline infusions, regular oral cyclosporin have recently been reviewed.[51]

Box 1 **Factors that support diagnosis of cystic fibrosis asthma**

- History of recurrent wheezing
- Positive family history atopy in first degree relative
- Patient has history of atopy (eczema, hay fever, food allergy)
- Positive skin prick tests or serum radioallergosorbent tests to aeroallergens (excluding aspergillus)
- High serum IgE (excluding ABPA)
- Physiology supportive (spirometry, bronchodilator responsiveness, BHR)
- Other diagnoses excluded (gastro-oesophageal reflux, malacic airways, ABPA, obliterative bronchiolitis)
- Response to anti-asthma medication.

CONCLUSION

It is difficult to determine which CF patients have asthma and which have asthma-like symptoms caused by CF lung inflammation. The diagnosis of asthma in CF patients is mainly clinical with several suggestive factors (Box 1). The patient's history is all important and, although cough is irrelevant, recurrent wheezing is a cardinal symptom. Bronchial hyperreactivity and bronchodilator responsiveness are common in CF patients but a strong family and personal history of atopy may also point to asthma, as might a response to anti-asthma medication. Whatever the therapy prescribed by the physician or paediatrician it should only be continued if the benefits are objectively proven.

REFERENCES

1 Konstan MW, Butler SM, Schidlow 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

2 Balfour-Lynn IM, Elborn S. ''CF asthma'': what is it and what do we do about it? *Thorax* 2002;**57**:742–8

3 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

4 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

5 Cooper PJ, Robertson CF, Hudson IL, *et al.* Variability of pulmonary function tests in cystic fibrosis. *Pediatr Pulmonol* 1990;**8**:16–22

6 Warner JO, Götz M, Landau LI, *et al.* Management of asthma: a consensus statement. *Arch Dis Child* 1989;**64**:1065–79

7 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

8 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

9 Conway SP, Watson A. Nebulised bronchodilators, corticosteroids, and rhDNase in adult patients with cystic fibrosis. *Thorax* 1997; **52**(suppl 2):S64–8

10 Brand PLP. Bronchodilators in cystic fibrosis. *J R Soc Med* 2000; **93**(suppl 38):37–9

11 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 Resp J* 1992;**5**:1083–8

12 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

13 Holzer FJ, Olinsky A, Phelan PD. Variability of airways hyperreactivity and allergy in cystic fibrosis. *Arch Dis Child* 1981;**56**:455–9

14 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

15 Balfour-Lynn IM. Cardiopulmonary function testing: paediatrics. In: Pryor JA, Prasad SA, eds. *Physiotherapy for Respiratory and Cardiac Problems: Children and Adults*, 3rd edn. Edinburgh: Harcourt Sciences, 2002:102–26

16 Cypcar D, Lemanske Jr RF. Asthma and exercise. *Clin Chest Med* 1994;**15**:351–68

17 Day G, Mearns MB. Bronchial lability in cystic fibrosis. *Arch Dis Child* 1973;**48**:355–9

18 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

19 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

20 Warner JO, Kilburn SA. Cystic fibrosis and allergy. *Pediatr Allergy Immunol* 1996;**7**(suppl 9):67–9

21 Wilmott RW. The relationship between atopy and cystic fibrosis. *Clin Rev Allergy* 1991;**9**:29–46

22 Konstan MW, Berger M. Current understanding of the inflammatory process in cystic fibrosis: onset and etiology. *Pediatr Pulmonol* 1997; **24**:137–42

23 Bousquet J, Jeffrey PK, Busse WW, *et al.* Asthma. From bronchoconstriction to airways inflammation and remodelling. *Am J Resp Crit Care Med* 2000;**161**:1720–45

24 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

25 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

26 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

27 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

28 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 Resp J* 2000;**16**:464–71

29 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

30 The 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

31 McCormick A, Fleming D, Charlton J. *Morbidity Statistics from General Practice: 4th National Study 1991–2*, Series MB5, No. 3 London: HMSO, 1995

32 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

33 British guideline on the management of asthma. *Thorax* 2003;**58** (suppl 1):1–94

34 Cropp GJ. Effectiveness of bronchodilators in cystic fibrosis. *Am J Med* 1996;**100**(suppl 1A):19S–29S

35 Ziebach R, Pietsch-Breitfeld E, 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

36 Spencer DA. Nebulised bronchodilators, antibiotics and rhDNase for children with cystic fibrosis. *Thorax* 1997;**52**(suppl 2):S89–91

37 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

38 Dezateux C, Walters S, Balfour-Lynn IM. Inhaled corticosteroids for cystic fibrosis. (Cochrane Review.) In: *The Cochrane Library*. Oxford: Update Software, 2002:issue 3

39 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

40 Bargon J, Viel K, Dauletbaev N, *et al.* Short-term effects of regular salmeterol treatment on adult cystic fibrosis patients. *Eur Resp J* 1997;**10**:2307–11

41 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

42 Hordvik NL, Sammut PH, Judy CG, Colombo JL. Effectiveness and tolerability of high-dose salmeterol in cystic fibrosis. *Pediatr Pulmonol* 2002;**34**:287–96

43 Wanner A. Effects of methylxanthines on airway mucociliary function. *Am J Med* 1985;**79**:16–21

44 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

45 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

46 Lammers J-W. Leukotrienes and cystic fibrosis. *Clin Exp Allergy Rev* 2001;**1**:175–7

47 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

48 Morice AH, Kastelik JA, Aziz I. Montelukast sodium in cystic fibrosis. *Thorax* 2001;**56**:244–5

49 Konstan MW, Walenga RW, Berger M. Prospect of LTB4 receptor antagonism as an anti-inflammatory therapy in CF. *Pediatr Pulmonol* 2002;**34**(suppl 24):144–5

50 Eigen H, Rosenstein BJ, FitzSimmons S, *et al.* and the 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

51 Jaffé A, Balfour-Lynn IM. Treatment of severe small airways disease in children with cystic fibrosis: alternatives to corticosteroids. *Paediatric Drugs* 2002;**4**:381–9