Anti-inflammatory approaches to cystic fibrosis airways disease

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Purpose of review

Therapy aimed at combating excessive lung inflammation should benefit patients with cystic fibrosis. This article reviews anti-inflammatory strategies, focusing on new evidence published since 2006.

Recent findings

Use of oral corticosteroids was associated with benefit in an epidemiological study but they are still not recommended; high dose inhaled corticosteroids may cause harm (effect on growth), but they can safely be withdrawn in many patients. Some small beneficial effect of ibuprofen was seen in a multicentre study, but it is unlikely that this will change practice. Altering the imbalance seen in fatty acid metabolism with ω3 polyunsaturated fatty acid supplementation may be helpful but therapeutic benefit is not yet proven. Combating cysteinyl leukotrienes has potential but benefit remains to be proved. The beneficial effect of macrolides has been confirmed in patients with milder disease, but caution is needed because of emerging resistance patterns. Renewed research interest in antiproteases has not demonstrated any significant benefit.

Summary

The ideal therapeutic drug, with the optimal balance of benefit and harm, is not yet available.

Keywords

anti-inflammatory, cystic fibrosis, inflammation

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Abbreviations

BAL	bronchoalveolar lavage
DHA	docosahexaenoic acid
FEV_1	forced expiratory volume in 1 s
PUFA	polyunsaturated fatty acid

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Introduction

For more than a decade there has been controversy over whether lung inflammation is an inherent part of cystic fibrosis, or whether it is always secondary to infection (recently reviewed by Rao and Grigg [1]). For the clinician, this debate is largely irrelevant because infection is always a major target for treatment anyway. So is inflammation, albeit to a lesser extent, but unfortunately there is no ideal anti-inflammatory agent available. Interest in finding such a drug has not waned, but in the past 12 months nothing has been published that strongly supports any particular therapy. Nevertheless, this review looks at the therapeutic approaches that are available, focusing on reports published from 2006 to May 2007.

Measuring inflammation

The importance of being able to measure lung inflammation is its use as an outcome measure in clinical trials of anti-inflammatory therapy. A number of studies examining different noninvasive methods have been reported (recently reviewed by Ratjen [2]).

Exhaled nitric oxide has not been shown to be useful, and the jury is still out on exhaled breath condensate measures, particularly because cytokine levels are close to the limits of detection in condensate [3]. Induced sputum is looking encouraging in terms of reproducibility [4] and the fact that intravenous antibiotics can produce a signal (reductions in concentrations of interleukin-8 and neutrophils) [5]. Inducing sputum is more useful than it might seem, because many children do not produce sputum routinely (they are usually too young or too well), and so regular sputum collection can be problematic in trials. A large study that looked at data from four multicentre studies (which included 269 cystic fibrosis patients aged 9–54 years) [6] showed that noninduced sputum biomarkers (neutrophil counts, elastase and interleukin-8) correlated well with forced expiratory volume in 1 s (FEV_1), and there is no reason to suggest that this will not be the case with induced sputum. It was recently shown that sputum 8-iso-prostaglandin $F_{2\alpha}$ (a marker of airway oxidative stress) was significantly elevated during acute exacerbations of cystic fibrosis (but not in patients with stable disease) as compared with normal healthy control individuals (in whom sputum was induced) [7]. Both prostaglandin E_2 and cysteinyl leukotriene levels (other bioactive lipid mediators) were significantly elevated in patients with acute and stable cystic fibrosis compared with control individuals. However, although intravenous antibiotics reduced the sputum total cell counts, they did

not affect levels of 8-iso-prostaglandin $F_{2\alpha}$, prostaglandin E_2, or cysteinyl leukotrienes.

The problem with bronchoalveolar lavage (BAL), apart from its invasive nature (making repeat measures difficult in a trial), is the lack of a suitable marker of dilution. This makes repeat measurements of picomolar or micromolar concentrations of inflammatory markers in BAL less valid than many would suggest. Blood markers have also been tried, and a recent cross-sectional study conducted in adults aged over 30 years [8] showed that serum C-reactive protein and IgG (but not white cell count, neutrophil count, serum IgE, or α_1-antitrypsin) were significantly associated with FEV_1.

Corticosteroids

Corticosteroids have been tried via oral, inhaled and intravenous routes.

Oral

More than a decade ago oral corticosteroids were shown to slow progression of lung disease, but this was at too high a cost (e.g. cataracts, irreversible poor growth and impaired glucose metabolism) with long-term use [9]. Importantly, the significant adverse effects only came to light in the large multicentre study of 285 patients [10] that followed the initial encouraging and side effect-free single centre study of just 45 patients [11]. There have been no further trials, but surprisingly their use is still advocated by some. Interestingly, a recent analysis of the North American Epidemiologic Study of Cystic Fibrosis database [12•] examined the lung function of 755 children aged 6–12 years treated in cystic fibrosis centres whose average lung function fell into the upper quartile for all centres, and compared their function with that of 743 children from centres in the lower quartile. Among a number of factors, they found that in their first 3 years those children in the upper quartile had greater use of oral corticosteroids (as well as intravenous antibiotics, mast cell stabilizers and mucolytics). These cross-sectional epidemiological data can only show association, not cause, and these results are certainly not enough to recommend long-term use of oral corticosteroids. (Note that those in the lower quartile centres used more chest physiotherapy, but this does not mean that we would stop recommending its use.)

Data on short-term use or oral corticosteroids during pulmonary exacerbations are lacking, with just one abstract from Dovey *et al.*, with negative findings, presented at the North American Cystic Fibrosis Conference (St. Louis, Missouri, USA) in October 2004 (Dovey M, unpublished data, 2004). Nevertheless, they are often used in this situation, and a survey of UK chest physicians (81% response rate) [13] showed that all of the responders used corticosteroids with intravenous antibiotics during chest exacerbations, with 21% using them fairly regularly and 8% often.

Inhaled

Benefit from inhaled corticosteroids as long-term anti-inflammatory therapy has not been proved, despite a number of (often flawed) studies [14]. Despite this, their use is common, especially in children, although admittedly this is often for symptomatic wheezing. For those who are not obviously symptomatic, or in whom response has not been clearly shown, reducing the dose of and then stopping inhaled corticosteroid treatment should be considered. A recent randomized trial of withdrawal of inhaled corticosteroids in children and adults who had been taking them regularly [15••] showed that there was no increase in pulmonary exacerbations or any increase in use of antibiotics or rescue bronchodilators, and no adverse effect on lung function, in those who stopped inhaled corticosteroid treatment. The Cochrane review also concluded that there was no evidence of harm caused by inhaled corticosteroids in cystic fibrosis [14]. A recent study [16••] (not yet included in the systematic review), however, showed a significant ($P < 0.003$) slowing in linear growth in prepubertal children receiving 1000 μg/day dry powder fluticasone propionate over 12 months (mean standard deviation score −0.38) in comparison with the placebo group (mean standard deviation score −0.01). Furthermore, there was no catch-up growth in the 1–2 years after discontinuation of inhaled corticosteroids. There have been several case series published over the past few years highlighting the occasional dangers of high-dose inhaled corticosteroids in asthmatic children, including adrenal failure, coma and even death. Clearly, then, inhaled corticosteroids should not be used without proper justification.

Intravenous

Some time ago a small study [17] showed that intravenous hydrocortisone had some late (1–2 months after admission) benefit on lung function in infants receiving intravenous antibiotics for chest exacerbations, although no difference was seen during the first 10 days of the admission. There has been little else published since then on the use of intravenous corticosteroids in cystic fibrosis. A novel approach was recently used to deliver low doses of steroids for long periods, however, through infusion of autologous erythrocytes loaded with dexamethasone [18•]. In a small open label pilot study, nine patients received monthly intravenous infusions for 2 years and were compared with nine patients receiving standard therapy. In fact, 17 patients began the therapy but eight dropped out (after fewer than four cycles) because the regimen was too onerous. No steroid side effects were seen, but the FEV_1 in the experimental group exhibited a constant improvement, as compared with a gradual decrease in the standard therapy group.

The authors wish to conduct a randomized controlled trial (they calculate that 300 patients are required, although they do not state whether this takes into account the potential 50% drop-out rate), but it is highly unlikely that patients would wish to undertake this form of therapy.

Ibuprofen

The initial study indicating that high-dose ibuprofen slowed the decline in lung function in cystic fibrosis patients with mild disease was published over a decade ago. Widespread use of ibuprofen never happened, however, because of concerns over potential renal and gastrointestinal side effects, as well as logistical difficulties in measuring plasma ibuprofen levels. Although US Cystic Fibrosis Foundation registry data indicated that there was no statistically significant difference in the incidence of renal failure or gastrointestinal haemorrhage in those taking ibuprofen, the incidence of both of these was more than doubled (reviewed in Hilliard and Balfour-Lynn [19]). Recently, a report from a single centre study [20] indicated that 21 out of 51 (45%) children had to discontinue their high-dose ibuprofen because of adverse effects, the most common of which was abdominal pain.

The Cochrane systematic review [21] was encouraging, but it suggested that further and larger studies were needed. In an attempt to address this need, a multicentre Canadian study of high-dose ibuprofen in mild lung disease ($FEV_1 > 60\%$), initially reported 5 years ago, was recently published [22••]. Unfortunately, recruitment fell well below that required based on their power estimations (142 patients rather than 440). Nevertheless, there was a statistically significant, although quite small decrease in annual rate of decline of forced vital capacity (-0.07% vs. -1.62% predicted per year) but no change in FEV_1 in those taking ibuprofen. Fewer days were spent in hospital in the active group, and there was no increase in adverse effects (although one patient developed significant gastrointestinal bleeding). Despite the two major studies, it is likely ibuprofen will continue to be used by a minority of cystic fibrosis centres. Its use in the UK is even less than in the USA, and the results of the Canadian study will not change practice in our own centre, where ibuprofen is not used, apart from as occasional analgesia.

Arachidonic acid metabolism

Leukotriene B_4 is a potent neutrophil chemoattractant that is active in the airways of patients with cystic fibrosis. It was hoped that the specific leukotriene B_4 antagonist BIIL 284 BS (amelubant) would reduce airway inflammation, but a large phase II trial conducted in children and adults with mild to moderate disease was stopped prematurely because of an excess of significant adverse events (hospitalization for pulmonary exacerbations). This unexpected finding was presented at the North American Cystic Fibrosis Conference (Baltimore, Maryland, USA) in October 2005, but there has been no final publication of the data. Another way to inhibit leukotriene B_4 is by using a 5-lipoxygenase inhibitor, such as zileuton; this has not been tried in cystic fibrosis, probably because of concerns over liver toxicity.

The role of fatty acid metabolism in lung inflammation may also be relevant [23]. An imbalance in the ratio of arachidonic acid (excess) and docosahexaenoic acid (DHA) (deficiency) has been found in cystic fibrosis tissues and is believed to promote inflammation. The metabolism of arachidonic acid can be diverted from leukotriene B_4 to leukotriene B_5 with the ω-3 fatty acids eicosapentaenoic acid and DHA derived from fish oil [24]. ω-3 Fatty acid supplementation has been studied in a small number of patients with cystic fibrosis over a short duration, and there is currently insufficient evidence to draw firm conclusions. It is likely, however, that the amount that would need to be ingested for any chance of therapeutic benefit would not be tolerated [25]. In a recent small ($n = 17$), placebo-controlled study (not yet included in the Cochrane review), ω-3 polyunsaturated fatty acid (PUFA) supplementation for 6 months led to PUFAs being incorporated into peripheral blood neutrophil membranes and a significant modification in the production ratio of leukotriene B_4 : leukotriene B_5 [26•]. There was no change in interleukin-8 induced neutrophil chemotaxis, however. There was also no change in clinical parameters, although the size of the study meant that it was unlikely to show any such change. The authors concluded that ω-3 PUFA intake could modulate inflammation, and inevitably they believe that a larger trial is needed.

In a recent, even smaller study, 13 adults with cystic fibrosis were given a weekly intravenous dose of fish oil emulsion enriched with ω-3 fatty acids for 3 months [27•]. It induced a significant modification in platelet fatty acid composition but no modification of oxidative markers. In four out of 13 patients, however, it induced significant weight loss and a decreased level of reduced glutathione, which were potentially deleterious. This again shows that anti-inflammatory therapy cannot always be assumed to be beneficial. Finally, a pilot study of DHA/arachidonic acid supplemented formula milk in bottle-fed infants is underway.

Receptor antagonists of the cysteinyl leukotrienes, montelukast and zafirlukast, are used in asthma. Small exploratory studies were published a while ago (reviewed by Schmitt-Grohé and Zielen [28]), and a more recent pilot study was encouraging in terms of improved lung function and reduced inflammatory markers [29]. Larger randomized controlled trials are still lacking, however,

and so their efficacy as anti-inflammatory agents in cystic fibrosis has not been fully established. They may find a role in those patients with symptomatic cystic fibrosis asthma, and perhaps in reducing the effects of respiratory viral infections on the airways. A recent letter [30] reported a 5-year follow up in 15 out of 16 children who had been part of an earlier small study. It showed a continued decrease in eosinophilic inflammation and no change in FEV_1, but a significant increase in maximum expiratory flow 25%.

Macrolides

The beneficial effects of azithromycin in cystic fibrosis lung disease are well established, but clinical trials have failed to demonstrate a convincing direct anti-inflammatory action. An Australian study [31] found a reduction in serum C-reactive protein; a study conducted in the USA [32] found that sputum neutrophil elastase activity remained the same in the active group but increased in the placebo group, with no change in interleukin-8; and a UK study [33] demonstrated no change in sputum interleukin-8 and neutrophil elastase (in the subgroup of sputum producers). Outside their use as antibiotics, the mechanisms of action of azithromycin in cystic fibrosis are still unclear. A recent small study conducted in nine adults [34] aimed to explore possible mechanisms of action of macrolides, including the following: upregulation of cystic fibrosis transmembrane conductance regulator; upregulation of multidrug resistance proteins; improved ion transport in the absence of protein upregulation, for example by enhanced cystic fibrosis transmembrane conductance regulator trafficking or function; and reduced adherence of *Pseudomonas aeruginosa*. From their data, the authors concluded that these mechanisms were unlikely to be contributory, but they speculated that the benefit may be due to breakdown of *P. aeruginosa* biofilms by azithromycin, allowing access of antibiotics and inflammatory cells to the bacteria.

A further multicentre clinical trial on azithromycin has been conducted in France [35••]. The trial included 82 patients, aged 6–21 years, who received azithromycin three times weekly for 1 year. The main differences from previous studies were that only 25% of patients were chronically infected with *P. aeruginosa* and the study was longer. The investigators found a significant reduction in the number of pulmonary exacerbations and time to first exacerbation, and a reduction in oral antibiotic use. There was no change in FEV_1, however, most likely because recruitment failed to reach the number estimated to be able to show significance in lung function. The study demonstrated the effectiveness of azithromycin in milder lung disease. Importantly, it showed equal effectiveness in the 75% of patients free from chronic infection with *P. aeruginosa*, which is similar to the findings of the UK study [33], in which 50% of patients were free from *P. aeruginosa* (analysed but not reported at the time). This would indicate that azithromycin need not be restricted to patients positive for *P. aeruginosa* (as was the case in the US study [32]), although in practice the patients who have poorer lung function – and in whom we are more likely to use it – tend to be the older children infected with *P. aeruginosa*.

Although long-term azithromycin treatment appears to be relatively free from side effects, concerns have been expressed regarding the development of macrolide resistance. A Dutch study [36•] looked at sputum isolates from 155 patients with cystic fibrosis (41% of whom had received azithromycin at some stage) over 4 years following the introduction of azithromycin into their practice. The investigators found that erythromycin resistance in *Staphylococcus aureus* isolates increased from 7% to 54%, and clarithromycin resistance in *Haemophilus* spp. rose from 4% to 38% (although there was reduced isolation of those organisms). Resistance patterns did not change over the same time period for those organisms in patients who did not have cystic fibrosis. The authors did not comment on actual azithromycin resistance. Another Dutch study [37•] looked at *S. aureus* resistance in 100 patients with cystic fibrosis before and during 3 years of subsequent daily azithromycin therapy. The investigators found that sputum or upper airway *S. aureus* colonization rates did not change (remaining at around 50%), but before introduction of azithromycin macrolide resistance was found in only 10% of *S. aureus* strains; this rose to 83% in the first year, 97% in the second year and 100% in the third year. They also found that although lung function improved over the first year, it declined in the second and third years, and so they concluded that emergence of macrolide-resistant *S. aureus* was not related to lung function decline. This study was not designed as a prospective randomized trial of the effect of azithromycin on lung function, but nevertheless it is interesting that the initial improvement in lung function was not maintained after the first year.

Antiproteases

Antiprotease defences are overwhelmed in cystic fibrosis airways by accumulation of large quantities of harmful neutrophil-derived proteases; therefore, supplementation with exogenous antiproteases might restore the balance and perhaps limit lung damage. Several initial studies with aerosolized α_1-antitrypsin and recombinant secretory leukoprotease inhibitor were reported, which were encouraging but not taken any further [38]. There are now three recent reports, indicating renewed interest in this potential therapy.

In a small study an aerosolized therapeutic preparation of α_1-proteinase inhibitor was given to 17 adults for 10 days

[39]. Sputum neutrophil elastase activity was unchanged but there was a significant decease in sputum taurine (which can correlate with respiratory exacerbations). The decrease in taurine led the authors to suggest that even in the absence of sustained elastase inhibition, this agent may have a beneficial effect on airway inflammation (which is somewhat optimistic because a reduction in neutrophil elastase is one of the main aims of anti-inflammatory therapy). In another open-labelled study, 52 patients with cystic fibrosis aged over 8 years underwent daily inhalation of α_1-antitrypsin for 4 weeks [40••]. In sputum there were significant reductions in free elastase activity, neutrophils, proinflammatory mediators (interleukin-8, tumour necrosis factor-α, interleukin-1β and leukotriene B_4) and *P. aeruginosa* counts. There was no change in lung function, but there is no indication that the study was powered to demonstrate any such effect. Both of these studies do not really provide an answer to the question of whether antiproteases are likely to be beneficial because they were too small, too short and included no placebo arms.

The third study was a placebo-controlled pilot study of recombinant transgenic α_1-antitrypsin [41•]. Daily nebulized treatment was given for 4 weeks to 39 adults with cystic fibrosis, followed by 2–4 weeks washout then a 2-week re-challenge phase. The drug was well tolerated and there were no allergic effects, but the study failed to demonstrate significant differences in elastase activity, other inflammatory markers, or lung function. Unfortunately, this essentially negative study is in keeping with the previous larger 6-month study of 131 children and adults, in whom there was only a trend toward improvement in lung function and exacerbations (reported at the North American Cystic Fibrosis Conference, Seattle, Washington, USA in October 1999, but not yet published).

A number of synthetic antiprotease compounds have been produced (e.g. oral DMP777 or nebulized FK706), but after initial encouraging data were reported, nothing further has been published and they seem to have disappeared from the research agenda. A more recent synthetic compound is EPI-hNE4 (depelstat), a potent inhibitor of human neutrophil elastase, which is thought to be of potential use as an aerosol in patients with cystic fibrosis [42]. Clinical studies have been conducted and results are awaited. It would be a shame if a large randomized controlled trial of an antiprotease never took place, as a result of negative smaller pilot studies that were never powered to show major differences, particularly in lung function. Nevertheless, it may be that neutrophil elastase levels are simply too great in patients with established lung disease, and that this form of therapy can only work in young patients with relatively clear lungs.

Miscellaneous

A number of other agents have been evaluated, none of which has been subject to proper randomized controlled trials; these include oral cyclosporin, aerosolized reduced glutathione and intravenous immunoglobulin [19]. The US Cystic Fibrosis Foundation website lists a number of ongoing studies of other types of anti-inflammatory therapy. These include pilot studies of simvastatin (conducted to determine whether it leads to an increase in nitric oxide production in the cystic fibrosis lung), pioglitazone (currently used in type II diabetes), hydroxychloroquine and low-dose methotrexate.

Neutrophils release excessive amounts of oxidants in cystic fibrosis airways, and this contributes to the systemic redox imbalance observed in cystic fibrosis. Blood neutrophils are deficient in the antioxidant glutathione, and in a phase I trial [43] it has been shown that this deficiency can be corrected by giving the glutathione prodrug oral *N*-acetylcysteine at high doses for 4 weeks. Importantly, neutrophil counts in induced sputum were reduced, and sputum elastase levels were markedly reduced. Predictably, in a short-term study of only 18 patients, lung function was not altered. A phase II study testing the clinical effectiveness of oral *N*-acetylcysteine has now completed enrolment.

Conclusion

Evidence for benefit of an anti-inflammatory regimen must be weighed against potential for harm, and it is clear that the ideal agent is not yet available. One obstacle is that even if a new form of therapy is shown to reduce lung inflammation, and there is no resultant decrease in symptoms and exacerbations, or improvement in lung function, it will be difficult to persuade patients to take the treatment. This is especially so if the treatment is inconvenient (such as a daily nebulizer) or has potential adverse effects. Even adherence to a simple therapy, such as twice daily inhaled corticosteroids, is likely to be low if no immediate benefit is felt by the patient. Indeed, the Cystic Fibrosis Withdrawal of Inhaled Steroids Evaluation study [15••], which took the novel approach of withdrawing a treatment that the patients had been taking for a while, did not have trouble with recruitment because of patients' concerns over stopping an established treatment. Importantly, the results indicated that inhaled corticosteroids could safely be discontinued in the majority of patients.

Anti-inflammatory therapy is likely to have its best effects in healthier lungs, with the main objective being to prevent inflammatory damage in the first place. It is probably too late in the more severe lung disease that is often seen in young adults. This means that clinical

trials must be conducted in young children – the very group in whom many of the traditional outcomes are harder or impossible to measure. A final note of caution is that a degree of inflammation is a valuable part of the host defence against infection; cystic fibrosis patients do not die from overwhelming pseudomonal or staphylococcal sepsis. It may be that total eradication of the inflammatory response using, for example, potent anticytokine monoclonal antibodies, will have significant harmful effects. Even the selective but potent leukotriene B_4 antagonist BIIL 284 BS had unexpected significant adverse effects. Therapies must be rigorously tested in large trials before their widespread use; otherwise, some of the longer term side effects may not come to light, as exemplified by the experience with alternate day high-dose oral corticosteroids.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 556–557).

1 Rao S, Grigg J. New insights into pulmonary inflammation in cystic fibrosis. Arch Dis Child 2006; 91:786–788.

2 Ratjen F. What's new in CF airway inflammation: an update. Paediatr Respir Rev 2006; 7 (Suppl 1):S70–S72.

3 Robroeks CM, Jobsis Q, Damoiseaux JG, *et al.* Cytokines in exhaled breath condensate of children with asthma and cystic fibrosis. Ann Allergy Asthma Immunol 2006; 96:349–355.

4 Ordonez CL, Kartashov AI, Wohl ME. Variability of markers of inflammation and infection in induced sputum in children with cystic fibrosis. Pediatr 2004; 145:689–692.

5 Ordonez CL, Henig NR, Mayer-Hamblett N, *et al.* Inflammatory and microbiologic markers in induced sputum after intravenous antibiotics in cystic fibrosis. Am J Respir Crit Care Med 2003; 168:1471–1475.

6 Mayer-Hamblett N, Aitken ML, Accurso FJ, *et al.* Association between pulmonary function and sputum biomarkers in cystic fibrosis. Am J Respir Crit Care Med 2007; 175:822–828.

7 Reid DW, Misso N, Aggarwal S, *et al.* Oxidative stress and lipid-derived inflammatory mediators during acute exacerbations of cystic fibrosis. Respirology 2007; 12:63–69.

8 Levy H, Kalish LA, Huntington I, *et al.* Inflammatory markers of lung disease in adult patients with cystic fibrosis. Pediatr Pulmonol 2007; 42:256–262.

9 Cheng K, Ashby D, Smyth R. Oral steroids for cystic fibrosis. Cochrane Database Syst Rev 2000, 2:CD000407.

10 Eigen H, Rosenstein BJ, FitzSimmons S, Schidlow DV, Cystic Fibrosis Foundation Prednisone Trial Group. A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. J Pediatr 1995; 126:515–523.

11 Auerbach HS, Williams M, Kirkpatrick JA, Cotten HR. Alternate day prednisolone reduces the morbidity and improves pulmonary function in cystic fibrosis. Lancet 1985; ii:686–688.

12 • Padman R, McColley SA, Miller DP, *et al.* Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Infant care patterns at epidemiologic study of cystic fibrosis sites that achieve superior childhood lung function. Pediatrics 2007; 119:e531–e537.

This report provides interesting data on a large number of children, but inevitably it highlights associations with a number of possible explanations, rather than proving causation. Its findings should not be used to recommend long-term use of oral corticosteroids.

13 Hester KL, Powell T, Downey DG, *et al.* Glucocorticoids as an adjuvant treatment to intravenous antibiotics for cystic fibrosis pulmonary exacerbations: a UK survey. J Cyst Fibros 2007; 6:311–313.

14 Balfour-Lynn I, Walters S, Dezateux C. Inhaled corticosteroids for cystic fibrosis. Cochrane Database Syst Rev 2000, 2:CD001915.

15 •• Balfour-Lynn IM, Lees B, Hall P, *et al.* CF WISE (Withdrawal of Inhaled Steroids Evaluation) Investigators. Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis. Am J Respir Crit Care Med 2006; 173:1356–1362.

Inhaled corticosteroids are probably over-used in cystic fibrosis. This novel approach of placebo-controlled withdrawal of a long-term therapy was well received by patients at recruitment. The results highlighted that we should consider reducing doses or stopping inhaled corticosteroids altogether, in a similar approach to that taken in asthma clinics.

16 •• De Boeck K, De Baets F, Malfroot A, *et al.* Do inhaled corticosteroids impair long-term growth in prepubertal cystic fibrosis patients? Eur J Pediatr 2007; 166:23–28.

This is an important paper because although it was a relatively small trial, it proved that high dose inhaled corticosteroids can cause harm in children with cystic fibrosis.

17 Tepper RS, Eigen H, Stevens J, *et al.* Lower respiratory illness in infants and young children with cystic fibrosis: evaluation of treatment with intravenous hydrocortisone. Pediatr Pulmonol 1997; 24:48–51.

18 • Lucidi V, Tozzi AE, Bella S, *et al.* A pilot trial on safety and efficacy of erythrocyte-mediated steroid treatment in CF patients. BMC Pediatr 2006; 6:17.

The approach presented is certainly novel, and it is probably too onerous for patients. Nevertheless, the concept may prove to be useful with time, perhaps using other agents.

19 Hilliard TN, Balfour-Lynn IM. Anti-inflammatory agents: a clinical perspective. In: Bush A, editor. Progress in respiratory research: cystic fibrosis. Basel: S Karger AG; 2005. pp. 187-194.

20 Fennell PB, Quante J, Wilson K, *et al.* Use of high-dose ibuprofen in a pediatric cystic fibrosis center. J Cyst Fibros 2007; 6:153–158.

21 Dezateux C, Crighton A. Oral nonsteroidal anti-inflammatory drug therapy for cystic fibrosis. Cochrane Database Syst Rev 2000, 2:CD001505.

22 •• Lands LC, Milner R, Cantin AM, *et al.* High-dose ibuprofen in cystic fibrosis: Canadian safety and effectiveness trial. J Pediatr 2007 [Epub ahead of print].

This large (but under-powered) study showed that high-dose ibuprofen might have a small benefit in mild to moderate disease. It is unlikely that the results are convincing enough to change practice by persuading more clinicians to use this form of therapy.

23 Van Biervliet S, Van Biervliet JP, Robberecht E, *et al.* Docosahexaenoic acid trials in cystic fibrosis: a review of the rationale behind the clinical trials. J Cyst Fibros 2005; 4:27–34.

24 Konstan MW, Davis PB. Pharmacological approaches for the discovery and development of new anti-inflammatory agents for the treatment of cystic fibrosis. Adv Drug Deliv Rev 2002; 54:1409–1423.

25 Beckles Willson N, Elliott TM, Everard ML. Omega-3 fatty acids (from fish oils) for cystic fibrosis. Cochrane Database Syst Rev 2002, 3:CD002201.

26 • Panchaud A, Sauty A, Kernen Y, *et al.* Biological effects of a dietary omega-3 polyunsaturated fatty acids supplementation in cystic fibrosis patients: a randomized, crossover placebo-controlled trial. Clin Nutr 2006; 25:418–427.

This study is small but it provides proof of concept that ω-3 PUFAs may have an anti-inflammatory role, although it is a long way from proving real therapeutic benefit.

27 • Durieu I, Vericel E, Guichardant D, *et al.* Fatty acids platelets and oxidative markers following intravenous n-3 fatty acids administration in cystic fibrosis: An open pilot observational study. J Cyst Fibros 2007 [Epub ahead of print].

This report is important because it shows a potential deleterious effect of an anti-inflammatory approach.

28 Schmitt-Grohé S, Zielen S. Leukotriene receptor antagonists in children with cystic fibrosis lung disease: anti-inflammatory and clinical effects. Paediatr Drugs 2005; 7:353–363.

29 Stelmach I, Korzeniewska A, Stelmach W, *et al.* Effects of montelukast treatment on clinical and inflammatory variables in patients with cystic fibrosis. Ann Allergy Asthma Immunol 2005; 95:372–380.

30 Schmitt-Grohé S, Eickmeier O, Naujoks C, *et al.* Effects of long-term treatment with montelukast in mild cystic fibrosis (long term treatment with montelukast in cystic fibrosis). Respir Med 2007; 101:684.

31 Wolter J, Seeney S, Bell S, *et al.* Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. Thorax 2002; 57:212–216.

32 Saiman L, Marshall BC, Mayer-Hamblett N, *et al.* Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA 2003; 290:1749–1756.

33 Equi A, Balfour-Lynn IM, Bush A, *et al.* Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. Lancet 2002; 360:978–984.

34 Equi AC, Davies JC, Painter H, *et al.* Exploring the mechanisms of macrolides in cystic fibrosis. Respir Med 2006; 100:687–697.

35 •• Clement A, Tamalet A, Leroux E, *et al.* Long term effects of azithromycin in patients with cystic fibrosis: A double blind, placebo controlled trial. Thorax 2006; 61:895–902.
This trial proved benefit of azithromycin over 1 year in a group of patients with milder disease than previously studied, in terms of exacerbations. It was underpowered to show a difference in lung function, but it confirms previous work; it is unlikely to change practice.

36 • Phaff SJ, Tiddens HA, Verbrugh HA, *et al.* Macrolide resistance of *Staphylococcus aureus* and *Haemophilus* species associated with long-term azithromycin use in cystic fibrosis. J Antimicrob Chemother 2006; 57:741–746.
This report provides a note of caution regarding widespread use of azithromycin, with marked increase in resistance patterns of *S. aureus* and *Haemophilus* spp. The report is unlikely to stop azithromycin use, but the effects on other organisms must at least be considered.

37 • Tramper-Stranders GA, Wolfs TF, Fleer A, *et al.* Maintenance azithromycin treatment in pediatric patients with cystic fibrosis: long-term outcomes related to macrolide resistance and pulmonary function. Pediatr Infect Dis J 2007; 26:8–12.
The report presents similar concerns over emerging resistance. The authors also found that improvement in lung function was not sustained beyond the first year, although the study was not designed to look for this.

38 Balfour-Lynn IM. The protease-antiprotease battle in the cystic fibrosis lung. J R Soc Med 1999; 92 (Suppl 37):23–30.

39 Cantin AM, Berthiaume Y, Cloutier D, *et al.* Prolastin aerosol therapy and sputum taurine in cystic fibrosis. Clin Invest Med 2006; 29:201–207.

40 •• Griese M, Latzin P, Kappler M, *et al.* α_1-Antitrypsin inhalation reduces airway inflammation in cystic fibrosis patients. Eur Respir J 2007; 29:240–250.
Rekindling interest in aerosolized α_1-antitrypsin, this study again demonstrated reduced lung inflammation, but it was under-powered to show clinical benefit. Will a large trial ever take place?

41 • Martin SL, Downey D, Bilton D, *et al.,* Recombinant AAT CF Study Team. Safety and efficacy of recombinant alpha$_1$-antitrypsin therapy in cystic fibrosis. Pediatr Pulmonol 2006; 41:177–183.
This study is important because it demonstrated safety of transgenic sheep-derived α1-antitrypsin; unfortunately, it does not appear to work too effectively.

42 Attucci S, Gauthier A, Korkmaz B, *et al.* EPI-hNE4, a proteolysis-resistant inhibitor of human neutrophil elastase and potential anti-inflammatory drug for treating cystic fibrosis. J Pharmacol Exp Ther 2006; 318:803–809.

43 Tirouvanziam R, Conrad CK, Bottiglieri T, *et al.* High-dose oral N-acetylcysteine, a glutathione prodrug, modulates inflammation in cystic fibrosis. Proc Natl Acad Sci USA 2006; 103:4628–4633.