REVIEW SERIES

Exacerbations in cystic fibrosis: 2 · Prevention

Scott C Bell, Philip J Robinson

Thorax 2007;**62**:723–732. doi: 10.1136/thx.2006.060897

The life span of people with cystic fibrosis (CF) has increased dramatically over the past 50 years. Many factors have contributed to this improvement. Respiratory exacerbations of CF lung disease are associated with the need for hospitalisation and antibiotic treatment, reduction in the quality of life, fragmented sleep and mortality. A number of preventive treatment strategies have been developed to reduce the frequency and severity of respiratory exacerbations in CF including mucolytic agents, physiotherapy and exercise, antibiotics, nutritional strategies, anti-inflammatory treatments and vaccinations against common respiratory pathogens. The evidence for each of these treatments and their potential impact is discussed.

Dramatic improvement in survival from cystic fibrosis (CF) has occurred over the past 50 years. The median survival of children born in the 1990s is estimated to exceed 40 years, and more than 85% of children will reach adulthood and will require transition to adult CF care.[1 2] More than 90% of the mortality and most of the morbidity from CF are related to the consequences of suppurative lung disease. A number of factors have been suggested to be responsible for improved clinical outcomes for people with CF, including improved management of the neonatal complication meconium ileus, introduction of more effective formulations of pancreatic enzymes and aggressive nutritional support, the advent of newer and more effective mucolytic agents, airway clearance techniques, antibiotic treatment regimens and the establishment of centre-based care for patients with CF.[3–5] These changes in management may also have contributed to the reduction in the rate of decline of lung function in both children and adults with CF which have recently been reported.[6 7]

Respiratory exacerbations of CF lung disease have been associated with increased mortality,[8] hospitalisation (and the associated patient and family dislocation), increased health costs,[9 10] sleep disturbance[11] and reduced quality of life.[12] Annual rates of hospitalisation for patients with CF attending individual CF centres in the USA range widely from 4% to 78% of children with CF (median ~35%) and from zero to 85% (median ~45%) of adults with CF.[13] Most hospital admissions were for treatment of respiratory exacerbations, particularly the treatment of *Pseudomonas aeruginosa* infection. The prevalence of *P aeruginosa* in the USA in young children is approximately 30%, increasing to 80% in adults with CF.[13]

The management of chronic bacterial infection and complicating respiratory exacerbations in patients with CF is a major component of healthcare delivery at paediatric and, particularly, adult CF centres. Strategies to reduce the frequency and severity of respiratory exacerbations are vital to ensure continued advances in clinical outcomes.

This review summarises the evidence currently available for therapeutic interventions which may reduce the number or severity of respiratory exacerbations for people with CF (online data supplement available at http://thorax.bmj.com/supplemental).

METHODS

The authors performed a search of the Cochrane database of systematic reviews in May 2006 for clinical intervention trials in patients with CF focusing on mucolytic agents, physiotherapy, exercise, antibiotics, anti-inflammatory and nutrition support therapies, newborn screening and vaccinations. Thirteen Cochrane reviews were identified and are included in this review paper.[14–26] The reference lists of included and excluded studies in each of the Cochrane reviews were also reviewed for RCTs which addressed the above topics and included where appropriate. A MEDLINE search was also performed including the terms "cystic fibrosis", "systematic reviews" and "clinical trials"; any studies not previously identified were analysed for evidence with respect to respiratory exacerbations in CF.

Most of the studies cited in this review have not explicitly studied either the frequency or severity of respiratory exacerbations. Furthermore, the definition of respiratory exacerbations is not always provided and, where it is, different parameters have been applied. In recent large multicentre clinical trials, definitions are increasingly being applied as reviewed by Goss and Burns.[27] Most studies provide data regarding hospitalisation episodes, duration of hospitalisation (hospital days), parenteral antibiotic episodes and/or the duration of parenteral antibiotics. We have elected to include these measures as estimates of respiratory exacerbations (frequency and/or severity) when specific information is not available. Where protocol definitions of exacerbations are given, this is explicitly stated within this review.

PREVENTION OF RESPIRATORY EXACERBATIONS

Mucolytic agents

The chronic endobronchial sepsis and profuse airway secretions which dominate pulmonary

Abbreviations: CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity

See end of article for authors' affiliations

Correspondence to: Dr S C Bell, Adult Cystic Fibrosis Centre, The Prince Charles Hospital, Rode Road, Chermside, Brisbane 4032, Australia; scott_bell@health.qld.gov.au

Received 10 August 2006
Accepted 31 January 2007

disease in CF make the use of mucolytic agents an appealing treatment. Mucolytic agents given as part of chronic maintenance treatment could conceptually be hoped to be effective in reducing acute exacerbations; however, until the last decade there was little evidence of this benefit.

N-Acetylcysteine

In a review of inhaled N-acetylcysteine treatment published in 1999, Duijverstijn and Brand[28] found no benefit on lung function in short-term trials. Long-term trials have not been conducted, and there is therefore no evidence that long-term nebulised treatment with N-acetylcysteine is effective in reducing the number of episodes or severity of respiratory exacerbations in patients with CF.

Recombinant human deoxyribonuclease (rhDNase)

In 1994 Fuchs *et al*[29] reported a randomised, double blind, placebo-controlled study involving two dosing regimens (once and twice daily) of rhDNase in 968 adults and children with CF. The mean (SD) age of the participants was 18.7 (9.0) years (range 5–54) with mean forced expiratory volume in 1 s (FEV_1) 61% predicted and forced vital capacity (FVC) 78% predicted. All patients received treatment for 24 weeks and the incidence of respiratory exacerbations (defined by protocol) was considered a secondary efficacy end point of the trial. One or more exacerbations occurred in 27% of patients given placebo, 22% in the group receiving once daily rhDNase and 19% in the group receiving twice daily rhDNase. The risk of an exacerbation was reduced by 22% with rhDNase once daily (relative risk 0.78, 95% CI 0.57 to 1.06; $p = 0.11$) and by 34% with rhDNase twice daily (relative risk 0.66, 95% CI 0.48 to 0.91; $p = 0.01$). Compared with placebo, the administration of rhDNase once or twice daily reduced the age-adjusted risk of respiratory exacerbations by 28% (relative risk 0.72, 95% CI 0.52 to 0.98; $p = 0.04$) and 37% (relative risk 0.63, 95% CI 0.46 to 0.87; $p<0.01$) respectively.

In a similar study, Quan *et al* reported the use of rhDNase in a 96-week randomised, double blind, placebo-controlled multicentre international trial (PEIT study) involving 574 patients (239 rhDNase and 235 placebo) from 49 CF centres.[30] Children aged 6–10 years with well preserved lung function (FVC >85% predicted) were enrolled in the trial. The incidence of respiratory exacerbations was a secondary efficacy end point. rhDNase decreased the risk of respiratory exacerbations by 34% compared with the placebo group (relative risk 0.66, 95% CI 0.44 to 1.00; $p = 0.48$). The time to first event analysis (respiratory exacerbations defined by protocol) showed that patients receiving rhDNase had a lower risk of exacerbations throughout the 96-week study; 40 patients (17%) in the rhDNase group had 62 respiratory exacerbations (28 in the first 48 weeks and 34 after week 48) and 56 patients (24%) in the placebo group had 92 exacerbations (47 in the first 48 weeks and 45 after week 48). The statistical significance of these results was not reported in the paper.

There is no evidence that rhDNase is effective in preventing pulmonary exacerbations in patients with severe or advanced CF lung disease.[31] A 12-week study examining the effect of inhaled rhDNase in a group of 320 patients with advanced lung disease (FEV_1 <40% predicted) showed that, while patients receiving rhDNase had a statistically greater improvement in FEV_1 from baseline than those patients receiving placebo (9.4% increase vs 2.1%; $p<0.001$), there were no differences between treatment groups in dyspnoea score, number of days receiving intravenous antibiotics or length of hospital stay.[31]

Shah *et al* reported a case-control study with rhDNase, evaluating the impact of disease progression over a 4-year period.[32] Thirty-eight patients were divided into two groups—those who received rhDNase and those who did not—and the two groups were matched for pulmonary function, age and gender. More respiratory exacerbations per patient-year were occurred in the control group (3.13, 95% CI 1.25 to 4.25) than in the recombinant rhDNase group (1.25, 95% CI 0.63 to 3.0, $p = 0.035$) over the 4-year treatment period. Similarly, intravenous antibiotic requirements were greater with a median use of 43.75 (17.5–60.0) days per patient in the control group compared with 16.25 (8.5–44.0) days per patient in the rhDNase group ($p = 0.034$).

These studies would suggest that rhDNase usage is effective in reducing the short-term incidence of respiratory exacerbations in patients with CF with mild to moderate lung disease. The long-term impact of this reduction has not yet been established, and no similar data exist as yet in children under the age of 5 years.

Hypertonic saline

Inhaled hypertonic saline has been shown to increase mucociliary clearance and, in short-term trials, to produce improvements in lung function in people with CF.[33] In a Cochrane review of inhaled hypertonic saline therapy in CF, Wark and colleagues examined the results from nine trials including a total of 235 patients; however, none of these short-term trials used respiratory exacerbations as a primary or secondary efficacy end point.[34] In a comparative crossover trial of nebulised hypertonic saline with nebulised rhDNase, Suri reported that 48 patients received, in random order, 12-week treatments of either once daily rhDNase (2.5 mg), alternate day rhDNase (2.5 mg) and twice daily 7% hypertonic saline (5 ml).[35] During hypertonic saline, daily rhDNase and alternate day rhDNase treatments, 15, 18 and 17 children had one or more pulmonary exacerbations. There was no evidence of differences between treatments.[35]

Elkins *et al* have recently reported the results from a 1-year double blind, parallel group trial of 164 patients with CF over the age of 6 years who were randomised when clinically stable.[36] The mean age of the study participants was 18.5 years, mean FEV_1 was 74% predicted and FVC was 86% predicted. Patients received either 7% hypertonic saline (4 ml) or 0.9% physiological saline (4 ml) twice daily. In this study two definitions of respiratory exacerbations were used. The first was the clinical need for intravenous antibiotics as indicated by the presence of 4 of 12 possible signs or symptoms including change of sputum (volume or colour), new or increased haemoptysis, increased cough, increased dyspnoea, malaise, fatigue, lethargy, pyrexia (>38℃), anorexia or weight loss, sinus pain or tenderness, change of sinus discharge, change of findings on chest examination, decrease in pulmonary function of >10% or radiographic changes of pulmonary infection. The secondary definition consisted of the presence of any 4 of these 12 symptoms and signs regardless of any treatment subsequently given to the patient.

The hypertonic saline treated group had significantly fewer respiratory pulmonary exacerbations (relative reduction 56%, $p = 0.02$)) and a significantly higher percentage of patients without exacerbations (76% compared with 62% in the control group, $p = 0.03$). Fewer exacerbations requiring intravenous antibiotic therapy were seen in the group treated with hypertonic saline than in the control group. The mean number of exacerbations per participant in the control group was 0.89 compared with 0.39 in the hypertonic saline group ($p = 0.02$). The mean number of days in which participants met the exacerbation definition was 17 days in the control group and 6 days in the hypertonic saline group. The interval during which participants remained free of exacerbations was significantly longer in the hypertonic saline group than in the control group ($p<0.001$) with a 48-week exacerbation-free

survival rate of 76% in the hypertonic saline group and 62% in the control group.

When exacerbations were defined according to signs and symptoms alone, regardless of resultant treatment, the results again favoured the hypertonic saline group. The mean number of exacerbations defined were 2.7 per participant in the control group and 1.3 in the hypertonic saline group (mean difference 1.4, 95% CI 0.9 to 2.0; p<0.001). The mean number of days during which participants met the criteria for a symptom-defined exacerbation was 69 days in the control group and 22 days in the hypertonic saline group (mean difference 47 days, 95% CI 30 to 63; p<0.001). The time participants remained free of exacerbations was significantly longer in the hypertonic saline group with a 48-week exacerbation-free survival rate of 41% in the hypertonic saline group and 16% in the control group (p<0.001). These effects of hypertonic saline on exacerbations did not differ significantly between participants who were also prescribed rhDNase and those who were not. Participants in the hypertonic saline group had significantly fewer days on which they were absent from school or work or unable to participate in other usual activities than those in the control group (7 days vs 24 days; p<0.001).

This study suggests that, in addition to significant improvements in lung function, long-term hypertonic saline reduces respiratory exacerbation episodes and the treatment required to control them. Whether the results of this trial are sufficient to allow extrapolation to other groups of patients with CF not included in the trial (such as those under the age of 6 years and those with severe lung disease) is as yet unclear.

Physiotherapy and exercise

The impaired clearance of abnormally viscous airway secretions has long been recognised as a key feature of the lung disease in CF, and attempts to promote airway clearance through either exercise or physiotherapy remain foundation treatments for patients with CF.

Bradley and colleagues have recently reviewed the evidence for these treatments in five Cochrane reviews.[16 18 20 21 25 37] Little evidence at present exists from well conducted trials on the efficacy of regular airway clearance techniques in patients, particularly young infants with minimal lung disease, in the prevention of respiratory exacerbations. Their review described seven studies which included 231 participants. While the studies provided some limited evidence from both short-term and long-term studies that aerobic or anaerobic physical training had a positive effect on primary outcomes such as exercise capacity, strength and lung function, no randomised controlled trials have examined the influence of physical therapy on altering the rate of respiratory exacerbations.

In several studies, conventional chest physiotherapy has been compared with alternative methods of airway clearance including high frequency chest compression, manual or acoustic percussion, forced expiration technique, airway isolating devices or exercise. Most of these studies have not considered the effect of these therapies on the frequency of respiratory exacerbations. Reisman and colleagues conducted a 3-year prospective study which compared the effects of postural drainage accompanied by percussion and the forced expiratory technique with the effect of the forced expiratory technique alone.[38] Patients who performed the forced expiratory technique alone had mean annual rates of decline that were significantly different from zero for FEV_1 (p<0.001), forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75}$) (p<0.001), and Shwachman clinical score (p<0.004). In the group performing conventional physiotherapy with percussion and postural drainage, only the mean annual rate of decline in $FEF_{25–75}$ was significantly different from zero (p<0.03), and it was significantly different from the mean rate of decline associated with the forced expiratory technique alone (p<0.04). There was no difference between the two groups in the number of hospital admissions or the number of oral and intravenous antibiotics. Homnick *et al* reported the results of a 6-month parallel trial of an intrapulmonary percussive ventilator versus standard manual chest physiotherapy in 16 children and adults with CF.[39] No differences were found between the two groups in the number of hospital admissions or the use of oral or intravenous antibiotic therapy.

McIlwaine and colleagues examined the long-term effects of physiotherapy with an isolating positive pressure device (flutter) compared with physiotherapy with the use of a positive expiratory pressure (PEP) mask in 40 children with CF over a 12-month period.[40] Patients treated with the flutter device showed a greater mean annual rate of decline in FVC than the PEP group. There was a significant increase in the rate of hospital admissions in the group treated with the flutter device compared with the PEP group (18 vs 5 admissions; p = 0.03).

Several trials have examined the efficacy of the addition of exercise to airway clearance therapy. Schneiderman-Walker evaluated the effect of a 3-year home exercise programme on pulmonary function and exercise tolerance in 72 patients with mild to moderate lung disease aged 7–19 years.[41] Patients were randomly assigned to an exercise group receiving a minimum of 20 min aerobic exercise three times weekly or a control group who conducted only usual physical activity. The control group had a greater annual decline in FVC % predicted than the exercise group. No significant difference was found in the number of acute exacerbations requiring admission to hospital between the two groups. The effects of anaerobic training on respiratory exacerbations in patients with CF have not been examined. In 2004 Klijn *et al*[42] reported the results of a 12-week study examining the effects of anaerobic training in children with CF. Twenty patients were randomly assigned to either a training group or control group. The training group trained for 2 days a week for the 12-week period with each session lasting 30–45 min, whereas control subjects were directed not to change their normal daily activities. The training programme consisted of a set of eight basic training sessions that were repeated every 4 weeks and supervised by the child's own physiotherapist. Aerobic performance and quality of life were significantly improved in patients in the training group, but no significant changes were seen in other parameters. No specific comments relating to the rate of respiratory exacerbations were offered by the authors.

Antibiotics

Several strategies of antibiotic treatment to reduce respiratory exacerbations are explored in this section, including the evidence for prevention of *Staphylococcus aureus* infection in young children with CF, treatment of early *Pseudomonas aeruginosa* infection (first isolation), the effect of nebulised antibiotics, the role of macrolide antibiotics and the timing of parenteral antibiotics.

Antistaphylococcal treatment

Staphylococcus aureus is a common early pathogen in young children with CF,[43] and the administration of specific anti-staphylococcal antibiotics including flucloxacillin and cephalosporins is common practice in many CF centres.[13 44 45] Despite this, concerns remain that *S aureus* prophylaxis may predispose to the acquisition of *P aeruginosa* infection.[46] The effect of treatment on *P aeruginosa* infection rates is supported by several other studies in which *S aureus* prophylaxis has been associated with increased *P aeruginosa* isolation.[47 48] In their recent Cochrane review, Smyth and Wolter identified four studies involving 401 children with CF who received oral prophylactic

antistaphylococcal antibiotics or ''as required'' antibiotics for at least 1 year.[23 49–52] The major findings of this review were that fewer children receiving antistaphylococcal antibiotics had evidence of *S aureus* in airway secretions and there was a trend towards a higher rate of *P aeruginosa* infection from 4 to 6 years.[23]

Respiratory exacerbations (number or duration) were not specifically assessed in this review.[23] However, the number of patients requiring hospitalisation and days of hospitalisation were compared in three of the studies. No difference was found in either of these end points between those receiving antistaphylococcal prophylaxis and those receiving ''as required'' antibiotics: weighted mean difference in proportion of participants admitted to hospital during the trials 0.96 (95% CI 0.50 to 1.86); weighted mean difference in mean number of days in hospital 0.88 (95% CI −1.35 to 3.10). Smyth[53] has argued that the evidence for the benefits of *S aureus* prophylaxis remains inconclusive and has highlighted the need for additional carefully designed studies.

Treatment of *Pseudomonas aeruginosa* in young children (first isolation)

Valarius reported the successful eradication of *P aeruginosa* with 3 months of oral ciprofloxacin and nebulised colomycin (colistin).[54] In this study, treated patients were compared with historical controls managed at the same CF centre. Since this early report, strategies to prevent chronic *P aeruginosa* infection have been subject to intense investigation during the past 20 years,[55–58] and several longitudinal studies are ongoing (C E Wainwright and P J Robinson, personal communication).

In their Cochrane review, Wood and Smyth identified 15 trials, of which three were included in their analysis.[26] The authors concluded that there was evidence that antibiotic treatment (including quinolones, nebulised colistin and tobramycin) of early *P aeruginosa* infection results in short-term eradication, but the long-term clinical benefit remains to be established.[55 57] None of the studies analysed in the Cochrane review reported the effect of treatment on respiratory exacerbations, so it is not clear at present whether aggressive early treatment of initial *P aeruginosa* isolation prevents respiratory exacerbations.

Nebulised antipseudomonal antibiotics

A meta-analysis has recently been performed examining the effect of nebulised antipseudomonal antibiotics in patients with CF.[22 59] The Cochrane review included 14 trials involving 1100 patients.[22] In 13 randomised (or quasi-randomised) trials including 985 participants, nebulised antipseudomonal antibiotics were compared with placebo (or usual treatment). Notably, one trial contributed more than 50% of the total patients included in the meta-analysis. The primary outcomes of this Cochrane review were changes in lung function (FVC, FEV_1) and respiratory exacerbations (which included protocol-defined respiratory exacerbations, hospitalisation episodes, or parenteral antibiotic episodes). The authors concluded that nebulised antipseudomonal antibiotics improved lung function; however, there were wide variations in dosing regimens and administration which limited the ability for pooling of studies for analysis, including the effect of exacerbations of respiratory infections.[22]

The largest study in this review included a protocol definition for respiratory exacerbations (hospitalisation and/or need for parenteral antipseudomonal antibiotics).[60] The primary end point was change in FEV_1 % predicted. Treatment with tobramycin resulted in a mean increase of 10% in FEV_1 compared with a 2% decline in those receiving placebo ($p<0.001$). The effect of tobramycin on hospital admissions and respiratory exacerbations was reported in detail. Participants receiving tobramycin were less likely to require intravenous antipseudomonal antibiotics than the placebo group (26%, 95% CI 2% to 43%) and were less likely to be admitted to hospital (36%, 95% CI 17% to 51%). Participants in the tobramycin group received intravenous antipseudomonal antibiotics for an average of 9.6 days compared with 14.1 days in the placebo group. A smaller proportion of participants in the tobramycin group received one or more courses of intravenous antipseudomonal antibiotics than in the placebo group (39% vs 45%).[60]

The potential long-term consequences of nebulised antipseudomonal antibiotics remain unknown—particularly the effect on microbiological airway flora—and require ongoing study.[61]

Macrolides

Early reports of the benefit of azithromycin[62] led to several randomised controlled trials in paediatric and adult CF populations.[63–65] Short-term azithromycin administered for up to 6 months improves lung function and quality of life and reduces systemic markers of inflammation.[24] As hospital admissions were examined in different time scales (3 and 6 months), it was not possible to combine these data in a meta-analysis.[24] The effect of azithromycin on the number and length of hospital admissions and parenteral antibiotic episodes was reported in each of the studies.

In a crossover paediatric study from the UK, azithromycin reduced oral antipseudomonal antibiotics but no effect was seen on parenteral antibiotic courses during active drug treatment.[63] A study from the USA found that participants in the azithromycin group had less risk of experiencing an exacerbation (defined as either parenteral antipseudomonal antibiotics or >7 days of treatment with oral quinolone) than participants in the placebo group (relative risk 0.65, 95% CI 0.44 to 0.95; $p = 0.03$).[64 66] There was also a reduction in the number of participants admitted to hospital (relative risk reduction 0.46, 95% CI 0.04 to 0.85).[66] The azithromycin group experienced a 47% reduction in hospital days and a 39% reduction in the days of intravenous antibiotic use, although these differences were not statistically significant. Considerable heterogeneity was observed in terms of the number of respiratory exacerbations experienced during the trial; 79% (95% CI 70% to 86%) of the azithromycin group and only 57% (95% CI 47% to 66%) of the placebo group experienced one or no respiratory exacerbations during the study.[66]

In a study from Australia, participants receiving azithromycin had significantly fewer total days of intravenous antibiotic treatment for acute respiratory exacerbations during the 3-month trial than those receiving placebo (2.0 vs 7.1 days, $p = 0.009$), fewer days at home receiving intravenous antibiotics (0.2 vs 2.1 days, $p = 0.037$), and fewer courses of intravenous antibiotics during the study (0.4 vs 1.1, $p = 0.016$).[65] The number of days spent in hospital for antibiotic treatment of acute respiratory exacerbations was lower in the azithromycin group than in the placebo group (2.1 vs 5.2 days, $p = 0.056$).

A further randomised, placebo-controlled, multicentre trial has recently been published from France.[67] This study was a parallel group design and involved treatment for 12 months (500 mg three times per week in patients with body weight ⩾40 kg and 250 mg three times per week in those with body weight <40 kg). Eighty-two patients were randomised, approximately 25% of whom had evidence of *P aeruginosa* infection ($n = 19$). The mean (SD) number of respiratory exacerbations per patient was significantly reduced in the azithromycin group compared with placebo (1.5 (0.3) vs 3.0 (0.4), $p<0.005$). The reduction in respiratory exacerbations was significant in patients not infected with *P aeruginosa* ($p<0.001$). Similarly, the time to first respiratory exacerbation was longer

in the azithromycin group than in the placebo group (hazard ratio 0.37, 95% CI 0.22 to 0.63; p<0.001). The median time to exacerbation was 8.7 months in the azithromycin group and 2.9 months in the placebo group. The number of courses of oral antibiotics was significantly lower in the azithromycin group than in the placebo group (count ratio 0.55, 95% CI 0.36 to 0.85; p<0.01). This reduction was only significant in patients without evidence of *P aeruginosa* infection. The mean (SD) numbers of courses of intravenous antibiotics and total intravenous antibiotic days were lower in the azithromycin group than in the placebo group, but only significantly in those infected with *P aeruginosa* (34 (13) days vs 81 (19) days, p = 0.05).

These studies have resulted in a significant uptake of this treatment for patients with CF (5% of children and 11% of adults with CF in the USA).[13] However, concerns remain about the sustained benefits[24] and the potential adverse effects of macrolide treatment,[68] as long-term studies have not been performed to date.

Timing of antibiotic treatment

Regular parenteral antibiotics, irrespective of clinical status, have been advocated in Denmark where it has been routine clinical practice for more than 20 years.[69] It has been argued that this management strategy has made an important contribution to the rapid improvement in survival reported in Danish patients with CF.[70] In their meta-analysis, Yang and colleagues identified two studies examining the question of whether elective antibiotics are more effective than antibiotics administered for symptoms.[59] They concluded that elective antibiotics did not result in significant differences in clinical outcomes, including hospital or exacerbation rates, compared with antibiotics given for symptoms. While regular parenteral antibiotics may have a role for patients with advanced CF lung disease, this therapeutic approach remains unproven.

Nutritional supplementation

The relationship between severity of CF lung disease and nutritional status has been evident in both children and adults with CF.[71 72] In one study from the UK impaired nutritional status was an independent predictor of mortality,[73] and a longitudinal paediatric study has also shown that weight adjusted for age is an independent predictor of lung function in pre-adolescent patients with CF.[74] However, whether nutritional status is truly an independent predictor of mortality remains contentious.[75]

Enteral nutrition is common in children (US national rate 17.6%) and in adults (US national rate 12.5%) with severe undernutrition.[13] Several studies have shown improved or stabilisation of lung function decline in patients receiving enteral nutritional support,[76–81] but the long-term benefits—including the effects on frequency and severity of respiratory exacerbations—are unclear. This also applies to oral nutrition support.[82]

Newborn screening

The introduction of newborn screening for CF has produced clear benefits in terms of nutrition, both in infancy and subsequent childhood years.[83] Despite several prolonged longitudinal studies, there are as yet no definitive data to suggest that early identification of CF through newborn screening minimises the number and extent of respiratory exacerbations.

Anti-inflammatory treatment

Chronic bacterial infection in patients with CF is associated with an exuberant inflammatory response characterised by neutrophilic infiltration within a milieu of proinflammatory cytokines, oxygen-free radical release, and proteolytic enzymes including neutrophil elastase.[84] Despite intensive antibiotic therapy, airway inflammation persists, and vicious cycle of infection and inflammation is thought to contribute to lung damage in patients with CF.[84] An attractive therapeutic strategy to retard the progression of airway and pulmonary destruction is to reduce the extent and intensity of inflammation. Several anti-inflammatory approaches have been assessed recently in patients with CF, including oral and inhaled corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and leucotriene antagonists. The evidence for these approaches is reviewed.

Oral corticosteroids

Three randomised controlled trials (two of which were >3 months) have evaluated the role of oral corticosteroids in children with CF.[85–87] A Cochrane review was unable to perform a meta-analysis as trial end points and time course varied considerably between the studies.[17] Oral corticosteroids appeared to slow the rate of progression of lung disease in CF; however, a number of adverse effects were reported including the development of cataracts, glucose intolerance, cushingoid appearance, bone fractures and reduced growth of the children. One study reported hospital admissions for respiratory exacerbations.[86] Similar numbers of hospital admissions occurred in patients given high-dose prednisolone (2 mg/kg/day), those given moderate-dose prednisolone (1 mg/kg/day) and control subjects.[86] The number of days in hospital for respiratory exacerbations was not reported. The effect of oral steroids in adults with CF has not been evaluated.

Inhaled corticosteroids

Inhaled corticosteroids are commonly prescribed in patients with CF.[13 14 44] Potential mechanisms of inhaled corticosteroids in patients with CF may include a direct anti-inflammatory effect, treatment of co-existing asthma, and/or bronchial hyperreactivity complicating CF but independent of asthma. In a recent Cochrane review, Balfour-Lynn and colleagues evaluated 21 trials examining the role of inhaled steroids in patients with CF.[14] Their meta-analysis included 10 trials involving 293 participants. The authors concluded that, despite widespread usage, there is little evidence to support (or refute) the use of inhaled corticosteroids in patients with CF.

As a direct consequence of their Cochrane review, a multicentre randomised controlled trial was initiated in the UK to determine the effect of inhaled corticosteroids.[88] The investigators used an inhaled corticosteroid withdrawal trial design and assessed the feasibility and safety of inhaled corticosteroid withdrawal in children and adults with CF who were receiving them. The study was a randomised, double blind, placebo-controlled withdrawal study (2 month run-in period and 6 month study duration). Eligibility criteria included age ≥6 years, FEV_1 ≥40% predicted and inhaled corticosteroid use in the previous 3 months. All participants received fluticasone propionate during a 2 month run-in period. If participants were previously prescribed fluticasone the dose was unchanged, but a two to one dosage adjustment was made for participants who had previously received either budesonide or beclometasone dipropionate. Salbutamol was used as a rescue bronchodilator. The primary outcome was time to respiratory exacerbation defined by protocol.[29 88] There was no difference between the groups in time to first exacerbation (hazard ratio 1.07 (95% CI 0.68 to 1.70), intention-to-treat analysis). At 6 months, 49% of the fluticasone group and 46% of the placebo group had experienced at least one respiratory exacerbation (absolute difference 3%, 95% CI −12% to 18%). Eleven participants in the fluticasone group and 14 in the placebo group had two exacerbations, while five in the fluticasone group and eight in the placebo group had three or

more. There was no difference in secondary outcomes between the groups, including change in FEV_1, number of courses of parenteral or oral antibiotics, use of rescue treatment including β-agonists and oral corticosteroids, and growth in the first 6 months after inhaled steroid cessation. Notably, participants with recent oral corticosteroid usage (within the previous month) or very high dose inhaled corticosteroids were excluded from the trial. Participants who were eligible for the trial but whom the clinician wished to continue taking inhaled corticosteroids were entered as an open label inhaled corticosteroid registry group. This recently published randomised controlled trial suggests that there may be a limited role for people with CF.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Three randomised controlled trials have examined the role of NSAIDs in children and adults with CF.[89–91] A Cochrane review analysing the outcomes of these studies concluded that NSAIDs may prevent pulmonary deterioration in patients with mild CF-related lung disease.[19] Only one trial provided information about respiratory exacerbations.[89] Participants in the study were aged 5–39 years with mild lung disease (FEV_1 ⩾60% predicted); 49% of the patients in the ibuprofen group and 40% of those in the placebo group were not admitted to hospital during the trial. The patients receiving ibuprofen tended to have fewer hospital admissions and days of care than the patients receiving placebo, but the differences were not significant even when only hospital admissions for respiratory symptoms were considered.[13]

A study from a paediatric CF centre in Washington reported that the use of ibuprofen has fallen over the past decade in paediatric and adolescent patients.[92] This retrospective analysis of 90 patients showed that almost half of the patients treated with high-dose ibuprofen discontinued treatment, and this was frequently due to adverse effects, particularly gastrointestinal side effects.[92]

Leucotriene B4 receptor antagonists

A recent study (published in abstract form) reported the results of a double blind, randomised clinical trial of BIIL 284 BS, a leucotriene B4 receptor antagonist.[93] The primary end points of the study were change in post-bronchodilator FEV_1 and the incidence of respiratory exacerbations. The trial was prematurely terminated by the safety monitoring committee (420 participants randomised of planned 600 participants) due to a significant increase in the risk of respiratory exacerbations in the adult participants receiving BIIL 284 BS. Ninety-five of 420 participants had a serious adverse effect requiring hospitalisation for a respiratory exacerbation. The relative risk of having a respiratory exacerbation in the adult participants was 2.1 for the lower dose (75 mg) and 1.3 for the higher dose (150 mg). Similarly, the proportion of the adult participants admitted to hospital for treatment of a respiratory exacerbation was higher in participants receiving BIIL 284 BS than in those given placebo. This effect was not observed in the paediatric participants.

The mechanism of this potential effect of a leucotriene B_4 receptor antagonist was not evaluated in the trial; however, the results are a timely reminder that manipulation of inflammatory pathways in CF-related pulmonary disease may have deleterious effects and great care is required in the study of anti-inflammatory treatments in patients with CF.

Treatment of specific pathogens

Infection with specific bacteria is frequently associated with respiratory exacerbations.[94 95] None of the treatment modalities discussed previously have systematically evaluated the potential therapeutic effect on the numbers or severity of respiratory exacerbations in patients with CF who have chronic pulmonary infection with multiresistant pathogens such as *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*. Infection with *B cepacia* complex has been associated with adverse outcomes including increased mortality, poor outcomes following lung transplantation and accelerated loss of lung function.[96–103] It has frequently been a specific exclusion criterion for recruitment in many of the recent multicentre clinical trials (eg, tobramycin for inhalation, hypertonic saline and azithromycin[18 60 64]). It is not possible at this time to know if the specific interventions discussed here are effective in patients with CF and multiresistant bacterial infection.

In a study by Block *et al*,[95] factors predictive of respiratory exacerbations in a cohort of patients infected with multiresistant infections were examined. The factors which were predictive of exacerbations included younger age (odds ratio (OR) 0.98, 95% CI 0.96 to 0.99), female gender (OR 1.45, 95% CI 1.07 to 1.99), poorer FEV_1 (OR 0.98, 95% CI 0.97 to 0.99) and multiple previous respiratory exacerbations (OR 3.16, 95% CI 1.93 to 5.17).[95] Notably, patients taking azithromycin were less likely to have a respiratory exacerbation (protocol-defined) (OR 0.28, 95% CI 0.11 to 0.72) and patients taking inhaled corticosteroids were more likely to have a respiratory exacerbation in the first year of the 4.5-year study (OR 1.92, 95% CI 1.00 to 3.71). While this study was not designed to assess the efficacy of a therapeutic intervention, it is an example of the importance of large multicentre, and probably international, research collaborations which allow sufficient patient numbers to provide adequate study power to examine the efficacy of treatments in patients with specific airway infections other than *P aeruginosa*.

Vaccinations

According to many national recommendations and the clinical practice of many CF centres, influenza vaccination is regularly performed in people with CF,[104] but evidence from randomised controlled trials to support this recommendation is lacking. A recent Cochrane review by Bhalla *et al*[15] identified four randomised controlled trials which examined the use of influenza vaccine in CF.[105–108] However, none of these studies compared a vaccine with placebo, concentrating instead on different routes of administration and dosages of vaccinations. The effects of influenza vaccination on the number or severity of respiratory exacerbations in CF have not been studied.

Although invasive pneumococcal disease is infrequent in CF, it is often recommended that patients with CF should receive pneumococcal immunisation.[104] Lahiri and Waltz[109] measured pre-immunisation antipneumococcal antibody levels in an observational study of 100 patients with CF aged 1–39 years. Pre-immunisation antipneumococcal antibody levels against six serotypes were measured and most patients (61–100%, depending on age and serotype) were found to have protective levels of pneumococcal antibody. There was a significant positive correlation between antibody level and age for five of the six serotypes tested. While a significant proportion (17–39%, depending on the serotype) did not exhibit adequate levels, no randomised controlled trial has examined the effectiveness of pneumococcal vaccination in reducing acute exacerbations.

Disappointing results of a large double blind, randomised, placebo-controlled phase III trial of an antipseudomonal vaccine involving 476 patients from 46 centres in four European countries have recently been released. Patients without *P aeruginosa* infection were vaccinated with Aerugen (a vaccine candidate for the prevention of *P aeruginosa* infection in CF) or a placebo vaccine. The primary end point of the study was the prevention of infection with one or more of the

Table 2 Yearly costs of some pulmonary treatments often dispensed to a patient with CF with significant pulmonary disease

Nebulised tobramycin for inhalation (300 mg twice daily for 6 months)	£5200, €5200, US$9750
Nebulised salbutamol (5 mg twice daily)	£69, €46, US$86
Nebulised Pulmozyme (2.5 mg once daily)	£5200, €5200, US$9750
Nebulised hypertonic saline (6% 4 ml twice daily)	£9, €14, US$18
Azithromycin (500 mg 3× weekly)	£533, €800, US$1000
Inhaled fluticasone (250 μg twice daily)	£134, €200, US$250

serotypes of *P aeruginosa* in the candidate vaccine. The results did not confirm the efficacy indicated in an earlier observational study. Based on these results, development of the vaccine has been suspended (http://cws.huginonline.com/C/132631/PR/200607/1064252_5.html).

COSTS OF CF CARE TO THE HEALTH SYSTEM, PATIENT AND FAMILY

Advances in antibacterial treatment regimes, physiotherapy, pancreatic and nutritional supplements have all aided in achieving the increased length and quality of life for people with CF. Many new treatments are costly (table 2), so any treatment that reduces the number of episodes and duration of hospitalisation may reduce the total cost of patient care. Annual cost of care studies have been reported from North America and Europe.[9 10 110–114] In all studies the cost of inpatient treatment was estimated to approach 30–40% of the overall annual cost of patient care.

The introduction of rhDNase has significantly increased the proportion of outpatient pharmacy in the overall cost of CF care.[110] In the PEIT study, for example, overall inpatient treatment was reduced by 34% in the rhDNase-treated group, but this was a group who had mild lung disease.[30] It is likely that the introduction of ''preventive therapies'' such as rhDNase to this group may increase short-term CF care costs. A reduction in the number of patients requiring inpatient treatment may lead to early intervention treatments being more cost effective. Evidence to support these assertions is currently lacking and will require long-term cost effectiveness studies.

With the advent of evidence for new treatments and new indications for ''old'' treatments, the burden of treatment in terms of time taken to undertake it on a daily basis is important. Many patients with CF who have significant respiratory symptoms may now be prescribed multiple aerosol treatments. The time taken to perform physiotherapy, exercise and a series of nebulised treatments including rhDNase, bronchodilator therapy, antibiotics and hypertonic saline may be >2–3 h/day. In the current era, most children with CF are able to continue schooling without long-term interruption of education by hospitalisation and many adults with CF are working.[13] Healthcare professionals caring for people with CF need to be mindful of just how achievable long-term complex treatments are when consulting with their patients (fig 1, table 3).

It is well known that adherence in patients with CF can be less than 50% of what is prescribed in the clinic, and will partially depend upon the complexity of treatment.[115–117] Close communication between the patient (and family) and the healthcare team is vital, so that decisions can be made as to which treatments are important and how they can be undertaken without adding an intolerable burden. New technologies of drug delivery will have an important role in assisting with

Figure 1 One month's supply of treatment for a typical patient with cystic fibrosis who has significant pulmonary disease. Photograph courtesy of Ms Judith Burrows, Adult Cystic Fibrosis Centre, TPCH.

the management of increasingly complex treatment regimens. These include advances in nebuliser device technologies to increase the speed and efficiency of drug delivery.[118 119] Furthermore, development of antibiotic[120 121] and mucolytic[122] treatments which can be delivered in aerosol formulation rather than by more time-consuming nebulisation are undergoing evaluation and may improve the tolerability of the delivery of treatment for patients with CF.

CONCLUSIONS FROM EVIDENCE TO DATE

At present there is considerable discussion about the optimal end point for therapeutic trials. While the gold standard primary end point for CF clinical trials has been the spirometric measure FEV_1, alternative end points are increasingly being studied in clinical trials. Recent studies have therefore started to address ''time to respiratory exacerbation'' and ''numbers of exacerbations'' as study end points.[64 88 94] These are important studies as they have incorporated estimates of the size of the study population required to assess these outcomes with adequate power.

Table 3 Daily treatments frequently required by many patients with CF who have significant pulmonary disease

Nebulised tobramycin or colistin (colomycin): twice daily
Inhaled or nebulised bronchodilators: often twice daily
Nebulised Pulmozyme: once daily
Nebulised hypertonic saline: twice daily
Oral antibiotics: intermittent or chronically
Exercise: daily
Airway clearance/physiotherapy: up to twice daily
Pancreatic enzymes: with meals and snacks
Fat soluble vitamins: daily
High energy supplements, night feeds: daily in patients with undernutrition
Salt replacement: depending on climatic conditions
Acid suppression (PPI): if symptomatic gastro-oesophageal reflux, daily treatment
Insulin: if disease complicated by diabetes, usually several times per day

Future studies should also consider the potential effect of other treatments on respiratory exacerbations as trial end points, an issue which has received little attention to date. For example, future trials of a new mucolytic agent should ask the question: ''Are other therapies which may potentially impact on respiratory exacerbations balanced in each of the treatment groups in the trial?''. In addition, further research is required to examine the possible additive effects of two or more treatments in respiratory exacerbations (rates and duration) and the effect of individual treatments in specific subgroups of patients (such as very young patients and patients with specific bacterial pathogens).

Finally, it should not be assumed that a lack of evidence for the benefit of a specific treatment on respiratory exacerbations means a lack of benefit, but may reflect the fact that appropriately powered studies in a specific population of patients for an adequate duration are yet to be performed.[123 124]

In conclusion, for many years a large part of CF clinical care has been empirically based with little evidence of therapeutic efficacy from randomised controlled trials. Over the past 20 years, however, clinicians have been provided with increasing levels of quality research studies documenting improvements in old treatments and establishment of newer treatments. Many of these treatments—but certainly not all—have shown their efficacy, at least in part, by a reduction in the incidence of respiratory exacerbations. While the exact definition of an exacerbation in CF is often controversial or at best open to debate, there is evidence that several pharmacological agents including rhDNase, hypertonic saline, tobramycin and macrolide therapy are able to reduce the level of respiratory exacerbations in patients with CF. Future research will aim at identifying other treatments—including not only pharmacological agents but physical and nutritional interventions—that will help reduce exacerbations in CF.

ACKNOWLEDGEMENTS

The authors are grateful for the expert secretarial support of Ms Lyn Monro and Ms Silvia Pozzuto and the review of the manuscript by Dr Julia Courtney and Dr Shawn Aaron.

Table 1 is available as a data supplement online at http://thorax.bmj.com/supplemental.

Authors' affiliations

Scott C Bell, Adult Cystic Fibrosis Centre, The Prince Charles Hospital, Brisbane and School of Medicine, University of Queensland, Australia
Philip J Robinson, Department of Respiratory Medicine, Royal Children's Hospital, Melbourne, Australia

Competing interests: None.

REFERENCES

1 **Dodge JA**, Lewis PA. Cystic fibrosis is no longer an important cause of childhood death in the UK. *Arch Dis Child* 2005;**90**:547.
2 **Elborn JS**, Shale DJ, Britton JR. Cystic fibrosis: current survival and population estimates to the year 2000. *Thorax* 1991;**46**:881–5.
3 **Mahadeva R**, Webb K, Westerbeek RC, *et al.* Clinical outcome in relation to care in centres specialising in cystic fibrosis: cross sectional study. *BMJ* 1998;**316**:1771–5.
4 **Ratjen F**, Doring G. Cystic fibrosis. *Lancet* 2003;**361**:681–9.
5 **Yankaskas JR**, Fernald GW. Adult social issues. In: Yankaskas JR, Knowles MR, eds. *Cystic fibrosis in adults*.Lippincott-Raven Publishers, 1999:465–76.
6 **Que C**, Cullinan P, Geddes D. Improving rate of decline of FEV_1 in young adults with cystic fibrosis. *Thorax* 2006;**61**:155–7.
7 **Xu W**, Subbarao P, Corey M. Changing patterns of lung function decline in children with cystic fibrosis (abstract). *J Cyst Fibros* 2004;**3**(Suppl 1):S116.
8 **Liou TG**, Adler FR, Fitzsimmons SC, *et al.* Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001;**153**:345–52.
9 **Lieu TA**, Ray GT, Farmer G, *et al.* The cost of medical care for patients with cystic fibrosis in a health maintenance organization. *Pediatrics* 1999;**103**:e72.
10 **Robson M**, Abbott J, Webb K, *et al.* A cost description of an adult cystic fibrosis unit and cost analyses of different categories of patients. *Thorax* 1992;**47**:684–9.
11 **Dobbin CJ**, Bartlett D, Melehan K, *et al.* The effect of infective exacerbations on sleep and neurobehavioral function in cystic fibrosis. *Am J Respir Crit Care Med* 2005;**172**:99–104.
12 **Britto MT**, Kotagal UR, Hornung RW, *et al.* Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest* 2002;**121**:64–72.
13 **Cystic Fibrosis Foundation**. *Patient Registry Annual Data Report 2003*. Bethesda, Maryland: Cystic Fibrosis Foundation, 2003.
14 **Balfour-Lynn I**, Walters S, Dezateux C. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database Syst Rev* 2000;(1):CD001915.
15 **Bhalla P**, Tan A, Smyth R. Vaccines for preventing influenza in people with cystic fibrosis. *Cochrane Database Syst Rev* 2000;(1):CD001753.
16 **Bradley JM**, Moran FM, Elborn JS. Evidence for physical therapies (airway clearance and physical training) in cystic fibrosis: an overview of five Cochrane systematic reviews. *Respir Med* 2006;**100**:191–201.
17 **Cheng K**, Ashby D, Smyth R. Oral steroids for cystic fibrosis. *Cochrane Database Syst Rev* 1999;(4):CD000407.
18 **Elkins MR**, Jones A, van der Schans C. Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis. *Cochrane Database Syst Rev* 2006;(2):CD003147.
19 **Lands LC**, Dezateux C, Crighton C. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. *Cochrane Database Syst Rev* 1999;(2):CD001505.
20 **Main E**, Prasad A, van der Schans C. Conventional chest physiotherapy compared to other airway clearance techniques for cystic fibrosis. *Cochrane Database Syst Rev* 2005;(1):CD002011.
21 **Moran F**, Bradley J. Non-invasive ventilation for cystic fibrosis. *Cochrane Database Syst Rev* 2003;(2):CD002769.
22 **Ryan G**, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2003;(3):CD001021.
23 **Smyth A**, Walters S. Prophylactic anti-staphylococcal antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2003;(3):CD001912.
24 **Southern KW**, Barker PM, Solis A. Macrolide antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2004;(2):CD002203.
25 **van der Schans C**, Prasad A, Main E. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. *Cochrane Database Syst Rev* 2000;(2):CD001401.
26 **Wood DM**, Smyth AR. Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis. *Cochrane Database Syst Rev* 2006;(1):CD004197.
27 **Goss CH**, Burns JL. Exacerbations in cystic fibrosis: epidemiology and pathogenesis. *Thorax* 2007;**62**:360–7.
28 **Duijvestijn YC**, Brand PL. Systematic review of N-acetylcysteine in cystic fibrosis. *Acta Paediatr* 1999;**88**:38–41.
29 **Fuchs HJ**, Borowitz DS, Christiansen DH, *et al.* Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994;**331**:637–42.
30 **Quan JM**, Tiddens HA, Sy JP, *et al.* A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001;**139**:813–20.
31 **McCoy K**, Hamilton S, Johnson C. Effects of 12 weeks administration of dornase alfa in patients with advanced cystic fibrosis lung disease. *Chest* 1996;**110**:889–95.
32 **Shah PL**, Conway S, Scott SF, *et al.* A case-controlled study with dornase alfa to evaluate impact on disease progression over a 4-year period. *Respiration* 2001;**68**:160–4.
33 **Robinson M**, Regnis JA, Bailey DL, *et al.* Effect of hypertonic saline, amiloride, and cough on mucociliary clearance in patients with cystic fibrosis. *Am J Respir Crit Care Med* 1996;**153**:1503–9.
34 **Wark PAB**, McDonald V, Jones AP. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database Syst Rev* 2005;(3):CD001506.
35 **Suri R**, Metcalfe C, Lees B, *et al.* Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial. *Lancet* 2001;**358**:1316–21.
36 **Elkins MR**, Robinson M, Rose BR, *et al.* A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;**354**:229–40.
37 **Bradley J**, Moran F. Physical training for cystic fibrosis. *Cochrane Database Syst Rev* 2002;(2):CD002768.
38 **Reisman JJ**, Rivington-Law B, Corey M, *et al.* Role of conventional physiotherapy in cystic fibrosis. *J Pediatr* 1988;**113**:632–6.
39 **Homnick DN**, White F, de Castro C. Comparison of effects of an intrapulmonary percussive ventilator to standard aerosol and chest physiotherapy in treatment of cystic fibrosis. *Pediatr Pulmonol* 1995;**20**:50–5.
40 **McIlwaine PM**, Wong LT, Peacock D, *et al.* Long-term comparative trial of conventional postural drainage and percussion versus positive expiratory pressure physiotherapy in the treatment of cystic fibrosis. *J Pediatr* 1997;**131**:570–4.
41 **Schneiderman-Walker J**, Pollock SL, Corey M, *et al.* A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. *J Pediatr* 2000;**136**:304–10.
42 **Klijn PH**, Oudshoorn A, van der Ent CK, *et al.* Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study. *Chest* 2004;**125**:1299–305.

43 **Armstrong DS**, Grimwood K, Carzino R, *et al.* Lower respiratory infection and inflammation in infants with newly diagnosed cystic fibrosis. *BMJ* 1995;**310**:1571–2.
44 **Cystic Fibrosis Australia**. Annual report from the Australian Cystic Fibrosis Data Registry. *Cystic fibrosis in Australia*. Sydney: Cystic Fibrosis Australia, 2003.
45 **Martin B**, McKay K, Selvadurai H, *et al.* Prophylactic oral antibiotics in cystic fibrosis may predispose to Pseudomonas aeruginosa acquistion (abstract). *Respirology* 2006;**11**(Suppl 2):A11.
46 **Nolan G**, Moivor P, Levison H, *et al.* Antibiotic prophylaxis in cystic fibrosis: inhaled cephaloridine as an adjunct to oral cloxacillin. *J Pediatr* 1982;**101**:626–30.
47 **Loening-Baucke VA**, Mischler E, Myers MG. A placebo-controlled trial of cephalexin therapy in the ambulatory management of patients with cystic fibrosis. *J Pediatr* 1979;**95**:630–7.
48 **Ratjen F**, Comes G, Paul K, *et al.* Effect of continuous antistaphylococcal therapy on the rate of P. aeruginosa acquisition in patients with cystic fibrosis. *Pediatr Pulmonol* 2001;**31**:13–6.
49 **Chatfield S**, Owen G, Ryley HC, *et al.* Neonatal screening for cystic fibrosis in Wales and the West Midlands: clinical assessment after five years of screening. *Arch Dis Child* 1991;**66**:29–33.
50 **Schlesinger E**, Muller W, von der Hardt H, *et al.* Effect of longterm continuous anti-staphylococcal antibiotic treatment in young children with cystic fibrosis (abstract). *Proceedings of the 9th International Cystic Fibrosis Congress* 1984:4.14.
51 **Stutman HR**, Lieberman JM, Nussbaum E, *et al.* Antibiotic prophylaxis in infants and young children with cystic fibrosis: a randomized controlled trial. *J Pediatr* 2002;**140**:299–305.
52 **Weaver LT**, Green MR, Nicholson K, *et al.* Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period. *Arch Dis Child* 1994;**70**:84–9.
53 **Smyth A**. Prophylactic antibiotics in cystic fibrosis: a conviction without evidence? *Pediatr Pulmonol* 2005;**40**:471–6.
54 **Valerius NH**, Koch C, Hoiby N. Prevention of chronic Pseudomonas aeruginosa colonisation in cystic fibrosis by early treatment. *Lancet* 1991;**338**:725–6.
55 **Gibson RL**, Emerson J, McNamara S, *et al.* A randomized, controlled trial of inhaled tobramycin in young children with cystic fibrosis (abstract). *Pediatr Pulmonol* 2002;**34**(Suppl 24):300.
56 **Gibson RL**, Emerson J, McNamara S, *et al.* Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. *Am J Respir Crit Care Med* 2003;**167**:841–9.
57 **Ratjen F**, Doring G, Nikolaizik WH. Effect of inhaled tobramycin on early Pseudomonas aeruginosa colonisation in patients with cystic fibrosis. *Lancet* 2001;**358**:983–4.
58 **Wiesemann HG**, Steinkamp G, Ratjen F, *et al.* Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of Pseudomonas aeruginosa colonization in cystic fibrosis. *Pediatr Pulmonol* 1998;**25**:88–92.
59 **Yang I**, Kim ST, Bell SC. Antibiotics in COPD, bronchiectasis, and cystic fibrosis. In: Gibson PG, eds. *Evidence-based respiratory medicine*. Oxford: Blackwell Publishing, 2005:389–413.
60 **Ramsey BW**, Pepe MS, Quan JM, *et al.* Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999;**340**:23–30.
61 **Burns JL**, Van Dalfsen JM, Shawar RM, *et al.* Effect of chronic intermittent administration of inhaled tobramycin on respiratory microbial flora in patients with cystic fibrosis. *J Infect Dis* 1999;**179**:1190–6.
62 **Jaffe A**, Francis J, Rosenthal M, *et al.* Long-term azithromycin may improve lung function in children with cystic fibrosis. *Lancet* 1998;**351**:420.
63 **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**:978–84.
64 **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**:1749–56.
65 **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**:212–6.
66 **Saiman L**, Mayer-Hamblett N, Campbell P, *et al.* Heterogeneity of treatment response to azithromycin in patients with cystic fibrosis. *Am J Respir Crit Care Med* 2005;**172**:1008–12.
67 **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.
68 **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**:741–6.
69 **Szaff M**, Hoiby N, Flensborg EW. Frequent antibiotic therapy improves survival of cystic fibrosis patients with chronic Pseudomonas aeruginosa infection. *Acta Paediatr Scand* 1983;**72**:651–7.
70 **Hoiby N**, Koch C. Cystic fibrosis. 1. Pseudomonas aeruginosa infection in cystic fibrosis and its management. *Thorax* 1990;**45**:881–4.
71 **Bell SC**, Bowerman AR, Davies CA, *et al.* Nutrition in adults with cystic fibrosis. *Clin Nutr* 1998;**17**:211–5.
72 **Huang NN**, Macri CN, Girone J, *et al.* Survival of patients with cystic fibrosis. *Am J Dis Child* 1970;**120**:289–95.
73 **Sharma R**, Florea VG, Bolger AP, *et al.* Wasting as an independent predictor of mortality in patients with cystic fibrosis. *Thorax* 2001;**56**:746–50.
74 **Zemel BS**, Jawad AF, FitzSimmons S, *et al.* Longitudinal relationship among growth, nutritional status, and pulmonary function in children with cystic fibrosis: analysis of the Cystic Fibrosis Foundation National CF Patient Registry. *J Pediatr* 2000;**137**:374–80.
75 **Corey M**. Modelling survival in cystic fibrosis. *Thorax* 2001;**56**:743.
76 **Boland MP**, Stoski DS, Patrick J. Long-term nutritional rehabilitation in cystic fibrosis. *J Pediatr* 1986;**108**:489–90.
77 **Levy LD**, Durie PR, Pencharz PB, *et al.* Effects of long-term nutritional rehabilitation on body composition and clinical status in malnourished children and adolescents with cystic fibrosis. *J Pediatr* 1985;**107**:225–30.
78 **Moore MC**, Greene HL, Donald WD, *et al.* Enteral-tube feeding as adjunct therapy in malnourished patients with cystic fibrosis: a clinical study and literature review. *Am J Clin Nutr* 1986;**44**:33–41.
79 **Shepherd RW**, Holt TL, Cleghorn G, *et al.* Short-term nutritional supplementation during management of pulmonary exacerbations in cystic fibrosis: a controlled study, including effects of protein turnover. *Am J Clin Nutr* 1988;**48**:235–9.
80 **Shepherd RW**, Thomas BJ, Bennett D, *et al.* Changes in body composition and muscle protein degradation during nutritional supplementation in nutritionally growth-retarded children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1983;**2**:439–46.
81 **Steinkamp G**, Rodeck B, Seidenberg J, *et al.* [Stabilization of lung function in cystic fibrosis during long-term tube feeding via a percutaneous endoscopic gastrostomy]. *Pneumologie* 1990;**44**:1151–3.
82 **Poustie VJ**, Russell JE, Watling RM, *et al.* Oral protein energy supplements for children with cystic fibrosis: CALICO multicentre randomised controlled trial. *BMJ* 2006;**332**:632–6.
83 **Farrell PM**, Kosorok MR, Laxova A, *et al.* Nutritional benefits of neonatal screening for cystic fibrosis. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. *N Engl J Med* 1997;**337**:963–9.
84 **Berger M**, Konstan MW. Immunopathogenesis of cystic fibrosis lung disease. In: Yankaskas JR, Knowles MR, eds. *Cystic fibrosis in adults*.Lippincott-Raven, 1999:115–43.
85 **Auerbach HS**, Williams M, Kirkpatrick JA, *et al.* Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis. *Lancet* 1985;**2**:686–8.
86 **Eigen H**, Rosenstein BJ, FitzSimmons S, *et al.* A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. Cystic Fibrosis Foundation Prednisone Trial Group. *J Pediatr* 1995;**126**:515–23.
87 **Greally P**, Hussain MJ, Vergani D, *et al.* Interleukin-1 alpha, soluble interleukin-2 receptor, and IgG concentrations in cystic fibrosis treated with prednisolone. *Arch Dis Child* 1994;**71**:35–9.
88 **Balfour-Lynn IM**, Lees B, Hall P, *et al.* Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis. *Am J Respir Crit Care Med* 2006;**173**:1356–62.
89 **Konstan MW**, Byard PJ, Hoppel CL, *et al.* Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 1995;**332**:848–54.
90 **Konstan MW**, Hoppel CL, Chai BL, *et al.* Ibuprofen in children with cystic fibrosis: pharmacokinetics and adverse effects. *J Pediatr* 1991;**118**:956–64.
91 **Sodelli DO**, Macri CN, Maillie AJ. A preliminary report of the effect of anti-inflammatory treatment in cystic fibrosis patients with Pseudomonas aeruginosa infection. *Int J Immunopathol Pharmacol* 1994;**7**:109–17.
92 **Fennell PB**, Quante J, Wilson K, *et al.* Use of high-dose ibuprofen in a pediatric cystic fibrosis center. *J Cyst Fibros* 2007;**6**:153–8.
93 **Konstan MW**, Doring G, Lands L, *et al.* Results of a phase II clinical trial of BIIL 284 BS (an LTB4 receptor antagonist) for the treatment of CF lung disease (abstract). *Pediatr Pulmol* 2005;**40**(S28):125.
94 **Aaron SD**, Vandemheen KL, Ferris W, *et al.* Combination antibiotic susceptibility testing to treat exacerbations of cystic fibrosis associated with multiresistant bacteria: a randomised, double-blind, controlled clinical trial. *Lancet* 2005;**366**:463–71.
95 **Block JK**, Vandemheen KL, Tullis E, *et al.* Predictors of pulmonary exacerbations in patients with cystic fibrosis infected with multi-resistant bacteria. *Thorax* 2006;**61**:969–74.
96 **Aris RM**, Routh JC, LiPuma JJ, *et al.* Lung transplantation for cystic fibrosis patients with Burkholderia cepacia complex. Survival linked to genomovar type. *Am J Respir Crit Care Med* 2001;**164**:2102–6.
97 **Chaparro C**, Maurer J, Gutierrez C, *et al.* Infection with Burkholderia cepacia in cystic fibrosis: outcome following lung transplantation. *Am J Respir Crit Care Med* 2001;**163**:43–8.
98 **Courtney JM**, Dunbar KE, McDowell A, *et al.* Clinical outcome of Burkholderia cepacia complex infection in cystic fibrosis adults. *J Cyst Fibros* 2004;**3**:93–8.
99 **De Soyza A**, McDowell A, Archer L, *et al.* Burkholderia cepacia complex genomovars and pulmonary transplantation outcomes in patients with cystic fibrosis. *Lancet* 2001;**358**:1780–1.
100 **Jones AM**, Dodd ME, Govan JR, *et al.* Burkholderia cenocepacia and Burkholderia multivorans: influence on survival in cystic fibrosis. *Thorax* 2004;**59**:948–51.
101 **Ledson MJ**, Walshaw MJ. Burkholderia infection and survival in CF. *Thorax* 2005;**60**:439.
102 **Lewin LO**, Byard PJ, Davis PB. Effect of Pseudomonas cepacia colonization on survival and pulmonary function of cystic fibrosis patients. *J Clin Epidemiol* 1990;**43**:125–31.
103 **Nelson JW**, Doherty CJ, Brown PH, *et al.* Pseudomonas cepacia in inpatients with cystic fibrosis. *Lancet* 1991;**338**:1525.
104 **Malfroot A**, Adam G, Ciofu O, *et al.* Immunisation in the current management of cystic fibrosis patients. *J Cyst Fibros* 2005;**4**:77–87.
105 **Adlard P**, Bryett K. Influenza immunization in children with cystic fibrosis. *J Int Med Res* 1987;**15**:344–51.

106 **Gruber WC**, Campbell PW, Thompson JM, *et al*. Comparison of live attenuated and inactivated influenza vaccines in cystic fibrosis patients and their families: results of a 3-year study. *J Infect Dis* 1994;**169**:241–7.
107 **King JC Jr**, Gross PA, Denning CR, *et al*. Comparison of live and inactivated influenza vaccine in high risk children. *Vaccine* 1987;**5**:234–8.
108 **Schaad UB**, Buhlmann U, Burger R, *et al*. Comparison of immunogenicity and safety of a virosome influenza vaccine with those of a subunit influenza vaccine in pediatric patients with cystic fibrosis. *Antimicrob Agents Chemother* 2000;**44**:1163–7.
109 **Lahiri T**, Waltz DA. Preimmunization anti-pneumococcal antibody levels are protective in a majority of patients with cystic fibrosis. *Pediatrics* 2001;**108**:E62.
110 **Krauth C**, Jalilvand N, Welte T, *et al*. Cystic fibrosis: cost of illness and considerations for the economic evaluation of potential therapies. *Pharmacoeconomics* 2003;**21**:1001–24.
111 **Pauly MV**. The economics of cystic fibrosis. In: Lloyd-Still JD, eds. *Textbook of cystic fibrosis*. Boston, USA: John Wright PSG Inc, 1983:465–76.
112 **US Congress Office of Technology Assessment**. *Cystic fibrosis and DNA tests: implications of carrier screening*. Washington, USA: US Government Printing Office, 1992.
113 **Wildhagen MF**, Verheij JB, Verzijl JG, *et al*. Cost of care of patients with cystic fibrosis in The Netherlands in 1990–1. *Thorax* 1996;**51**:298–301.
114 **Wildhagen MF**, Verheij JB, Verzijl JG, *et al*. The nonhospital costs of care of patients with CF in The Netherlands: results of a questionnaire. *Eur Respir J* 1996;**9**:2215–9.
115 **Abbott J**, Dodd M, Bilton D, *et al*. Treatment compliance in adults with cystic fibrosis. *Thorax* 1994;**49**:115–20.
116 **Abbott J**, Dodd M, Webb AK. Health perceptions and treatment adherence in adults with cystic fibrosis. *Thorax* 1996;**51**:1233–8.
117 **Conway SP**, Pond MN, Hamnett T, *et al*. Compliance with treatment in adult patients with cystic fibrosis. *Thorax* 1996;**51**:29–33.
118 **Gibson RL**, Retsch-Bogart GZ, Oermann C, *et al*. Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. *Pediatr Pulmonol* 2006;**41**:656–65.
119 **Knoch M**, Keller M. The customised electronic nebuliser: a new category of liquid aerosol drug delivery systems. *Expert Opin Drug Deliv* 2005;**2**:377–90.
120 **de Boer AH**, Le Brun PP, van der Woude HG, *et al*. Dry powder inhalation of antibiotics in cystic fibrosis therapy, part 1: development of a powder formulation with colistin sulfate for a special test inhaler with an air classifier as de-agglomeration principle. *Eur J Pharm Biopharm* 2002;**54**:17–24.
121 **Le Brun PP**, de Boer AH, Mannes GP, *et al*. Dry powder inhalation of antibiotics in cystic fibrosis therapy: Part 2. Inhalation of a novel colistin dry powder formulation: a feasibility study in healthy volunteers and patients. *Eur J Pharm Biopharm* 2002;**54**:25–32.
122 **Charlton B**, Lassig A. CF-201 Study Investigators. Inhaled dry powder mannitol (bronchitol) improves FEV1 in cystic fibrosis (abstract). *J Cyst Fibros* 2006;**5**(suppl 1):S11.
123 **Reilly BM**. The essence of EBM. *BMJ* 2004;**329**:991–2.
124 **Sackett DL**, Rosenberg WM, Gray JA, *et al*. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;**312**:71–2.
125 **Elborn JS**, Prescott RJ, Stack BH, *et al*. Elective versus symptomatic antibiotic treatment in cystic fibrosis patients with chronic Pseudomonas infection of the lungs. *Thorax* 2000;**55**:355–8.