Cystic Fibrosis Pulmonary Guidelines
Chronic Medications for Maintenance of Lung Health

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***Rationale*: Cystic fibrosis is a recessive genetic disease characterized by dehydration of the airway surface liquid and impaired mucociliary clearance. As a result, individuals with the disease have difficulty clearing pathogens from the lung and experience chronic pulmonary infections and inflammation. Death is usually a result of respiratory failure. Newly introduced therapies and aggressive management of the lung disease have resulted in great improvements in length and quality of life, with the result that the median expected survival age has reached 36 years. However, as the number of treatments expands, the medical regimen becomes increasingly burdensome in time, money, and health resources. Hence, it is important that treatments should be recommended on the basis of available evidence of efficacy and safety.**

***Objectives*: The Cystic Fibrosis Foundation therefore established a committee to examine the clinical evidence for each therapy and to provide guidance for the prescription of these therapies.**

***Methods:* The committee members developed and refined a series of questions related to drug therapies used in the maintenance of pulmonary function. We addressed the questions in one of three ways, based on available evidence: (*1*) commissioned systematic review, (*2*) modified systematic review, or (*3*) summary of existing Cochrane reviews.**

***Conclusions:* It is hoped that the guidelines provided in this article will facilitate the appropriate application of these treatments to improve and extend the lives of all individuals with cystic fibrosis.**

Keywords: antibiotics; antiinflammatory agents; bronchodilators; mucolytics; saline solution, hypertonic

Cystic fibrosis (CF) is a complex multiorgan disease in which lung disease accounts for nearly 85% of the mortality (1). Lung destruction is caused by obstruction of the airways due to dehydrated, thickened secretions, resultant endobronchial infection, and an exaggerated inflammatory response leading to development of bronchiectasis and progressive obstructive airways disease. Physicians treating patients with CF are faced with a growing number of treatment options for the maintenance of lung health for children and adults with CF. At present, the Cystic Fibrosis Foundation has published consensus guidelines for only two of these therapies: aerosolized tobramycin (2) and recombinant human DNase (dornase alfa) (3), and additional studies have been published since the release of those guidelines. To provide guidance to the physician who must choose from an ever-expanding arsenal of treatments for chronic CF lung disease, the Cystic Fibrosis Foundation established the Pulmonary Therapies Committee. This document represents the committee's recommendations, based on available evidence, for the use of medications intended to maintain lung health. The guidelines are designed for general use in most patients, but may need to be adapted to meet individual needs as determined by the patient's health care provider. In addition, because of the limited number of studies available involving very young children, unless otherwise noted, recommendations are intended for individuals at least 6 years of age.

METHODS

A preliminary meeting was held in October 2005 to initiate the process of identifying and prioritizing topics to be covered in these guidelines. The committee was composed of 15 members, all from the United States, representing internal medicine, pediatrics, nursing, respiratory therapy, systematic review procedures, and the Cystic Fibrosis Foundation. Each member of the committee was involved in developing the recommendations and reviewed and commented on the final version of the guidelines. The committee members developed and refined a series of questions related to drug therapies used in the maintenance of pulmonary function. We addressed the questions in one of three ways, based on available evidence: (*1*) commissioned systematic review, (*2*) modified systematic review, or (*3*) summary of existing Cochrane reviews. *See* the online supplement for details on these methods.

Members of the committee were provided with summaries of the evidence. Subcommittees, formed to review the evidence for each specific treatment, drafted recommendations. Their assessment of the evidence and draft statements was then presented to the full committee for discussion. For each treatment under question, the body of evidence was evaluated by the full committee and recommendations were made on the basis of the U.S. Preventive Services Task Force grading scheme (4) (*see* Table 1). A draft of the recommendations was presented in November 2006 at the North American Cystic Fibrosis Conference and the committee solicited public commentary for 1 month after the presentation. This input was considered by the committee in the preparation of these guidelines.

(*Received in original form May 4, 2007; accepted in final form August 24, 2007*)

Supported by the Cystic Fibrosis Foundation.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 176. pp 957–969, 2007
Originally Published in Press as DOI: 10.1164/rccm.200705-664OC on August 29, 2007
Internet address: www.atsjournals.org

RESULTS

Assessment of Evidence

1. *Systematic reviews of original research*. A total of 2,670 unique citations were identified through the search process. Fifty-seven studies, published between 1983 and 2006, were deemed eligible for inclusion in this review (Figure 1).
2. *Modified systematic reviews*. A total of 416 unique citations were identified. Seventeen studies, published between 1983 and 2006, were deemed eligible for inclusion.
3. *Existing Cochrane systematic reviews*. We identified nine Cochrane reviews that addressed the effectiveness of aerosolized antibiotics, dornase alfa, hypertonic saline, oral corticosteroids, inhaled corticosteroids, oral nonsteroidal antiinflammatory drugs, macrolide antibiotics, inhaled bronchodilators (including β-agonists and anticholinergic medications), and oral antistaphylococcal antibiotics.

A summary of the number and type of studies and total number of patients involved in each trial category is shown in Table 2. The committee's assessment of the quality of evidence, the estimate of net benefit (benefits minus harms), and grade of the recommendation discussed below are also shown in Table 2.

TABLE 1. U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION GRADES*

Strength of Overall Evidence of Effectiveness	Estimate of Net Benefit (*benefit minus harms*)			
	Substantial	Moderate	Small	Zero/Negative
Good	A	B	C	D
Fair	B	B	C	D
Poor	I	I	I	I

Definition of abbreviation: I = insufficient evidence.

* Strength of overall evidence and estimate of net benefit determine the grade.

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Strength of recommendations (4): *Recommendation level A*—the committee strongly recommends that clinicians routinely provide [the service] to eligible patients. (The committee found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.) *Recommendation level B*—the committee recommends that clinicians routinely provide [the service] to eligible patients. (The committee found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.) *Recommendation level C*—the committee makes no recommendation for or against routine provision of [the service]. (The committee found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of the benefits and harms is too close to justify a general recommendation.) *Recommendation level D*—the committee recommends against routinely providing [the service] to patients. (The committee found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.) *Recommendation level I*—the committee concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.)

Quality of evidence: *Good*—Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes. *Fair*—Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes. *Poor*—Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidenced, or lack of information on important health outcomes.

RECOMMENDATIONS

Aerosolized Antibiotics

The most common airway pathogen in patients with CF is *Pseudomonas aeruginosa.* Because chronic colonization of the airways with this bacterium is associated with a more rapid decline in lung function (5), aerosolized antibiotics have been advocated both for eradication of initial infection and for suppression of the chronic infection. The present systematic review of evidence was focused on the latter. Recommendations are stratified on the basis of the severity of lung disease, defined by FEV_1 percentage of predicted as follows: normal, greater than 90% predicted; mildly impaired, 70–89% predicted; moderately impaired, 40–69% predicted; and severely impaired, less than 40% predicted.

Tobramycin for moderate to severe disease. A systematic review of original research identified six eligible trials assessing the use of aerosolized tobramycin compared with placebo or standard therapy in patients with moderate to severe airway disease and established *P. aeruginosa* infection (Table 2). There were 679 participants in these studies with the largest study enrolling 520 subjects (6). Three studies (n = 619 patients) reported statistically significant improvement in FEV_1 for those taking tobramycin compared with placebo or standard treatment, with a net benefit to lung function ranging from 7.8 to 12% (6–8). One study (n = 22) reported no significant effects on FEV_1 (as a percentage of the predicted value), but the actual values were not provided (9). There were three studies assessing the influence of inhaled antibiotics on the frequency of pulmonary exacerbations (6–8). Ramsey and coworkers (8) reported a 26% reduction in hospitalizations and a 36% reduction in the use of intravenous antipseudomonal antibiotics for those taking inhaled tobramycin compared with placebo. Results from both MacLusky and coworkers (7) and Ramsey and coworkers (6) showed fewer days spent in hospital for subjects receiving inhaled tobramycin. Total days of other antibiotics were also lower for the inhaled tobramycin group in these two studies; however, these differences were significant only in the larger study (6). Quality of life was assessed in only one study (6); the tobramycin group reported higher scores on the Health-related Quality of Life scale compared with those in the placebo group, although the actual values were not presented. There were low rates of adverse events reported in all of the studies. Tinnitus occurred more frequently in the tobramycin-treated study participants, as did throat problems and voice alteration.

A Cochrane review of inhaled tobramycin for CF, with the most recent search dated 2006 (10), concluded that aerosolized antipseudomonal antibiotics improved lung function. An increase in antibiotic resistance was noted, but this was a low-frequency occurrence.

The quality of the summary of the evidence for inhaled tobramycin in cases of moderate to severe lung disease was deemed to be good, as the studies were well designed and well conducted, and the results were consistent. On the basis of the considerable improvement in lung function, reduction in exacerbations, and low risk of adverse events, the net benefit of aerosolized tobramycin was thought to be substantial.

Recommendation:
For patients with CF, 6 years of age and older, who have moderate to severe lung disease and with *P. aeruginosa* persistently present in cultures of the airways, the Cystic Fibrosis Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and reduce exacerbations. Level of evidence, good; net benefit, substantial; grade of recommendation, A.

Tobramycin for mild disease. Two trials (n = 202) identified by systematic review assessed the use of aerosolized tobramycin in

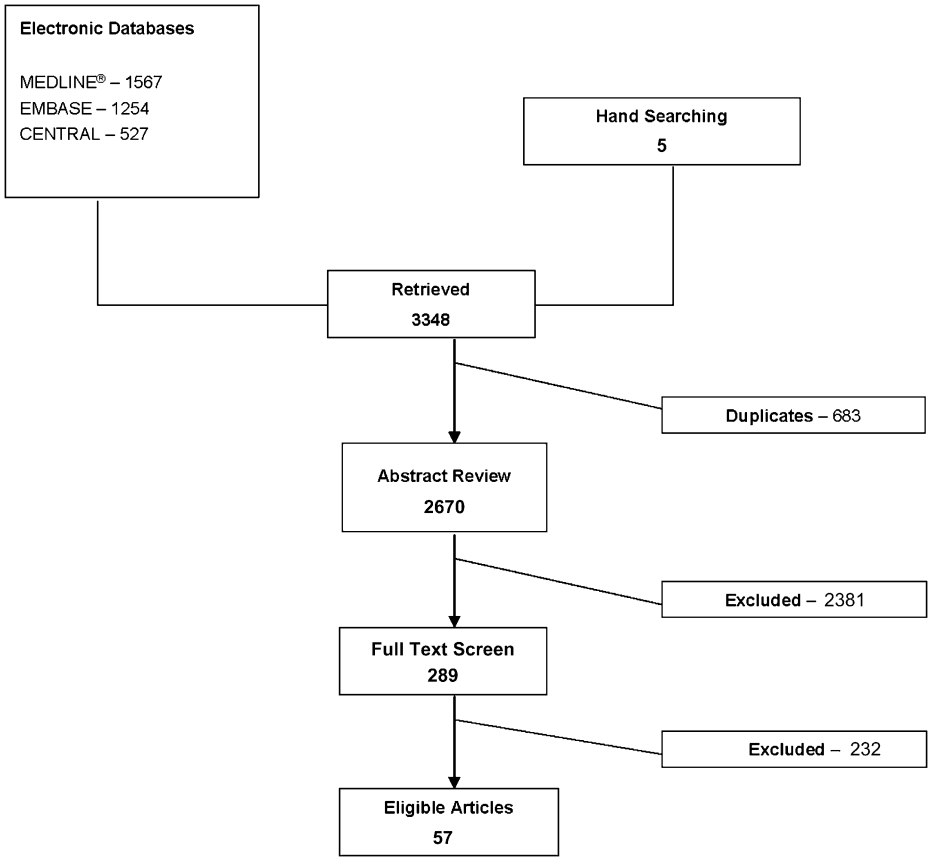

Figure 1. Summary of search and review process. MEDLINE was accessed via PubMed. EMBASE = Excerpta Medica database; CENTRAL = Cochrane Central Register of Controlled Trials.

patients with asymptomatic or mild airway disease (Table 2). Gibson and coworkers (11) studied 21 patients less than 6 years of age with *P. aeruginosa* present in bronchoalveolar lavage and found that *P. aeruginosa* density was decreased in patients receiving inhaled tobramycin. Because of the young age and generally mild lung disease of the study population, lung function and exacerbation frequency were not primary outcome measures of the trial. In the second trial, Murphy and coworkers (12) compared aerosolized tobramycin with standard therapy in 181 patients (6 to 15 yr of age) over 56 weeks. Of note, the study was halted early because patients treated with standard therapy experienced a greater number of exacerbations requiring hospitalization. Overall, patients receiving aerosolized tobramycin had fewer exacerbations (11.0 vs. 25.6%) than did those receiving standard therapy. There was no improvement in FEV_1, but those receiving aerosolized tobramycin did have a significant improvement (10%) in the measurement of forced expiratory flow (midexpiratory phase).

The quality of the evidence for the use of inhaled tobramycin in patients with mild disease is limited by the number of studies, and patients in the larger study were limited because it was halted early, and so was rated as fair in quality overall. Evidence for its use in the youngest population (i.e., less than 6 yr) is too poor to permit any recommendations. The larger study was halted early because of the benefit of a reduction in exacerbations, which we have rated as a moderate net benefit.

Recommendation:
For patients with CF, age 6 years and older who are asymptomatic or with mild lung disease, and with *P. aeruginosa* persistently present in cultures of the airways, the Cystic Fibrosis Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations. Level of evidence, fair; net benefit, moderate; grade of recommendation, B.

Other inhaled antibiotics. Inhaled colistin is used frequently for treatment of patients with CF and who are infected with *P. aeruginosa*. However, only two eligible trials of colistin including a total of 155 patients were uncovered by our search (Table 2). Jensen and coworkers (13) compared colistin with placebo in 40 patients over 90 days after a course of intravenous antibiotics. Both groups experienced a decrease in FEV_1 (11–17%) during treatment; no advantage was seen in the colistin group. Hodson and coworkers (14) compared colistin with tobramycin in 115 patients over 4 weeks. The patients treated with colistin did not show any measured improvement in lung function, whereas patients receiving tobramycin experienced an increase in FEV_1 of 6.7%. No data were provided on exacerbations or quality of life.

There are even fewer data available for other inhaled antibiotics (15, 16). Overall, the committee believed the evidence was insufficient to assess the effects on health outcomes of inhaled antibiotics other than tobramycin because of the limited number and power of studies.

Recommendation:
For patients with CF, age 6 years and older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., colistin, gentamicin, ceftazidime) to improve lung function and reduce exacerbations. Level of evidence, poor; net benefit, small; grade of recommendation, I.

Recombinant Human DNase

Airway obstruction by thickened secretions and cellular debris is the hallmark of CF lung disease. Recombinant human DNase

TABLE 2. EVALUATION OF EVIDENCE

Treatment Question	Type of Review*	Studies*	Total (*n*)	Strength of Evidence	Estimate of Net Benefit	Recommendation
Inhaled tobramycin						
Moderate–severe lung disease	S	3 RCT (6, 7, 9); 1 RCO (8); 2 one-arm trials (98, 99)	679	Good	Substantial	A
	C (10)					
Asymptomatic–mild disease	S	2 RCT (11, 12)	202	Fair	Moderate	B
Other inhaled antibiotics (colistin, gentamicin, ceftazidime)	S	2 RCT (13, 14); 2 RCO (15, 16)	206	Poor	Small	I
Dornase alfa						
Moderate to severe lung disease	S	10 RCT (17–20, 22–26, 28); 3 cross-over (21, 27, 100); 6 trials without comparison groups (101–106)	3,140	Good	Substantial	A
	C (29)					
Asymptomatic–mild lung disease	S	3 RCT (30–32); 1 cross-over (107)	520	Fair	Moderate	B
Hypertonic saline	S	2 RCT (34, 35); 2 RCO (compared with dornase alfa) (36, 37)	284	Fair	Moderate	B
	C (38)					
Inhaled corticosteroids	S	5 RCT (41, 43–46); 2 RCO (42, 47)	388	Fair	Zero	D
	C (48)					
Oral corticosteroids						
Age, 6–18 yr	S	3 RCT (49–51)	354	Good	Negative	D
	C (52)					
Age, >18 yr	S	1 cross-over (53)	20	Poor	None	I
Oral nonsteroidal antiinflammatory drugs	S	3 RCT (54–56)	145	Fair	Moderate	B
	C (57)					
Leukotriene modifiers	M	2 RCO (59, 60); 1 controlled trial (61)	64	Poor	None	I
Cromolyn	M	2 RCT (63, 64); 1 clinical trial (62)	44	Poor	None	I
Macrolide antibiotics	S	2 RCT (67, 68); 1 cross-over (69); 1 clinical trial (66)	296	Fair	Substantial	B
	C (70)					
Antistaphylococcal antibiotics	M	3 RCT (71, 73, 74); 1 cross-over (72)	306	Fair	Negative	D
	C (75)					
Inhaled β_2-adrenergic receptor agonists	C (76)	14 RCO: nebulized (77–83) and metered dose (84–90)	257	Good	Moderate	B
Inhaled anticholinergics	C (76)	5 RCO (77, 79, 82, 83, 87)	79	Poor	None/small	I
Oral *N*-acetylcysteine	M	1 Phase 1 trial (108); 1 RCO (109); 1 controlled trial (110); 2 cross-over (111, 112)	145	Poor	None	I

Definition of abbreviations: C = Cochrane; M = modified systematic; RCO = randomized cross-over trial; RCT = randomized controlled trial; S = systematic.
* References are given in parentheses.

(dornase alfa) was developed to degrade the large amount of free DNA that accumulates within CF mucus, thereby improving the viscoelastic properties of airway secretions and promoting airway clearance. The short-term (not more than 14 d) and long-term effects of dornase alfa on lung function, and the long-term effects of dornase alfa on pulmonary exacerbations, have been studied. As with inhaled tobramycin, recommendations were stratified on the basis of the severity of lung disease (*see above*).

Dornase alfa for moderate to severe disease. Nineteen trials of dornase alfa in a total of 3,140 patients with moderate to severe disease were identified by systematic review (Table 2). Five of these studies evaluated the long-term efficacy of dornase alfa (17–21), including large, multicenter trials lasting 12–96 weeks (17, 18, 20).

Most short-term studies of dornase alfa showed a significant improvement in lung function as measured by FEV_1. Treatment for 6–14 days increased FEV_1 by 11.2–15.4% when compared with placebo (22–25). Two studies failed to show a significant improvement over placebo in FEV_1 with short-term treatment in clinically stable patients (26, 27), yet long-term studies uniformly demonstrated improvement in lung function with dornase alfa. Fuchs and coworkers (18) found that FEV_1 increased 5.8% compared with placebo after 24 weeks of therapy with dornase alfa (n = 968). McCoy and coworkers (20) achieved a similar improvement in FEV_1 (net benefit, 7.3%) in patients (n = 320) with severe CF lung disease treated for 12 weeks. Five studies assessed the effect of dornase alfa on the incidence of pulmonary exacerbations (18, 20, 23, 24, 28), but only Fuchs and coworkers (18) reported a significant difference, with those in the dornase alfa group requiring fewer days in hospital or fewer days of antibiotics compared with the placebo group. Finally, four trials commented on quality of life measures (18, 23, 24, 28); all reported higher overall well-being scores for those patients receiving dornase alfa compared with placebo, although this achieved statistical significance in only one trial (18). Overall, dornase alfa was well tolerated; there were few adverse events that were increased by dornase alfa compared with placebo. The most common of these was voice alteration.

A Cochrane review of the use of dornase alfa by patients with CF, with the most recent search dated 2005 (29), suggested that overall improvement in lung function occurred in patients receiving dornase alfa in comparison with those receiving a placebo.

On the basis of the number of patients studied and the breadth of both short- and long-term studies, the quality of the evidence is good for patients with moderate–severe lung disease. Further, the improvement in lung function and low risk of adverse events indicate a substantial net benefit of dornase alfa.

Recommendation:
For patients with CF, 6 years of age and older, with moderate to severe lung disease, the Cystic Fibrosis Foundation strongly recommends the chronic use of dornase alfa to improve lung

function and reduce exacerbations. Level of evidence, good; net benefit, substantial; grade of recommendation, A.

Dornase alfa for mild disease. Four trials were identified that compared dornase alfa with placebo in a total of 520 patients with mild CF airway disease (Table 2). The studies ranged in duration between 2 and 96 weeks.

Quan and coworkers (30) reported improvement in FEV_1 (3.2%) in 239 children with mild lung disease using dornase alfa compared with 235 children receiving a placebo over 96 weeks. This improvement was not seen in a study of 25 children (11 receiving dornase alfa, 14 receiving placebo) after 52 weeks of treatment with dornase alfa (31). Quan and coworkers (30) also reported a 34% reduction in pulmonary exacerbations. In a separate trial involving 12 patients less than 5 years of age, Nasr and coworkers (32) reported improved quality of life for those patients using dornase alfa, but statistical analysis was not reported. As in the trials involving patients with more severe lung disease, the medication was well tolerated with the most common side effect, voice alteration, occurring in up to 18% of subjects (30).

The quality of the evidence identified by the systematic review for the use of dornase alfa in patients with mild lung disease is limited by the number of studies; although there were three randomized controlled trials, only one consisted of a large number of patients. Thus, the evidence was rated as fair. The net benefit of dornase alfa in this population was rated as moderate.

Recommendation:
For patients with CF, 6 years of age and older, and asymptomatic or with mild lung disease, the Cystic Fibrosis Foundation recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations. Level of evidence, fair; net benefit, moderate; grade of recommendation, B.

Hypertonic Saline

Hypertonic saline (HS) inhalation has been proposed as a therapy to increase hydration of airway surface liquid in patients with CF, thereby improving mucociliary clearance (33). Systematic review identified two trials of hypertonic (6–7%) saline compared with normal (0.9%) saline in a total of 222 patients, and two trials comparing HS with dornase alfa in a total of 62 patients (Table 2). The largest trial investigated the effect of twice daily treatments with 7% saline for 48 weeks in 164 patients (34), whereas the others involved fewer patients and shorter treatment durations (2–12 wk).

In a randomized controlled trial, Eng and coworkers (35) studied the effects of 6% saline administration inhaled twice daily for 14 days in 58 patients, 75% of whom were children. They found that HS therapy led to a mean increase in FEV_1 of 15.0% compared with 2.8% in the placebo (normal saline) group. The larger multicenter study of Elkins and coworkers (34) enrolled 164 patients (83 receiving HS); twice daily treatment with 7% saline did not result in a difference in FEV_1 compared with placebo. In the two cross-over trials, use of HS increased FEV_1 3–7.7% above baseline (36, 37) although there was a greater increase resulting from 12 weeks of once daily dornase alfa, with a net improvement of 8% over twice daily HS (37). Only Elkins and coworkers (34) assessed exacerbations, demonstrating a 56% reduction in pulmonary exacerbations for patients receiving 7% saline compared with normal saline. In the two studies evaluating quality of life (34, 35), only some domains of the Medical Outcomes Study 36-item Short-form General Health Survey (SF-36) were significantly improved by HS therapy.

A Cochrane review from 2005 on the use of hypertonic saline found that overall lung function improved with the use of HS compared with placebo, but the improvement was not as great as that seen with dornase alfa (38).

Overall, the quality of evidence for the use of HS in patients with CF is limited by the number of studies, although one consisted of a large number of patients over a prolonged period of time, and there were consistent findings. Thus, the evidence was determined to be fair in quality. In general, HS was well tolerated, particularly if the patients were pretreated with an inhaled bronchodilator; the most common side effect was cough or bronchospasm, which was clinically significant in only a few patients. The committee determined that HS provided a net benefit that was moderate.

Recommendation:
For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and to reduce exacerbations. Level of evidence, fair; net benefit, moderate; grade of recommendation, B.

Antiinflammatory Agents

Antiinflammatory therapies are often used in the treatment of CF lung disease because the inflammatory response in CF airways is excessive (39, 40). It is thought that this excessive and persistent inflammation is a major cause of destruction of the airways, over time leading to bronchiectasis and severe obstructive airway disease. The committee focused on the use of antiinflammatory agents for CF-related inflammation and excluded studies addressing patients with asthma or allergic bronchopulmonary aspergillosis (ABPA). The committee recognized the challenge of making the diagnosis of asthma in the patient with CF, and has made specific comments regarding this issue in Key Unanswered Questions (*see later*).

Inhaled corticosteroids. We identified seven trials evaluating the use of inhaled corticosteroids in CF, including a total of 388 patients with CF ranging in age from 4 to 53 years (Table 2). All of the studies evaluated lung function as an outcome measure, with two studies assessing the number of pulmonary exacerbations (41, 42). The duration of the studies varied from an unspecified time to 6 months. The dose of inhaled corticosteroid also varied: beclomethasone (400–1500 μg) was given two to four times daily (43, 44); fluticasone (400–500 μg) was given twice daily (42, 45); and budesonide (800 μg) was given twice daily (46, 47). The largest and most comprehensive study was a withdrawal study involving 171 patients, excluding those who had received oral corticosteroids within the prior month or who were using high-dose inhaled corticosteroids (41). In this study, patients were randomized to continue taking inhaled corticosteroids or to be given placebo over a period of 6 months.

No studies demonstrated a statistically significant improvement in lung function as measured by FEV_1 or FVC, nor were they powered to evaluate lung function decline. Of the two studies that presented detailed pulmonary exacerbation data, no differences were noted between the treatment and placebo groups (41, 42). The larger steroid-withdrawal study (41) had a primary outcome of time to exacerbations, and there was no difference between the treatment and placebo groups. A Cochrane review of inhaled corticosteroids in CF, with the most recent search dated 2006 (48), concluded no benefits or harms resulted from inhaled corticosteroids.

The quality of evidence for the benefit of inhaled corticosteroids in patients with CF was limited by the number of patients per trial and the duration of study, although the results

were consistent. Thus, the evidence was interpreted as fair. Although no statistically significant adverse events were reported, the committee determined that there was zero net clinical benefit of inhaled corticosteroid use in patients with CF.

Recommendation:
For patients with CF, 6 years of age and older, and without asthma or ABPA, the Cystic Fibrosis Foundation recommends against the routine use of inhaled corticosteroids to improve lung function and to reduce exacerbations. Level of evidence, fair; net benefit, zero; grade of recommendation, D.

Oral corticosteroids for children. We identified three randomized controlled trials evaluating the efficacy of systemic corticosteroids in a total of 354 children with CF (Table 2). All studies used alternate day dosing; age ranges of enrolled patients varied, as did treatment durations (3 wk to 4 yr). Two studies demonstrated significantly improved lung function with corticosteroids (49, 50). A third study, by Eigen and coworkers (51), demonstrated simply a difference in lung function between active and placebo-treated groups. This was the largest study, involving a total of 285 patients ranging in age from 6 to 14 years. The trial assessed the use of alternate day prednisone (1 or 2 mg/kg; maximum, 60 mg) or placebo (95 subjects per treatment group) for a treatment duration of 4 years. The study found that the mean percentage of predicted FEV_1 in the placebo group decreased from 79.2% at baseline to 73.8% at 48 months, but the percentage of predicted FEV_1 in the prednisone (1 mg/kg) group did not decrease significantly (84.0% at baseline and 82.7% at 48 mo). No differences were observed in relation to rates of hospitalization across any treatment group. However, all patients in both prednisone treatment groups were discontinued early by the data safety monitoring committee because of an excess number of adverse events in the active treatment arms including abnormalities in glucose metabolism, cataracts, linear growth retardation, and percentage of "colonization" with *P. aeruginosa*.

A Cochrane review, with the most recent search dated 2006 (52), also noted a benefit to lung function and an increase in adverse events with oral corticosteroids.

Because of the duration of the study by Eigen and coworkers (51), which was performed at multiple centers, and the consistency of the other studies, the overall quality of clinical evidence was interpreted as good. Although there appears to be a benefit to lung function with steroid therapy, the adverse events related to steroids result in a net negative effect for children with CF.

Recommendation:
For patients with CF, between 6 and 18 years of age, and without asthma or ABPA, the Cystic Fibrosis Foundation recommends against the chronic use of oral corticosteroids to improve lung function and to reduce exacerbations. Level of evidence, good; net benefit, negative; grade of recommendation, D.

Oral corticosteroids for adults. A systematic search revealed only one eligible trial of corticosteroids in 20 adults (Table 2). The study used daily dosing of prednisolone (30 mg) for 3 weeks (53). There was no change in lung function or quality of life when compared with placebo. No adverse events were reported. Some of the adverse effects of steroid use in children (e.g., linear growth retardation) are not relevant in adults. However, there is concern for development of osteoporosis and diabetes as a result of oral corticosteroid use, as these are recognized CF-related complications in adulthood. The committee determined there are insufficient data to recommend for or against oral corticosteroid use in adults with CF.

Recommendation:
For adult patients with CF (18 yr and older) without asthma or ABPA, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral corticosteroids to improve lung function and to reduce exacerbations. Level of evidence, poor; net benefit, zero; grade of recommendation, I.

Oral nonsteroidal antiinflammatory drugs. We identified three eligible trials of nonsteroidal antiinflammatory drugs (NSAIDs) in CF (Table 2). After a small dose-escalation study (54), Konstan and coworkers (55) performed a randomized, double-blind placebo-controlled trial of ibuprofen at doses of 16.2–31.6 mg/kg body weight in 85 patients with CF over a 4-year period. Patient ages ranged from 5 to 39 years with FEV_1 measurements indicating at least 60% predicted on study entry. The study demonstrated that twice daily, orally administered ibuprofen resulted in significant slowing of the rate of decline in FEV_1 when compared with placebo. The annual rate of change (slope) in FEV_1 (percentage of predicted value) was 40% less for the intent-to-treat analysis and 59% less for the completed-treatment analysis. The effect was most dramatic for patients with CF who were less than 13 years of age at the time of enrollment. The study found no differences in rates of hospitalization or adverse events.

A second NSAID was studied by Sordelli and coworkers (56) in 41 patients with CF, 5–37 years of age. Piroxicam was administered at doses of 5–20 mg/day according to weight, for 12–19 months. The trial failed to demonstrate any benefit in relation to lung function when compared with placebo. A Cochrane review, with the most recent search dated 2005 (57), concluded there were insufficient studies to recommend routine use of NSAIDs.

The limited trial of piroxicam represented a poor level of evidence and the committee was unable to make a recommendation for its use. Although the ibuprofen study was performed at only one center with a modest number of patients (55), it was well designed and executed over a long period; thus, the committee determined the level of evidence for the benefit of ibuprofen in patients with CF to be fair. Furthermore, the evident positive effect of ibuprofen on the rate of decline in FEV_1 and the theoretical potential benefit to improve survival suggest a substantial estimated net clinical benefit. Konstan and coworkers postulate that subtherapeutic doses of ibuprofen might actually exacerbate pulmonary inflammation (58) and thus they strongly recommend pharmacokinetic studies be done on each individual receiving high-dose ibuprofen to assure appropriate serum levels (54). The committee maintained concerns about potential adverse effects on renal function over time that would not be apparent in a study with a limited sample size, and determined the net clinical benefit for ibuprofen to be moderate.

Recommendation:
For patients with CF, 6 years of age and older, and with FEV_1 greater than 60% predicted, the Cystic Fibrosis Foundation recommends the chronic use of oral ibuprofen to slow the loss of lung function. Level of evidence, fair; net benefit, moderate; grade of recommendation, B.

Leukotriene modifiers. It has been suggested that products of arachidonic acid metabolism, specifically the leukotrienes (LTs), may contribute to CF lung disease. Cysteinyl leukotrienes

(LTC_4, LTD_4, and LTE_4) are produced predominantly by eosinophils, mast cells, and macrophages and have been found in increased concentrations in airway secretions from patients with CF. Such a finding suggests that inhibition of this inflammatory pathway may prove beneficial in CF.

Three studies on the use of leukotriene antagonists, involving a total of 64 patients with CF and ranging between 6 weeks and 4 months, met the inclusion criteria of the modified systematic review (Table 2). One of the studies, a placebo-controlled, randomized, double-blind cross-over study of 12 patients with CF, found that treatment with montelukast for 20 weeks resulted in an increase in FEV_1 of 8% of predicted (59). A trial of zafirlukast in 25 patients did not improve lung function (60). Lawrence and Sorrel used eicosapentaenoic acid in a placebo-controlled trial in 16 patients for 6 weeks (61). They reported improved lung function, given as actual volumes, and reduced sputum volume. Because of the limited number of trials and subjects, we determined the quality of the data to be poor, and no benefit can be determined for leukotriene receptor antagonists.

Recommendation:
For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against routinely providing the chronic use of leukotriene (i.e., LTD_4) modifiers to improve lung function and to reduce exacerbations. Level of evidence, poor; net benefit, zero; grade of recommendation, I.

Cromolyn. Cromolyn (sodium cromoglycate) has been used in the treatment of CF for bronchial hyperactivity. Three studies involving 44 patients using cromolyn were identified by modified systematic review (Table 2). Two were 1-day studies, investigating the ability of cromolyn to protect against bronchoprovocation (62, 63). In one, Mitchell and coworkers (62) tested 15 patients with CF and methacholine-induced bronchoconstriction; 4 patients had less hyperreactivity and 2 patients had complete protection from the effects of methacholine when they were pretreated with cromolyn. In contrast, Chua and coworkers (63) studied 15 children with CF with ticarcillin-induced hyperreactivity and found that whereas albuterol completely blocked the bronchoprovocation, cromolyn only partially blocked the response to inhaled ticarcillin. The one longer study, a double-blind, placebo-controlled, cross-over study of 14 patients with CF, revealed no significant effect of cromolyn on clinical assessment, methacholine challenge, or pulmonary function (64).

These studies included few patients and demonstrated virtually no benefit, although there were no noted harms. Thus, the evidence that these therapies are effective is of poor quality, and the balance of benefits and harms cannot be determined.

Recommendation:
For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against routinely providing the chronic use of cromolyn to improve lung function and to reduce exacerbations. Level of evidence, poor; net benefit, zero; grade of recommendation, I.

Macrolide Antibiotics

Macrolide antibiotic therapy has been used in diffuse panbronchiolitis (a disease with similarities to CF lung disease) with good effect (65). The mechanism of action may be related to either the antimicrobial or antiinflammatory properties of these agents, or perhaps to both.

Systematic review identified four studies that addressed the chronic use of macrolide antibiotics in CF (Table 2). Although no changes in lung function were reported after 6 weeks of clarithromycin treatment in 10 adults with CF (66), a significant improvement in FEV_1 (3.6–6.2%) was seen in patients treated with azithromycin compared with placebo (67–69). These trials were longer term, with treatment lasting from 3 months (68) to 6 months (67, 69), and involving between 41 (69) and 185 (67) patients with CF. Azithromycin doses ranged from three times weekly at 250 or 500 mg (67) to 250 mg daily (68, 69). One trial, which enrolled only patients chronically infected with *P. aeruginosa*, demonstrated that those patients receiving azithromycin experienced a significant reduction in pulmonary exacerbations (67). Patients receiving azithromycin in all three trials required fewer courses or days of antibiotics (67–69). Measures of quality of life varied among the studies; Wolter and coworkers (68) reported improvement in quality of life as measured with the Chronic Respiratory Disease Questionnaire, but no differences were noted in other trials using CF-specific measures (67, 69). Significant adverse events reported with the use of macrolide antibiotics included nausea, diarrhea, and wheezing (67), but overall the treatment was well tolerated. Important exclusion criteria for these studies included a history of detection of *Burkholderia cepacia* complex (66, 67, 69) or atypical mycobacteria (66, 67) in sputum cultures, and liver disease or elevated liver function tests (67–69).

A Cochrane review of the use of macrolide antibiotics in CF, with the most recent search dated 2005 (70), found a small but significant improvement in lung function in patients with CF when macrolides were compared with placebo.

Because of the limited number of studies and patients, and the heterogeneity of dosing regimens, the committee graded the quality of the data as fair. However, the committee believed that there was substantial benefit in the studies supporting the use of azithromycin to improve lung function and to reduce the risk of exacerbations in patients colonized with *P. aeruginosa*.

Recommendation:
For patients with CF, 6 years of age and older, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the Cystic Fibrosis Foundation recommends the chronic use of azithromycin to improve lung function and to reduce exacerbations Level of evidence, fair; net benefit, substantial; grade of recommendation, B.

Antistaphylococcal Antibiotics

Staphylococcal bacteria are commonly identified in the sputum of young children with CF. Four studies of the effects of treatment with antistaphylococcal antibiotics were identified that met our inclusion criteria, using a modified systematic review (Table 2). Lower rates of *Staphylococcus aureus*–positive cultures were seen in patients receiving antistaphylococcal prophylaxis in two of the trials—a 2-year trial of flucloxacillin in 38 infants with CF (71) and a 2-year trial of cephalexin in 17 patients who were 1–33 years of age (72). There was no difference in pulmonary function in two studies (73, 74) including a double-blind, placebo-controlled study by Stutman and coworkers in 209 infants testing the effect of cephalexin given for 7 years (73). Only Loening-Baucke and coworkers (72) demonstrated significant improvement in lung function, occurring in patients infected with *Haemophilus influenzae* and thought to be related to coinfection with *S. aureus.* Rates of exacerbations and hospitalizations were reduced with prophylaxis in two studies (71, 72). Stutman and coworkers (73), conversely, did not find any differences in CF exacerbations,

that is, hospitalizations, infections, or hospital days. Cough was reduced in one study (71). Of concern was the finding that treatment with antistaphylococcal prophylaxis resulted in a greater occurrence of *Pseudomonas* in the sputum cultures of those receiving prophylaxis; this was reported in the study with the greatest number of patients and longest follow-up (73).

A Cochrane review on the use of antibiotics to prevent infection with *S aureus,* with the most recent search dated 2006 (75), concluded that fewer children had sputum isolates with *S. aureus* when treated prophylactically with antistaphylococcal agents, the clinical importance of which is uncertain.

Because there is a limited number of studies, with a heterogeneous selection of antibiotics used and variability in trial duration and ages of patients studied, the committee assessed the quality of evidence for the prophylactic use of antistaphylococcal therapy as fair. Further, any proposed benefits in lower rates of *S. aureus* infection or equivocal effects on hospitalization and exacerbation rates are outweighed by the risk of earlier or more frequent *P. aeruginosa* infection.

Recommendation:
For patients with CF, the Cystic Fibrosis Foundation recommends against the prophylactic use of oral antistaphylococcal antibiotics to improve lung function and to reduce exacerbations Level of evidence, fair; net benefit, negative; grade of recommendation, D.

Bronchodilators

β_2-Adrenergic receptor agonists. The experience with β_2-adrenergic receptor agonists in CF has been summarized in a Cochrane review (76). Of 43 referenced publications, they selected 14 trials for evaluation (Table 2). The review evaluated both short-acting (77–89) and long-acting β_2-adrenergic receptor agonists (81, 85, 90) in a total of 257 subjects from 6 to 39 years of age. Only some of the studies commented on reversible airway disease as an inclusion criterion. Short-acting β_2-adrenergic receptor agonists (salbutamol or albuterol) were administered at daily doses ranging from 80 to 600 μg (by metered dose inhaler) or from 0.5 to 5.0 mg (by nebulizer). The long-acting β_2-adrenergic receptor agonist (salmeterol) was administered at doses from 84 to 336 μg by metered dose inhaler.

Inhaled β_2-adrenergic receptor agonists consistently demonstrated an improvement in lung function in short-term studies, ranging from 2 days to 4 weeks, although this benefit was not sustained in long-term studies. Five short-term studies focused on patients with documented bronchodilator response or bronchial hyperreactivity (79, 84, 87, 88, 90); in this subset of patients, all subjects showed a significant improvement in lung function as measured by FEV_1 or peak expiratory flow rate. Three studies were long term, lasting 4 to 26 weeks (81, 84, 86) Two of these studies showed improved outcomes as defined by peak expiratory flow (84) or FEV_1 (81). The latter study compared long-acting with short-acting β_2-adrenergic receptor agonists and found a greater improvement with long-acting β_2-adrenergic receptor agonists. Both short- and long-acting β_2-adrenergic receptor agonists were well tolerated.

The quality of evidence for β_2-adrenergic receptor agonist use in patients with CF was believed to be good because of the number of studies with consistent results. The net benefit for β_2-adrenergic receptor agonists was interpreted as moderate in patients who demonstrate bronchial hyperresponsiveness or a bronchodilator response.

Recommendation:
For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation recommends the chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function. Level of evidence, good; net benefit, moderate; grade of recommendation, B.

Inhaled anticholinergic agents. The Cochrane review of bronchodilators cited above (76) also included analysis of short-acting inhaled anticholinergic medications; there are no data on the efficacy of a long-acting anticholinergic medication. Five studies (Table 2) were identified that assessed the potential benefit of inhaled ipratropium bromide in a total of 79 clinically stable patients with CF from 6 to 43 years of age with disparate lung disease severity (FEV_1 15.6–128.8% predicted). Ipratropium bromide was administered at doses from 40 to 80 μg by metered dose inhaler or from 50 to 500 μg by nebulizer. Lung function results after a single dose of ipratropium were compared with those measured after administration of a placebo or with baseline measurements obtained before administration of ipratropium bromide on the same day or the previous day. None of the studies assessed any long-term clinically relevant outcome measures.

Three studies demonstrated statistically significant increases in FEV_1 in response to inhalation of ipratropium bromide (82, 83, 87) Acute increases in FEV_1 greater than 10% after inhalation of ipratropium bromide were seen in a subgroup of patients with CF known to exhibit improved airflow in response to inhalation of short-acting β_2-adrenergic receptor agonists (82, 87). Paradoxical decreases in FEV_1 measurements (less than 10%) were observed in isolated patients with CF after inhalation of ipratropium bromide.

Because outcome measures were limited primarily to physiologic data, there were no long-term assessments, and the trials were small, the level of evidence for the benefit of inhaled ipratropium bromide in patients with CF was interpreted as poor. In addition, the estimated net clinical benefit was thought to be small.

Recommendation:
For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function. Level of evidence, poor; net benefit, small; grade of recommendation, I.

N-acetylcysteine

N-acetylcysteine (NAC) depolymerizes mucus by breaking disulfide bonds. It is hypothesized that breaking these bridges decreases mucus viscosity and improves airway clearance. There are several studies of oral and inhaled NAC in patients with CF, but most studies evaluated changes in rheologic properties of CF sputum. An earlier review of oral and inhaled NAC concluded that there was no benefit from inhaled NAC, but there was a trend toward a potential small benefit with oral therapy (91) The results of our modified systematic review of original research assessing the use of NAC compared with placebo or standard therapy in patients, including the number and type of studies, and the number of participants, are shown in Table 2. Study durations ranged between 2 weeks and 3 months. The quality of the evidence was determined to be of poor quality. None of the studies demonstrated a clinical benefit or any improvement in lung function. There were no significant adverse events reported.

Recommendation:
For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against routinely providing for the chronic

use of inhaled or oral *N*-acetylcysteine to improve lung function and to reduce exacerbations. Level of evidence, poor; net benefit, zero; grade of recommendation, I.

Key Unanswered Questions

There are a great many questions regarding chronic therapies for CF that remain unanswered by existing clinical trials. We now address some of them:

1. *Does "chronic" therapy mean lifelong therapy?* One of the challenges of this review is that clinical trials of these medications have ranged in duration from 2 weeks to 4 years, with the typical "long-term" duration of treatment being 6 months. It is conceivable that an important treatment benefit (or unintended or adverse event) could be missed in shorter studies or that a treatment effect detected in a short trial may not be durable over a longer period of time. We note that the ibuprofen study (55) demonstrated substantial benefit but only after a prolonged study period (4 yr). Also, an observation of sputum culture results in a group of patients who had been undergoing macrolide therapy for 3 years noted an incremental rise in staphylococcal resistance to macrolides over time, from 10% at baseline to 100% in the third year (92). The significance of this finding is not yet known. It is important for the clinician to closely monitor each patient and decide whether a particular therapy is continuing to benefit the patient or whether it should be discontinued.
2. *How should the clinician prioritize these therapies?* The committee recognizes that not all patients will benefit from each of these medications and many patients will benefit from using multiple therapies. In a patient with mild pulmonary disease or diagnosed asymptomatically in the newborn period, the clinician must determine when to introduce a new therapy with the intention of chronic use. Balancing the potential long-term benefit with the additional treatment burden is a difficult act. There are no studies that have evaluated when to introduce any of these medications; there is a great need for research in this area.
3. *In which order should patients perform their aerosolized therapies?* Many patients will be using more than one aerosolized therapy. Few studies have assessed the appropriate order of treatment, and more such studies are needed. Of note, one study showed a benefit to the use of dornase alfa before chest physiotherapy (93), although an earlier study did not (94); thus, there can be no consensus on the order of such therapies at present. A pragmatic suggestion that takes into account ways to optimize delivery (e.g., bronchodilation may improve distal delivery of drugs given subsequently) is to order the therapies as follows: inhaled bronchodilator, hypertonic saline, dornase alfa, aerosolized antibiotic. Airway clearance therapies, not addressed here, should be performed after dornase alfa administration and before administration of the antibiotics.
4. *Are there important interactions between these medications?* There are known *in vitro* drug interactions (e.g., dornase alfa is rendered inactive by high salt concentrations) but it is not known if this effect will occur *in vivo*. Most of the studies reviewed here included patients receiving a wide variety of medications; it is nearly impossible to control for all medication interactions. It is generally assumed in clinical practice that therapies will be additive; that is, there will be an independent beneficial effect to the medications. However, it is not known if there are synergistic, antagonistic, or additive effects of these medications. Again, further studies in this area are needed.
5. *Does the presence of specific bacteria affect the response to chronic pulmonary therapies?* A limitation of some of the studies reviewed here is that certain patients are excluded from participation because of the presence of specific pathogens in sputum cultures. Some pathogens (e.g., *B. cepacia* complex) have been associated with more rapid decline in lung function, and as they are present in a minority of patients, patients with these pathogens have often been excluded from studies so as not to bias results. As such, we are unable to determine whether patients harboring these organisms will benefit from specific medications, but we believe it is reasonable for a clinician to consider generalizing these recommendations to this subgroup of the patient population.
6. *Does the development of antibiotic resistance in patients taking chronic inhaled antibiotics affect the clinical response to the drug?* The use of any antibiotic (oral, intravenous, or inhaled) is associated with selection of pathogens with *in vitro* resistance by standard testing. Nevertheless, patients with highly resistant pathogens detected in sputum cultures may still derive clinical benefits from aerosolized tobramycin (95). This may be due to the substantial pharmacodynamic benefits of aerosolized antibiotics; that is, high concentrations of drug can be delivered to the site of infection with low risk of toxicity (96). However, it is not known if this benefit will continue over long periods of time.
7. *How should the clinician assess asthma or bronchodilator responsiveness?* Making the diagnosis of asthma in this population is challenging, and individual patients with CF demonstrate varying responses to bronchodilators over time as measured by spirometry. These facts complicate interpreting the present guidelines, as some recommendations specifically exclude patients with a diagnosis of asthma or ABPA. Because patients who demonstrate bronchial hyperreactivity or a bronchodilator response may represent a significant portion of the CF population the physician must assess airway hyperreactivity on an individual basis. Unfortunately, there are no studies that provide sufficient information about the appropriate use of testing such as bronchoprovocation or postbronchodilator testing to determine airway reactivity accurately in the CF population. It has been suggested that it may be useful to measure bronchodilator responsiveness in all patients on a regular basis and to treat those who show a positive response with inhaled bronchodilators (97). However, the caregiver should be cautious about labeling all such patients as having "asthma" and instituting inhaled corticosteroid or other asthma therapy. Once a patient has demonstrated bronchial reactivity, bronchodilators could be continued without repeating challenge tests. After that time, it is difficult to appreciate the utility of repeated testing with respect to therapeutic options.

8. *How should we best treat children less than 6 years of age?* There are few studies of chronic pulmonary therapies in pre–school age children. In part, this is because appropriate end points are difficult to identify. Furthermore, federal regulations make inclusion of young children in research studies more complicated because of concerns of beneficence; institutional review boards applying the Common Rule 45 CFR 46 hold pediatric studies to a higher standard. However, it is quite possible that early therapy, before lung disease is established, will provide the most significant long-term benefits for children with CF. Thus, studies including very young patients must be designed and undertaken.

Conclusions

We have reviewed and evaluated the evidence supporting the use of chronic medications used for the maintenance of lung function in patients with CF. We have developed recommendations based on the quality of the published evidence and the estimate of the net benefit demonstrated within those publications. We recognize the limitations of our review, due particularly to a lack of data regarding therapies in children less than 6 years of age. These recommendations will be amended as new data are reported.

This document should be viewed as a guideline regarding CF care. The introduction and use of specific medications will depend on the individual patient, their social situation, and parental or patient preferences. We are hopeful that clinicians will find these recommendations to be useful in their care of patients with CF.

Conflict of Interest Statement: P.A.F. received $1,000 from Novartis and $1,000 from Genentech in lecture fees, $140,000 from Novartis and $16,000 from Genentech for participating in multicenter clinical trials, and $3,000 from 2005 to 2007 from Genentech as a speaker in sponsored courses and $3,000 between 2005 and 2007 from Novartis as a speaker in sponsored courses. B.P.O. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.A.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.H.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.B.W.-C. received $20,635 from Genetech-Inverseh Research from May 2004 to April 2006 for participation in the Epidemiologic Study of Cystic Fibrosis. J.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. L.Q. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.R. serves on an advisory board for the Cystic Fibrosis Foundation Center Committee. R.L.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. L.H.'s institution received unrestricted educational grants from Novartis and Genentech, companies that manufacture drugs listed in this article. K.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors gratefully acknowledge valuable contributions to this project from the following: *Johns Hopkins University:* Rajender K. Agarwal, M.B.B.S., M.P.H.; Ting-Yuan Cheng, M.S.; J. Michael Collaco, M.D.; Annamarie N. Kisalu, M.B.Ch.B., M.P.H.; Lauren Kucirka, B.A., B.S.; Oladubu Michael Oluwamayowa, B.D.S., M.P.H.; Manjunath B. Shankar, M.B.B.S., M.H.A.; Stella S. Yi, M.P.H.; and Kelly J. Yu, M.P.H. *Cystic Fibrosis Foundation:* Robert J. Beall, Ph.D. Preston W. Campbell III, M.D.; Jennifer King, B.S.; and Terry B. White, Ph.D.

References

1. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry: 2005 Annual data report to the center directors. Bethesda, MD: Cystic Fibrosis Foundation; 2006.
2. Cystic Fibrosis Foundation. Concepts in Care consensus conference on use of aerosolized antibiotics in CF patients, September 22–23, 1997. Bethesda, MD: Cystic Fibrosis Foundation; 1997. Volume VIII, pp. 1–19.
3. Ramsey BW, Dorkin HL. Consensus conference: practical applications of Pulmozyme. *Pediatr Pulmonol* 1994;17:404–408.
4. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D; Methods Word Group, Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20(Suppl 3):21–35. Article reproduced on Agency for Healthcare Research and Quality website. Rockville, MD: AHRQ, Available from: http://www.ahrq.gov/clinic/ajpmsuppl/harris1.htm (cited 2007 Sep).
5. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol* 2002;34:91–100.
6. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, Vasiljev KM, Borowitz D, Bowman CM, Marshall BC, *et al.*; Cystic Fibrosis Inhaled Tobramycin Study Group. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *N Engl J Med* 1999;340:23–30.
7. MacLusky IB, Gold R, Corey M, Levison H. Long-term effects of inhaled tobramycin in patients with cystic fibrosis colonized with *Pseudomonas aeruginosa. Pediatr Pulmonol* 1989;7:42–48.
8. Ramsey BW, Dorkin HL, Eisenberg JD, Gibson RL, Harwood IR, Kravitz RM, Schidlow DV, Wilmott RW, Astley SJ, McBurnie MA, *et al.* Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N Engl J Med* 1993;328:1740–1746.
9. Wiesemann HG, Steinkamp G, Ratjen F, Bauernfeind A, Przyklenk B, Doring G, von der Hardt H. 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.
10. Ryan G, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* [serial on the Internet]. 2003 [updated 2006; accessed September 2007];3:CD001021. Available from http://www.cochrane.org/reviews/clibintro.htm
11. Gibson RL, Emerson J, McNamara S, Burns JL, Rosenfeld M, Yunker A, Hamblett N, Accurso F, Dovey M, Hiatt P, *et al.*; Cystic Fibrosis Therapeutics Development Network Study Group. Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. *Am J Respir Crit Care Med* 2003;167:841–849.
12. Murphy TD, Anbar RD, Lester LA, Nasr SZ, Nickerson B, VanDevanter DR, Colin AA. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. *Pediatr Pulmonol* 2004;38:314–320.
13. Jensen T, Pedersen SS, Garne S, Heilmann C, Høiby N, Koch C. Colistin inhalation therapy in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection. *J Antimicrob Chemother* 1987;19:831–838.
14. Hodson ME, Gallagher CG, Govan JRW. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. *Eur Respir J* 2002;20:658–664.
15. Kun P, Landau LI, Phelan PD. Nebulized gentamicin in children and adolescents with cystic fibrosis. *Aust Paediatr J* 1984;20:43–45.
16. Stead RJ, Hodson ME, Batten JC. Inhaled ceftazidime compared with gentamicin and carbenicillin in older patients with cystic fibrosis infected with *Pseudomonas aeruginosa. Br J Dis Chest* 1987;81:272–279.
17. Cimmino M, Nardone M, Cavaliere M, Plantulli A, Sepe A, Esposito V, Mazzarella G, Raia V. Dornase alfa as postoperative therapy in cystic fibrosis sinonasal disease. *Arch Otolaryngol Head Neck Surg* 2005;131:1097–1101.
18. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, Rosenstein BJ, Smith AL, Wohl ME; Pulmozyme Study Group. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994;331:637–642.
19. Grasemann H, Lax H, Treseler JW, Colin AA. Dornase alpha and exhaled NO in cystic fibrosis. *Pediatr Pulmonol* 2004;38:379–385.
20. McCoy K, Hamilton S, Johnson C. Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. *Chest* 1996;110:889–895.
21. Furuya MEY, Lezana-Fernández JL, Vargas MH, Hernández-Sierra JF, Ramírez-Figueroa JL. Efficacy of human recombinant DNase in pediatric patients with cystic fibrosis. *Arch Med Res* 2001;32:30–34.
22. Laube BL, Auci RM, Shields DE, Christiansen DH, Lucas MK, Fuchs HJ, Rosenstein BJ. Effect of rhDNase on airflow obstruction and

mucociliary clearance in cystic fibrosis. *Am J Respir Crit Care Med* 1996;153:752–760.
23. Ramsey BW, Astley SJ, Aitken ML, Burke W, Colin AA, Dorkin HL, Eisenberg JD, Gibson RL, Harwood IR, Schidlow DV, *et al.* Efficacy and safety of short-term administration of aerosolised recombinant human deoxyribonuclease in patients with cystic fibrosis. *Am Rev Respir Dis* 1993;148:145–151.
24. Ranasinha C, Assoufi B, Shak S, Christiansen D, Fuchs H, Empey D, Geddes D, Hodson M. Efficacy and safety of short-term administration of aerosolised recombinant human DNase I in adults with stable stage cystic fibrosis. *Lancet* 1993;342:199–202.
25. Shah PL, Scott SF, Knight RA, Marriott C, Ranasinha C, Hodson ME. *In vivo* effects of recombinant human DNase I on sputum in patients with cystic fibrosis. *Thorax* 1996;51:119–125.
26. Shah PI, Bush A, Canny GJ, Colin AA, Fuchs HJ, Geddes DM, Johnson CAC, Light MC, Scott SF, Tullis DE, *et al.* Recombinant human DNase I in cystic fibrosis patients with severe pulmonary disease: a short-term, double-blind study followed by six months open-label treatment. *Eur Respir J* 1995;8:954–958.
27. Robinson M, Hemming AL, Moriarty C, Eberl S, Bye PTP. Effect of a short course of rhDNase on cough and mucociliary clearance in patients with cystic fibrosis. *Pediatr Pulmonol* 2000;30:16–24.
28. Wilmott RW, Amin RS, Colin AA, DeVault A, Dozor AJ, Eigen H, Johnson C, Lester LA, McCoy K, McKean LP, *et al.* Aerosolized recombinant human DNase in hospitalized cystic fibrosis patients with acute pulmonary exacerbations. *Am J Respir Crit Care Med* 1996;153:1914–1917.
29. Jones AP, Wallis CE, Kearney CE. Recombinant human deoxyribonuclease for cystic fibrosis. *Cochrane Database Syst Rev* [serial on the Internet]. 2003 [updated 2005; accessed September 2007];3:CD001127. Available from http://www.cochrane.org/reviews/clibintro.htm
30. Quan JM, Tiddens HAWM, Sy JP, McKenzie SG, Montgomery MD, Robinson PJ, Wohl MEB, Konstan MW. 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: 813–820.
31. Robinson TE, Goris ML, Zhu HJ, Chen X, Bhise P, Sheikh F, Moss RB. Dornase alfa reduces air trapping in children with mild cystic fibrosis. *Chest* 2005;128:2327–2335.
32. Nasr SZ, Kuhns LR, Brown RW, Hurwitz ME, Sanders GM, Strouse PJ. Use of computerized tomography and chest x-rays in evaluating efficacy of aerosolized recombinant human DNase in cystic fibrosis patients younger than age 5 years: a preliminary study. *Pediatr Pulmonol* 2001;31:377–382.
33. Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med* 2006;354:241–250.
34. Elkins MR, Robinson M, Rose BR, Harbour C, Moriarty CP, Marks GB, Belousova EG, Xuan W, Bye PT. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;354:229–240.
35. Eng PA, Morton J, Douglass JA, Riedler J, Wilson J, Robertson CF. Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. *Pediatr Pulmonol* 1996;21:77–83.
36. Ballmann M, von der Hardt H. Hypertonic saline and recombinant human DNase: a randomised crossover pilot study in patients with cystic fibrosis. *J Cyst Fibros* 2002;1:35–37.
37. Suri R, Grieve R, Normand C, Metcalfe C, Thompson S, Wallis C, Bush A. Effects of hypertonic saline, alternate day and daily rhDNase on healthcare use, costs and outcomes in children with cystic fibrosis. *Thorax* 2002;57:841–846.
38. Wark PA, McDonald V, Jones AP. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database Syst Rev* [serial on the Internet]. 2005 [accessed September 2007];3:CD001506. Available from http://www.cochrane.org/reviews/clibintro.htm
39. Birrer P, McElvaney NG, Rudeberg A, Sommer CW, Liechti-Gallati S, Kraemer R, Hubbard R, Crystal RG. Protease–antiprotease imbalance in the lungs of children with cystic fibrosis. *Am J Respir Crit Care Med* 1994;150:207–213.
40. Konstan MW, Hilliard KA, Norvell TM, Berger M. Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation. *Am J Respir Crit Care Med* 1994;150:448–454.
41. Balfour-Lynn IM, Lees B, Hall P, Phillips G, Khan M, Flather M, Elborn JS. Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis. *Am J Respir Crit Care Med* 2006;173:1356–1362.
42. Balfour-Lynn IM, Klein NJ, Dinwiddie R. Randomised controlled trial of inhaled corticosteroids (fluticasone propionate) in cystic fibrosis. *Arch Dis Child* 1997;77:124–130.
43. Nikolaizik WH, Schöni MH. Pilot study to assess the effect of inhaled corticosteroids on lung function in patients with cystic fibrosis. *J Pediatr* 1996;128:271–274.
44. Schiotz PO, Jorgensen M, Flensborg EW, Faero O, Husby S, Hoiby N, Jacobsen SV, Nielsen H, Svehag SE. Chronic *Pseudomonas aeruginosa* lung infection in cystic fibrosis: a longitudinal study of immune complex activity and inflammatory response in sputum sol-phase of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infections: influence of local steroid treatment. *Acta Paediatr Scand* 1983;72:283–287.
45. Dauletbaev N, Viel K, Behr J, Loitsch S, Buhl R, Wagner TOF, Bargon J. Effects of short-term inhaled fluticasone on oxidative burst of sputum cells in cystic fibrosis patients. *Eur Respir J* 1999;14:1150–1155.
46. Bisgaard H, Pedersen SS, Nielsen KG, Skov M, Laursen EM, Kronborg G, Reimert CM, Høiby N, Koch C. Controlled trial of inhaled budesonide in patients with cystic fibrosis and chronic bronchopulmonary *Pseudomonas aeruginosa* infection. *Am J Respir Crit Care Med* 1997;156:1190–1196.
47. van Haren EHJ, Lammers J-WJ, Festen J, Heijerman HGM, Groot CAR, van Herwaarden CLA. The effects of the inhaled corticosteroid budesonide on lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis. *Respir Med* 1995;89:209–214.
48. Balfour-Lynn I, Walters S, Dezateux C. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database Syst Rev* [serial on the Internet]. 2000 [updated 2006; accessed September 2007];2:CD001915. Available from http://www.cochrane.org/reviews/clibintro.htm
49. Auerbach HS, Williams M, Kirkpatrick JA, Colten HR. Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis. *Lancet* 1985;2:686–688.
50. Greally P, Hussain MJ, Vergani D, Price JF. Interleukin-1α, soluble interleukin-2 receptor, and IgG concentrations in cystic fibrosis treated with prednisolone. *Arch Dis Child* 1994;71:35–39.
51. 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.
52. Cheng K, Ashby D, Smyth R. Oral steroids for cystic fibrosis. *Cochrane Database Syst Rev* [serial on the Internet]. 2000 [updated 2006; accessed September 2007];2:CD000407. Available from http://www.cochrane.org/reviews/clibintro.htm
53. Pantin CFA, Stead RJ, Hodson ME, Batten JC. Prednisolone in the treatment of airflow obstruction in adults with cystic fibrosis. *Thorax* 1986;41:34–38.
54. Konstan MW, Hoppel CL, Chai B, Davis PB. Ibuprofen in children with cystic fibrosis: pharmacokinetics and adverse effects. *J Pediatr* 1991;118:956–964.
55. Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 1995;332:848–854.
56. Sordelli DO, Macri CN, Maillie AJ, Cerquetti MC. A preliminary study on the effect of anti-inflammatory treatment in cystic fibrosis patients with *Pseudomonas aeruginosa* lung infection. *Int J Immunopathol Pharmacol* 1994;7:109–117.
57. Lands LC, Dezateux C, Crighton A. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. *Cochrane Database Syst Rev* [serial on the Internet]. 1999 [updated 2005; accessed September 2007];2:CD001505. Available from http://www.cochrane.org/reviews/clibintro.htm
58. Konstan MW, Krenicky JE, Finney MR, Kirchner HL, Hilliard KA, Hilliard JB, Davis PB, Hoppel CL. Effect of ibuprofen on neutrophil migration *in vivo* in cystic fibrosis and healthy subjects. *J Pharmacol Exp Ther* 2003;306:1086–1091.
59. Stelmach I, Korzeniewska A, Smejda K, Jarosz I, Stelmach W. [Effect of montelukast on lung function and clinical symptoms in patients with cystic fibrosis]. *Pneumonol Alergol Pol* 2004;72:85–89.
60. Conway SP, Etherington C, Peckham DG, Whitehead A. A pilot study of zafirlukast as an anti-inflammatory agent in the treatment of adults with cystic fibrosis. *J Cyst Fibros* 2003;2:25–28.
61. Lawrence R, Sorrell T. Eicosapentaenoic acid in cystic fibrosis: evidence of a pathogenetic role for leukotriene B_4. *Lancet* 1993;342: 465–469.

62. Mitchell I. Sodium cromoglycate–induced changes in the dose–response curve of inhaled methacholine in cystic fibrosis. *Ann Allergy* 1985;54: 233–235.
63. Chua HL, Walker SL, LeSouef PN, Sly PD. Comparison of efficacy of salbutamol and sodium cromoglycate in the prevention of ticarcillin-induced bronchoconstriction. *Pediatr Pulmonol* 1993;16:311–315.
64. Sivan Y, Arce P, Eigen H, Nickerson BG, Newth CJ. A double-blind, randomized study of sodium cromoglycate versus placebo in patients with cystic fibrosis and bronchial hyperreactivity. *J Allergy Clin Immunol* 1990;85:649–654.
65. Koyama H, Geddes DM. Erythromycin and diffuse panbronchiolitis. *Thorax* 1997;52:915–918.
66. Ordoñez CL, Stulbarg M, Grundland H, Liu JT, Boushey HA. Effect of clarithromycin on airway obstruction and inflammatory markers in induced sputum in cystic fibrosis: a pilot study. *Pediatr Pulmonol* 2001;32:29–37.
67. Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, Coquillette S, Fieberg AY, Accurso FJ, Campbell PW III. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. *JAMA* 2003;290:1749–1756.
68. Wolter J, Seeney S, Bell S, Bowler S, Masel P, McCormack J. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. *Thorax* 2002;57:212–216.
69. Equi A, Balfour-Lynn IM, Bush A, Rosenthal M. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. *Lancet* 2002;360:978–984.
70. Southern KW, Barker PM, Solis A. Macrolide antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* [serial on the Internet]. 2004 [updated 2005; accessed September 2007];2:CD002203. Available from http://www.cochrane.org/reviews/clibintro.htm
71. Weaver LT, Green MR, Nicholson K, Mills J, Heeley ME, Kuzemko JA, Austin S, Gregory GA, Dux AE, Davis JA. Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period. *Arch Dis Child* 1994;70:84–89.
72. 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;95:630–637.
73. Stutman HR, Lieberman JM, Nussbaum E, Marks MI. Antibiotic prophylaxis in infants and young children with cystic fibrosis: a randomized controlled trial. *J Pediatr* 2002;140:299–305.
74. Beardsmore CS, Thompson JR, Williams A, McArdle EK, Gregory GA, Weaver LT, Simpson H. Pulmonary function in infants with cystic fibrosis: the effect of antibiotic treatment. *Arch Dis Child* 1994;71:133–137.
75. Smyth A, Walters S. Prophylactic anti-staphylococcal antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* [serial on the Internet]. 2003 [updated 2006; accessed September 2007];3:CD001912. Available from http://www.cochrane.
org/reviews/clibintro.htm
76. Halfhide C, Evans HJ, Couriel J. Inhaled bronchodilators for cystic fibrosis. *Cochrane Database Syst Rev* [serial on the Internet]. 2005 [accessed September 2007];4:CD003428. Available from http://www.cochrane.org/reviews/clibintro.htm
77. Pitcher-Wilmott R, Matthew DJ, Ingram D, Tyson SL. Improvement in lung function after nebulised salbutamol and ipratropium in children with cystic fibrosis. Abstract presented at the 11th European Cystic Fibrosis Conference, Brussels, Belgium, 1982.
78. Duncan FR, Penketh ARL, Hodson ME, Batten JC. The use of bronchodilators as an adjunct to physiotherapy in adults with cystic fibrosis. Abstract presented at the 11th European Cystic Fibrosis Conference, Brussels, Belgium, 1982.
79. Avital A, Sanchez I, Chernick V. Efficacy of salbutamol and ipratropium bromide in decreasing bronchial hyperreactivity in children with cystic fibrosis. *Pediatr Pulmonol* 1992;13:34–37.
80. Hordvik NL, Sammut PH, Judy CG, Strizek SJ, Colombo JL. The effects of albuterol on the lung function of hospitalized patients with cystic fibrosis. *Am J Respir Crit Care Med* 1996;154:156–160.
81. Hordvik NL, Sammut PH, Judy CG, Colombo JL. Effectiveness and tolerability of high-dose salmeterol in cystic fibrosis. *Pediatr Pulmonol* 2002;34:287–296.
82. Sanchez I, Holbrow J, Chernick V. Acute bronchodilator response to a combination of β-adrenergic and anticholinergic agents in patients with cystic fibrosis. *J Pediatr* 1992;120:486–488.
83. Ziebach R, Pietsch-Breitfeld B, Bichler M, Busch A, Riethmuller J, Stern M. Bronchodilatory effects of salbutamol, ipratropium bromide, and their combination: double-blind, placebo-controlled crossover study in cystic fibrosis. *Pediatr Pulmonol* 2001;31:431–435.
84. Eggleston PA, Rosenstein BJ, Stackhouse CM, Mellits ED, Baumgardner RA. A controlled trial of long-term bronchodilator therapy in cystic fibrosis. *Chest* 1991;99:1088–1092.
85. Hordvik NL, Sammut PH, Judy CG, Colombo JL. Effects of standard and high doses of salmeterol on lung function of hospitalized patients with cystic fibrosis. *Pediatr Pulmonol* 1999;27:43–53.
86. Konig P, Poehler J, Barbero GJ. A placebo-controlled, double-blind trial of the long-term effects of albuterol administration in patients with cystic fibrosis. *Pediatr Pulmonol* 1998;25:32–36.
87. Sanchez I, De Koster J, Holbrow J, Chernick V. The effect of high doses of inhaled salbutamol and ipratropium bromide in patients with stable cystic fibrosis. *Chest* 1993;104:842–846.
88. Serisier DJ, Rice-McDonald G, Bowler SD, Coates AC, Breust B. β-Adrenergic agonists do not improve exercise capacity in cystic fibrosis. *Pediatr Pulmonol Suppl* 2000;20:305.
89. Dodd JD, Barry SC, Daly LE, Gallagher CG. Inhaled β-agonists improve lung function but not maximal exercise capacity in cystic fibrosis. *J Cyst Fibros* 2005;4:101–105.
90. Salvatore D, D'Andria M. Effects of salmeterol on arterial oxyhemoglobin saturations in patients with cystic fibrosis. *Pediatr Pulmonol* 2002;34:11–15.
91. Duijvestijn YC, Brand PL. Systematic review of *N*-acetylcysteine in cystic fibrosis. *Acta Paediatr* 1999;88:38–41.
92. Tramper-Stranders GA, Wolfs TF, Fleer A, Kimpen JL, van der Ent CK. 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.
93. van der Giessen LJ, de Jongste JC, Gosselink R, Hop WC, Tiddens HA. rhDNase before airway clearance therapy improves airway patency in children with CF. *Pediatr Pulmonol* 2007;42:624–630.
94. Fitzgerald DA, Hilton J, Jepson B, Smith L. A crossover, randomized, controlled trial of dornase alfa before versus after physiotherapy in cystic fibrosis. *Pediatrics* 2005;116:e549–e554.
95. LiPuma JJ. Microbiological and immunologic considerations with aerosolized drug delivery. *Chest* 2001;120:118S–123S.
96. Lipworth BJ. Pharmacokinetics of inhaled drugs. *Br J Clin Pharmacol* 1996;42:697–705.
97. Clinical Practice Guidelines for Cystic Fibrosis Committee. Clinical practice guidelines for cystic fibrosis. Bethesda, MD: Cystic Fibrosis Foundation; 1997.
98. Smith AL, Ramsey BW, Hedges DL, Hack B, Williams-Warren J, Weber A, Gore EJ, Redding GJ. Safety of aerosol tobramycin administration for 3 months to patients with cystic fibrosis. *Pediatr Pulmonol* 1989;7:265–271.
99. Steinkamp G, Tümmler B, Gappa M, Albus A, Potel J, Döring G, von der Hardt H. Long-term tobramycin aerosol therapy in cystic fibrosis. *Pediatr Pulmonol* 1989;6:91–98.
100. Hubbard RC, McElvaney NG, Birrer P, Shak S, Robinson WW, Jolley C, Wu M, Chernick MS, Crystal RG. A preliminary study of aerosolized recombinant human deoxyribonuclease I in the treatment of cystic fibrosis. *N Engl J Med* 1992;326:812–815.
101. Aitken ML, Burke W, McDonald G, Shak S, Montgomery AB, Smith A. Recombinant human DNase inhalation in normal subjects and patients with cystic fibrosis: a phase 1 study. *JAMA* 1992;267:1947–1951.
102. Eisenberg JD, Aitken ML, Dorkin HL, Harwood IR, Ramsey BW, Schidlow DV, Wilmott RW, Wohl ME, Fuchs HJ, Christiansen DH, *et al.* Safety of repeated intermittent courses of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. *J Pediatr* 1997;131:118–124.
103. Harms HK, Matouk E, Tournier G, von der Hardt H, Weller PH, Romano L, Heijerman HGM, FitzGerald MX, Richard D, Strandvik B, *et al.* Multicenter, open-label study of recombinant human DNase in cystic fibrosis patients with moderate lung disease. *Pediatr Pulmonol* 1998;26:155–161.
104. Heijerman HGM, van Rossem RN, Bakker W. Effect of rhDNase on lung function and quality of life in adult cystic fibrosis patients. *Neth J Med* 1995;46:293–297.
105. Ledson MJ, Tran J, Walshaw MJ. Prevalence and mechanisms of gastro-oesophageal reflux in adult cystic fibrosis patients. *J R Soc Med* 1998;91:7–9.
106. Shah PL, Scott SF, Geddes DM, Hodson ME. Two years experience with recombinant human DNase I in the treatment of pulmonary disease in cystic fibrosis. *Respir Med* 1995;89:499–502.

107. Berge MT, Wiel E, Tiddens HA, Merkus PJ, Hop WC, de Jongste JC. DNase in stable cystic fibrosis infants: a pilot study. *J Cyst Fibros* 2003;2:183–188.
108. Tirouvanziam R, Conrad CK, Bottiglieri T, Herzenberg LA, Moss RB. High-dose oral *N*-acetylcysteine, a glutathione prodrug, modulates inflammation in cystic fibrosis. *Proc Natl Acad Sci USA* 2006;103:4628–4633.
109. Stafanger G, Garne S, Howitz P, Morkassel E, Koch C. The clinical effect and the effect on the ciliary motility of oral *N*-acetylcysteine in patients with cystic fibrosis and primary ciliary dyskinesia. *Eur Respir J* 1988;1:161–167.
110. Ratjen F, Wonne R, Posselt HG, Stover B, Hofmann D, Bender SW. A double-blind placebo controlled trial with oral ambroxol and *N*-acetylcysteine for mucolytic treatment in cystic fibrosis. *Eur J Pediatr* 1985;144:374–378.
111. Mitchell EA, Elliott RB. Controlled trial of oral *N*-acetylcysteine in cystic fibrosis. *Aust Paediatr J* 1982;18:40–42.
112. Gotz M, Kraemer R, Kerrebijn KF, Popow C. Oral acetylcysteine in cystic fibrosis: a co-operative study. *Eur J Respir Dis Suppl* 1980; 111:122–126.