

## Cystic Fibrosis Pulmonary Guidelines Chronic Medications for Maintenance of Lung Health

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**Rationale:** Cystic fibrosis (CF) is an autosomal recessive disease characterized by abnormal airways secretions, chronic endobronchial infection, and progressive airway obstruction. The use of medications to slow the progression of lung disease has led to significant improvement in survival. An evidence review of chronic medications for CF lung disease was performed in 2007 to provide guidance to clinicians in evaluating and selecting appropriate treatment for individuals with this disease. We have undertaken a new review of the literature to update the recommendations, including consideration of new medications and additional evidence on previously reviewed therapies. A multidisciplinary committee of experts in CF pulmonary care was established to review the evidence for use of chronic medications for CF lung disease and make treatment recommendations. Published evidence for chronic lung therapies was systematically reviewed and resulting treatment recommendations were graded based on the United States Preventive Services Task Force scheme. These guidelines provide up-to-date evidence of safety and efficacy of chronic treatments of CF lung disease, including the use of novel therapies that have not previously been included in CF pulmonary guidelines.

**Keywords:** antibiotics; antiinflammatory agents; bronchodilators; CFTR modulators; hypertonic saline

To aid care providers in the use of chronic medications, the Cystic Fibrosis (CF) Foundation established the Pulmonary Clinical Practice Guidelines Committee, which published guidelines on chronic medications for the maintenance of lung health in 2007 (1). Since this publication, two novel medications have

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\*A complete list of the Pulmonary Clinical Practice Guidelines Committee can be found before the REFERENCES.

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been approved for use in the United States and additional data have been published on therapies previously reviewed. To consider this new evidence, as well as additional and revised questions on the use of therapies, the committee conducted an assessment of the current evidence to develop the updated recommendations presented here.

### METHODS

A multidisciplinary committee composed of 17 members reviewed the 2007 guidelines and developed a series of questions related to chronic drug therapies for CF. An evidence review was commissioned from The Johns Hopkins University, with systematic reviews completed for each question. New reviews were conducted for each question, as some questions were new or revised, new medications and indications were considered, and because a full systematic review was not completed for all questions in the development of the 2007 guidelines. The review was limited to parallel and cross-over randomized controlled trials (RCTs). Members of the committee disclosed any potential conflicts of interest. If any perceived conflict was present, members did not participate in any discussions or decisions on recommendations regarding that therapy.

Subcommittees were created to review the evidence summaries and draft recommendations for presentation to the entire committee. Final recommendations were graded using the U.S. Preventive Services Task Force scheme, which encompasses an estimate of net benefit and certainty of net benefit (2) (Table 1). Detailed methods are contained in the online supplement (E1).

### RESULTS

The search identified a total of 6,898 unique citations, of which 57 were included in the 2007 guidelines (Figure 1). The current guidelines are based on review of 137 articles describing 84 studies (Table 2). Because some questions addressed herein differ from those posed in the 2007 guidelines, 14 studies reviewed previously were not included in the current literature review. A summary of the recommendations can be found in Tables 3 and 4.

#### Unchanged Recommendations from Previous Guidelines

The current committee affirmed previous recommendations for several therapies, which can be found in Table 3. A comprehensive review of these recommendations can be found in the online supplement (#2).

#### Updated Recommendations of Previously Reviewed Medications

**$\beta_2$ -Adrenergic receptor agonists.** The 2007 guidelines recommended the use of  $\beta_2$ -adrenergic receptor agonists based on an

**TABLE 1. U.S. PREVENTIVE SERVICES TASK FORCE EVIDENCE GRADING**

| Certainty of Net Benefit | Magnitude of Net Benefit (Benefit Minus Harms) |          |       |               |
|--------------------------|--|----------|-------|---------------|
|                          | Substantial                                    | Moderate | Small | Zero/Negative |
| High                     | A  | B        | C     | D             |
| Moderate                 | B  | B        | C     | D             |
| Low                      | I (insufficient evidence)                      |          |       |               |

The overall strength of the evidence is based on the certainty of the magnitude of benefit defined as benefit minus harm. Adapted by permission from Reference 39.

*Strength of Recommendation:*

A. The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial.

B. The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

C. The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.

D. The committee recommends against the therapy. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Clinicians should discourage the use of this service.

I. The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

*Quality of the Evidence:*

*High.* The available evidence includes consistent results from well designed, well conducted studies in representative populations. This conclusion is therefore unlikely to be strongly affected by the results of future studies.

*Moderate.* The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

*Low.* The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings not generalizable; lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

appraisal of the Cochrane Review of both short-acting and long-acting  $\beta_2$ -adrenergic receptor agonists. The Cochran Review was updated in 2011 (3), and includes 18 studies with 369 participants. Given that the majority of these studies were of short duration, the committee reviewed the literature on the chronic use of these medications. We found only two RCTs ranging in size from 20 to 30 participants. König and coworkers (4) investigated albuterol (180  $\mu$ g by metered dose inhaler) twice daily for 6 months, and reported statistically significant increases in FEV<sub>1</sub> (12.1%), FVC (8.2%), and forced expiratory flow between 25% and 75% of FVC (FEF<sub>25-75%</sub>; 17.2%) from baseline compared with placebo. Eggleston and coworkers (5) used a cross-over design and evaluated the same dose of albuterol given four times daily over 4 months, in methacholine challenge responders versus nonresponders, as compared with placebo. However, no significant differences were seen in percent change in FEV<sub>1</sub>, FVC, and FEF<sub>25-75%</sub> compared with baseline for any of the groups. The evidence that the  $\beta_2$ -adrenergic receptor agonists favorably impact other important outcomes, such as exacerbations or quality of life (QOL), was relatively weak.

Short-term administration of  $\beta_2$ -adrenergic receptor agonists can benefit those individuals with airway hyperresponsiveness (3), which is common in individuals with CF (6). These

medications also have value in preventing bronchospasm associated with inhaled therapies. However, there is insufficient evidence to recommend chronic, daily use of a  $\beta_2$ -adrenergic receptor agonist. The committee rated the overall certainty of net benefit as low, and, therefore, cannot recommend for or against the chronic use of  $\beta_2$ -adrenergic receptor agonists.

**Oral, nonsteroidal antiinflammatory drugs.** The 2007 guidelines recommended the use of ibuprofen to prevent the loss of lung function in individuals with FEV<sub>1</sub> greater than 60% predicted. In addition to the three RCTs of oral, nonsteroidal antiinflammatory drugs that included 145 total patients reviewed previously (7–9), an additional RCT comparing ibuprofen to placebo in 142 patients aged 6–18 years was identified (10). A Cochrane Review that evaluated the same studies concluded that high-dose ibuprofen can slow the progression of lung disease in people with CF, especially in children (11).

Based on our review of the literature, the committee narrowed the previous recommendation to include only children 6–17 years of age, rating the certainty and magnitude of net benefit as moderate. Because of the scant data focusing on individuals with CF 18 years of age or older, the committee felt that there was insufficient information to make a recommendation for the adult population.

Studies of ibuprofen on neutrophil migration suggest that neutrophil migration increases rather than decreases at lower serum levels (12). Thus, maintaining an ibuprofen serum concentration of 50–100  $\mu$ g/ml should be considered a key aspect of ibuprofen therapy, and has, therefore, been included in the current recommendation.

**Azithromycin.** The 2007 guidelines recommended the use of azithromycin in individuals with persistent *Pseudomonas aeruginosa* in airway cultures. We also sought to determine the value of this therapy in individuals without *P. aeruginosa* infection. We identified five RCTs (13–17), three of which were not included in the prior guidelines (13, 14, 17), and one cross-over trial (18), with a total of 646 individuals. All the patients in one large study ( $n = 185$ ) had *P. aeruginosa* persistently present in cultures of the airways (15), whereas all the patients in another study ( $n = 263$ ) were not infected with *P. aeruginosa* (17). The other studies included both infected and noninfected patients. Based on our review, the committee believes that there were a sufficient number of individuals with and without *P. aeruginosa* infection studied to develop separate recommendations for these groups. Three of the trials reported significant absolute improvement of FEV<sub>1</sub> between 3.6 and 6.2% (15, 16, 18), and two also reported improvements in FVC (15, 16). The remaining trials reported no statistically significant differences in lung function between azithromycin and placebo (13, 14, 17). However, one of these was a small study designed to measure biomarkers, and lasted only 12 weeks (14). Although the largest trial of individuals without *P. aeruginosa* did not find a change in lung function, there was a 50% decrease in pulmonary exacerbations, which was significant (17). In fact, azithromycin therapy led to decreased exacerbations in four of the five trials reviewed (13, 15–17). A total of 10 studies of azithromycin, with a total of 959 individuals, were analyzed in a recent Cochrane Review (19), which concluded that azithromycin is effective for improving lung function and reducing exacerbations.

There is concern that the chronic use of azithromycin in individuals with occult or active nontuberculous mycobacteria (NTM) infection could lead to resistance, and thus complicate NTM treatment. For this reason, the committee suggests that patients should be screened for NTM before initiating azithromycin, and reassessed periodically at 6- to 12-month intervals. In addition, this monotherapy should be withheld in those infected with NTM.

TABLE 2. SUMMARY OF STUDIES REVIEWED

| Treatment Question   | Studies                              | Total (n) |
|--|--------------------------------------|-----------|
| Inhaled tobramycin—moderate to severe disease                                | 6 RCT (40–45)<br>1 RCO (46)          | 1,110     |
| Inhaled tobramycin—mild disease  | 3 RCT (47–49)                        | 234       |
| Dornase alfa—moderate to severe disease                                      | 8 RCT (50–57)<br>1 RCO (58)          | 1,800     |
| Dornase alfa—mild disease  | 4 RCT (59–62)<br>3 RCO (63–65)       | 649       |
| Inhaled hypertonic saline  | 2 RCT (66, 67)<br>1 RCO (68)         | 241       |
| Azithromycin with <i>P. aeruginosa</i>                                       | 4 RCT (13–15, 17)<br>1 RCO (18)      | 271       |
| Azithromycin without <i>P. aeruginosa</i>                                    | 4 RCT (13, 14, 16, 17)<br>1 RCO (18) | 365       |
| Oral antistaphylococcal antibiotics, prophylactic use                        | 1 RCT (21)<br>1 RCO (20)             | 226       |
| Oral antistaphylococcal antibiotics, chronic use                             | 1 RCT (21)<br>1 RCO (20)             | 226       |
| Inhaled corticosteroids  | 6 RCT (69–74)<br>2 RCO (75, 76)      | 426       |
| Chronic oral corticosteroids   | 3 RCT (77–79)                        | 354       |
| Other inhaled antibiotics (Carbenicillin, Ceftazidime, Colistin, Gentamicin) | 1 RCT (80)<br>5 RCO (81–84)          | 177       |
| Oral antipseudomonal antibiotics   | 1 RCT (85)                           | 40        |
| Leukotriene modifiers  | 2 RCO (86, 87)                       | 48        |
| Inhaled or oral <i>N</i> -acetylcysteine, or inhaled glutathione             | 2 RCT (88, 89)<br>1 RCO (90)         | 72        |
| Inhaled anticholinergics   | 0                                    | 0         |
| Ivacaftor  | 3 RCT (25–27)<br>1 RCO (27)          | 252       |
| Inhaled aztreonam—moderate to severe disease                                 | 3 RCT (30–32)                        | 515       |
| Inhaled aztreonam—mild disease   | 1 RCT (36)                           | 157       |
| Chronic use of Ibuprofen (age < 18 yr)                                       | 4 RCT (7–10)                         | 287       |
| Chronic use of Ibuprofen (age ≥ 18 yr)                                       | 1 RCT (7)                            | 41        |
| Chronic inhaled β <sub>2</sub> -adrenergic agents                            | 1 RCT (4)<br>1 RCO (5)               | 57        |

Definition of abbreviations: RCO = randomized cross-over trial; RCT = randomized controlled trial.

We developed two recommendations that take *P. aeruginosa* infection into account. The committee rated the certainty of net benefit supporting the use of chronic azithromycin as high for individuals infected with *P. aeruginosa*, and the estimate of benefit was rated as moderate. The certainty of benefit was judged to be moderate for individuals without *P. aeruginosa* infection, and the estimate of net benefit was small.

**Oral antibiotics for Staphylococcus aureus.** The 2007 guidelines recommended against the prophylactic use of oral antistaphylococcal antibiotics in individuals with CF. We also reviewed the evidence for oral antibiotic treatment of chronic infection with *S. aureus*, which consists of two trials (20, 21). A small cross-over trial ( $n = 17$ ) found that cephalexin therapy for 2 years significantly reduced exacerbations requiring antibiotics in the treatment group compared with the placebo group (25 vs. 53%) and the mean number of hospital admissions (4 vs. 22%) (20). In addition, FEV<sub>1</sub> and FVC also reportedly improved for the cephalexin group (although no further data were provided).

Stutman and coworkers (21) studied chronic prophylaxis with 80–100 mg/kg cephalexin used in 209 young children (<6 yr). A minority of subjects was already infected with *S. aureus* or *P. aeruginosa* or both. The trial showed no benefit in lung function (FEV<sub>1</sub>, FVC, FEF<sub>25–75%</sub>) or exacerbation outcomes. Although there was lower emergence of *S. aureus* in the treated group, these children had a higher rate of *P. aeruginosa* acquisition. A Cochrane Review of antistaphylococcal antibiotics, which evaluated four studies with 303 participants, concluded that the clinical significance of decreased *S. aureus* in treated children is unclear, especially given the potential for increased risk of *P. aeruginosa* infection (22).

Based on the potential for increased *P. aeruginosa* acquisition, the committee again recommended against the prophylactic use of oral antistaphylococcal antibiotics in individuals with CF. The committee determined that the certainty of net benefit is low for individuals chronically infected with *S. aureus*, so there is insufficient evidence to recommend therapy for these individuals.

### New Recommendations

**Ivacaftor.** Ivacaftor is a potentiator that activates defective CF transmembrane conductance regulator (CFTR) at the cell surface (23). The primary target for this therapy is mutated CFTR in which glycine has been replaced by aspartic acid at position 551 (G551D), interfering with the gating of the channel (24).

We identified two RCTs (25, 26) and one randomized cross-over study (25) of ivacaftor. Accurso and coworkers (25) conducted an RCT of 150 and 250 mg of ivacaftor twice daily compared with placebo for 28 days in 19 adults with a least one G551D CFTR mutation (25). The 150-mg dose of ivacaftor led to an 8.7% increase in FEV<sub>1</sub> compared with baseline ( $P = 0.008$ ).

Ramsey and coworkers (26) studied the effect of 48 weeks of ivacaftor, 150 mg twice daily, compared with placebo in 161 subjects aged 12 years or older with at least one G551D mutation. The FEV<sub>1</sub> increased 10.4% from baseline in the treated patients compared with –0.2% for those receiving placebo at 24 weeks ( $P < 0.001$ ). Subjects receiving ivacaftor were 55% less likely to have a pulmonary exacerbation than those receiving placebo ( $P < 0.001$ ). There were significant improvements

TABLE 3. SUMMARY OF RECOMMENDATIONS UNCHANGED FROM PREVIOUS GUIDELINES

| Treatment  | Recommendation  | Certainty of Net Benefit | Estimate of Net Benefit | Recommendation |
|--|---|--------------------------|-------------------------|----------------|
| Inhaled tobramycin—moderate to severe disease*                   | For individuals with CF, 6 years of age and older, with moderate to severe lung disease and <i>Pseudomonas aeruginosa</i> persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and quality of life, and reduce exacerbations.  | High                     | Substantial             | A              |
| Inhaled tobramycin—mild disease*                                 | For individuals with CF, 6 years of age and older, with mild lung disease and <i>P. aeruginosa</i> persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations.   | Moderate                 | Moderate                | B              |
| Dornase alfa—moderate to severe disease*                         | For individuals with CF, 6 years of age and older, with moderate to severe lung disease, the CF Foundation strongly recommends the chronic use of dornase alfa to improve lung function, improve the quality of life, and reduce exacerbations.   | High                     | Substantial             | A              |
| Dornase alfa—mild disease*                                       | For individuals with CF, 6 years of age and older, with asymptomatic or mild lung disease, the CF Foundation recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.  | High                     | Moderate                | B              |
| Inhaled hypertonic saline  | For individuals with CF, 6 years of age and older, the CF Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and quality of life and reduce exacerbations.   | Moderate                 | Moderate                | B              |
| Azithromycin with <i>P. aeruginosa</i>                           | For individuals with CF, 6 years of age and older, with <i>P. aeruginosa</i> persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin to improve lung function and reduce exacerbations.   | High                     | Moderate                | B              |
| Oral antistaphylococcal antibiotics, prophylactic use            | For individuals with CF, the CF Foundation recommends against the prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations.   | Moderate                 | Negative                | D              |
| Inhaled corticosteroids  | For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the routine use of inhaled corticosteroids to improve lung function or quality of life and reduce pulmonary exacerbations.   | High                     | Zero                    | D              |
| Oral corticosteroids   | For individuals with CF, 6 years of age and older, without asthma or allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations.   | High                     | Negative                | D              |
| Other inhaled antibiotics  | For individuals with CF, 6 years of age and older, with <i>P. aeruginosa</i> persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of other inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations. | Low                      | —                       | I              |
| Oral antipseudomonal antibiotics                                 | For individuals with CF, 6 years of age and older, with <i>P. aeruginosa</i> persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine use of chronic oral antipseudomonal antibiotics to improve lung function and quality of life or reduce exacerbations.   | Low                      | —                       | I              |
| Leukotriene modifiers  | For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine chronic use of leukotriene modifiers to improve lung function and quality of life or reduce exacerbations.   | Low                      | —                       | I              |
| Inhaled or oral <i>N</i> -acetylcysteine, or inhaled glutathione | For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled or oral <i>N</i> -acetylcysteine or inhaled glutathione to improve lung function and quality of life or reduce exacerbations.   | Low                      | —                       | I              |
| Inhaled anticholinergics   | For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations.   | Low                      | —                       | I              |

Definition of abbreviation: CF = cystic fibrosis.

\* Severity of lung disease is defined by FEV<sub>1</sub>% predicted as follows: normal, >90% predicted; mildly impaired, 70–89% predicted; moderately impaired, 40–69% predicted; and severely impaired, <40% predicted (1).

in QOL, as measured by CF Questionnaire–Revised, as well as nutritional status. The authors observed a 48.1 mmol/L decrease in sweat chloride concentration in treated patients compared with placebo ( $P < 0.001$ ), reflecting the impact of the drug on the basic defect in CF. The incidence of adverse events was similar in the two groups, with a lower proportion of serious adverse events in those treated with ivacaftor compared with placebo (24 vs. 42%).

Data published in abstract form after our systematic review reported similar results in 52 children, aged 6–11 years, with at

least one G551D mutation treated with ivacaftor (150 mg twice daily). After 24 weeks of treatment, FEV<sub>1</sub> increased 12.6% from baseline in the group receiving ivacaftor, compared with 0.04% in the placebo group ( $P < 0.0001$ ) (27).

Overall, the committee rated the certainty of net benefit for ivacaftor in patients with at least one G551D *CFTR* mutation as high and the net benefit as substantial. *In vitro* data suggest that there may be a role for ivacaftor in treating other mutations where *CFTR* protein is present at the cell surface (23), but there is insufficient information to make a recommendation for these

TABLE 4. NEW AND MODIFIED RECOMMENDATIONS

| Treatment  | Recommendation   | Certainty of Net Benefit | Estimate of Net Benefit | Recommendation |
|--|--|--------------------------|-------------------------|----------------|
| Ivacaftor*   | For individuals with CF, 6 years of age and older, with at least one G551D <i>CFTR</i> mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life and reduce exacerbations.  | High                     | Substantial             | A              |
| Inhaled aztreonam—moderate to severe disease†                | For individuals with CF, 6 years of age and older, with moderate to severe lung disease and <i>Pseudomonas aeruginosa</i> persistently present in cultures of the airways, the CF Foundation strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.  | High                     | Substantial             | A              |
| Inhaled aztreonam—mild disease†                              | For individuals with CF, 6 years of age and older, with mild lung disease and <i>P. aeruginosa</i> persistently present in cultures of the airways, the CF Foundation recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.  | Moderate                 | Moderate                | B              |
| Chronic use of ibuprofen (age < 18 yr)                       | For individuals with CF, between 6 and 17 years of age, with an FEV <sub>1</sub> ≥ 60% predicted, the CF Foundation recommends the chronic use of oral ibuprofen, at a peak plasma concentration of 50–100 μg/ml, to slow the loss of lung function.   | Moderate                 | Moderate                | B              |
| Chronic use of ibuprofen (age ≥ 18 yr)                       | For individuals with CF, 18 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations.   | Low                      | —                       | I              |
| Azithromycin without <i>P. aeruginosa</i>                    | For individuals with CF, 6 years of age and older, without <i>P. aeruginosa</i> persistently present in cultures of the airways, the CF Foundation recommends the chronic use of azithromycin should be considered to reduce exacerbations.  | Moderate                 | Small                   | C              |
| Chronic inhaled β <sub>2</sub> -adrenergic receptor agonists | For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against chronic use of inhaled β <sub>2</sub> -adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations.   | Low                      | —                       | I              |
| Oral antistaphylococcal antibiotics, chronic use             | For individuals with CF, 6 years of age and older, with <i>Staphylococcus aureus</i> persistently present in cultures of the airways, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations. | Low                      | —                       | I              |

For definition of abbreviation, see Table 3.

\*CF Foundation personnel did not participate in any activity related to ivacaftor.

† Severity of lung disease is defined by FEV<sub>1</sub>% predicted as follows: normal, >90% predicted; mildly impaired, 70–89% predicted; moderately impaired, 40–69% predicted; and severely impaired, <40% predicted (1).

mutations at this time. However, there is evidence that the use of ivacaftor alone for individuals with two F508del *CFTR* mutations, the most frequent genotype in CF, is not effective (28).

**Aerosolized aztreonam for moderate to severe disease.** *P. aeruginosa* is the most common pathogen in the airways of individuals with CF, and its acquisition is associated with more rapid decline of lung function and decreased survival (29). We identified three studies of inhaled aztreonam using doses ranging from 75 to 225 mg administered two to three times in 515 individuals with FEV<sub>1</sub> between 25 and 75% predicted (30–32). Two trials found statistically significant absolute improvement in FEV<sub>1</sub> after aztreonam treatment for 28 days compared with placebo (6.3–10.3%) (30, 32). A study that assessed lung function after 14 days of treatment found no difference between the groups receiving aztreonam or placebo (31). McCoy and coworkers (30) found that individuals receiving aztreonam twice daily had a statistically prolonged time to an exacerbation compared with placebo (92 vs. 71 d;  $P = 0.002$ ), but no such difference was found for three-times-daily dosing (87 vs. 71 d;  $P = 0.182$ ). Retsch-Bogart and coworkers (32) demonstrated a decrease in hospital days for individuals treated with aztreonam compared with placebo (0.5 vs. 1.5 d;  $P = 0.049$ ). QOL was significantly improved in patients receiving aztreonam compared with placebo (30, 32).

The trials of inhaled aztreonam were well designed and enrolled a large number of subjects. However, they were short term with limited follow up. Long-term, placebo-controlled trials in the current era are not possible, as inhaled antibiotics are standard of care for individuals with *P. aeruginosa* persistently present in airway cultures. An 18-month open label study suggested that long-term use of inhaled aztreonam every other month is safe and effective (33), and not associated with increased resistance to aztreonam (34). In addition, a study of 273 individuals

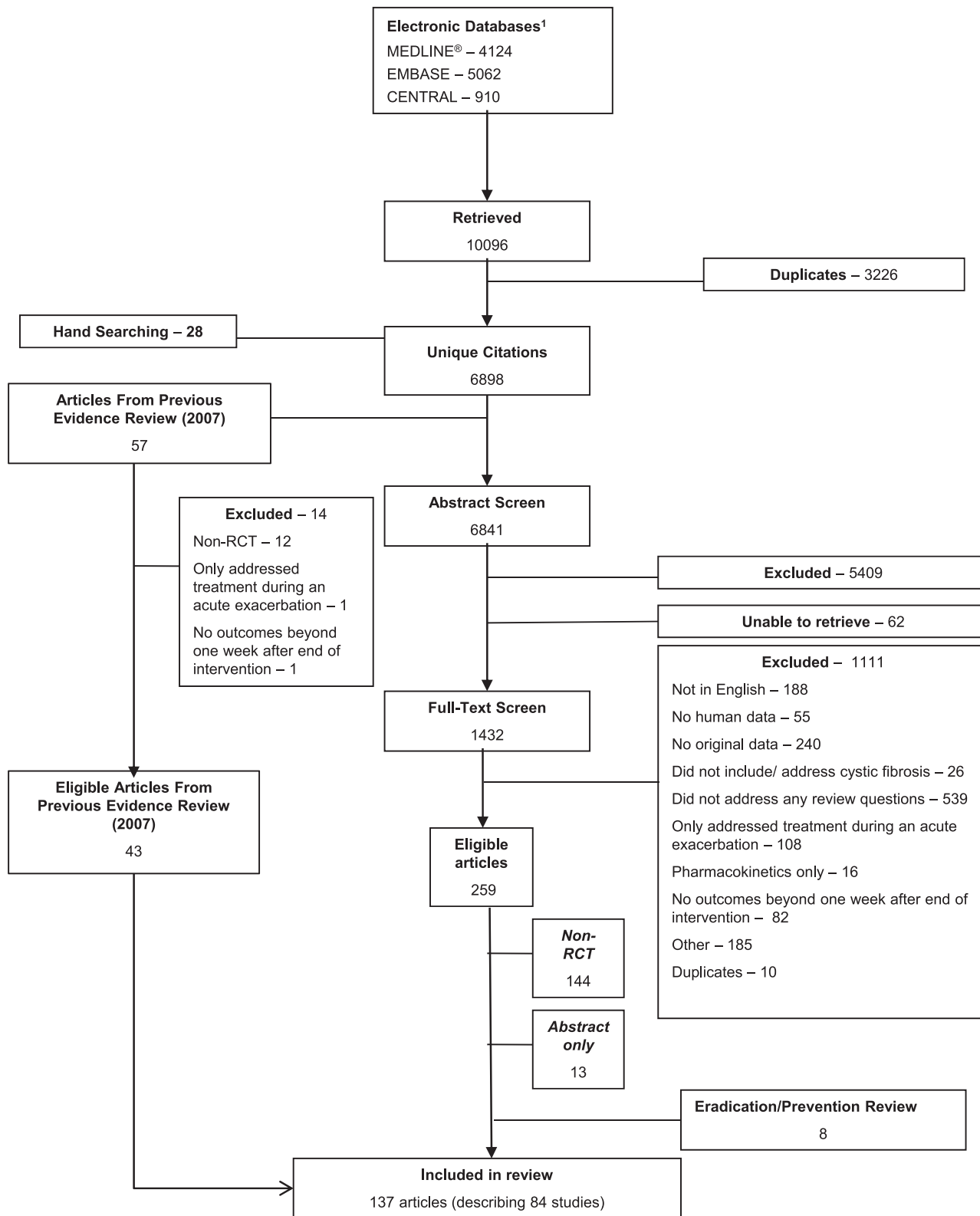
with CF aged 6 years or older demonstrated improved lung function and fewer exacerbations over three 28-day cycles of inhaled aztreonam compared with inhaled tobramycin (35). Therefore, the committee recommends inhaled aztreonam for chronic use with a high degree of certainty for a substantial net benefit.

**Aerosolized aztreonam for mild disease.** There is one study of inhaled aztreonam in patients with FEV<sub>1</sub> greater than 75% predicted. Wainwright and coworkers (36) studied the effect of 28 days of aztreonam (75 mg thrice daily) on 157 patients, 6 years of age or older, with mild lung disease and *P. aeruginosa* infection. Aztreonam led to a 2.7% relative improvement in FEV<sub>1</sub> compared with placebo ( $P = 0.021$ ) and a modest improvement in QOL. Given this one well designed study with a large number of subjects, the committee rated both the certainty and magnitude of net benefit as moderate.

## KEY UNANSWERED QUESTIONS

Many of the issues highlighted in the 2007 version of these guidelines remain unresolved today, including: prioritization of therapies; interactions between medications; effect of bacterial resistance; optimal use of medications in children under 6 years of age; and unintended consequences of long-term medication use. There remain few data to determine the sequence in which medications should be administered for optimal effectiveness. The CF Foundation has recommended the following order of inhaled medications: bronchodilator; hypertonic saline; dornase alfa; airway clearance; and aerosolized antibiotic. We agree that this is a rational approach; however, further study is warranted to assure that it is the optimal approach.

Recommendations for chronic use of medications are based on relatively short trials. The committee recognizes that many



<sup>1</sup>MEDLINE was accessed via PubMed; EMBASE - the Excerpta Medica database, CENTRAL – Cochrane CENTRAL Register of Controlled Trials;

Figure 1. Summary of search and review process.

intervention trials, even those ideally designed, have a finite duration. It is likely that patients will use medications for years or even decades, and that side effects (or benefits) might arise after

very long-term use that were not anticipated based on shorter studies. Thus, clinicians must continue to monitor individuals for possible unanticipated side effects of these therapies.

Determining the relative effectiveness of therapies is difficult. There are limited data directly comparing medications, such as mucus-active drugs or antibiotics to one another. In addition, understanding the benefits and potential harms of combination therapy commonly used in practice is critically important. Although traditional RCTs may be impractical in addressing these issues, this could be a fertile area for comparative effectiveness research studies using observational study designs of patient registry data and pragmatic interventional study designs.

In the past, there has been little guidance for the use of medications in children under 6 years of age. More recently, studies have been conducted in young children to determine the effectiveness of medications previously recommended for use in older children and adults (37). We anticipate that, as more medications are studied in young children, evidence-based decision making for this vulnerable population will become easier.

There has been a multiplication of delivery devices for inhaled medications designed to decrease administration time and improve efficacy. Inhaled therapeutics are often paired with a specific device optimized for delivery, creating the potential for less effective delivery when an inappropriate device is used. In addition, using proper administration technique is required to ensure adequate medication delivery. Therefore, it is important for CF health care professionals to educate individuals with CF and their families about proper device use for each prescribed medication.

There are numerous other important questions regarding chronic pulmonary medications for which data from RCTs are lacking. We raise a few of these questions as potential areas of future research.

1. *When should medications be initiated?* As there is likely a component of injury to the airways that rapidly becomes irreversible, it would seem logical that medications with the potential to alter the course of the disease should be initiated at diagnosis or shortly thereafter to prevent injury. However, evaluating medications in young children or those with mild lung disease is challenging due to difficulty in objective measurement of lung disease progression. Studies designed to optimize therapy in these vulnerable populations are key to the ultimate success of future therapies.
2. *How will the use of CFTR-modulating therapies alter the use of other medications?* A new responsibility for CF health care professionals will be to manage expectations of efficacy of CFTR-modulating agents. Even if CFTR function can be returned to near-normal levels, residual damage to airways and other organs will likely necessitate the continuation of many current therapies. It is important to note that individuals participating in studies of ivacaftor continued to use their routine therapies with the exception of hypertonic saline. How to use current therapies in the era of CFTR-modulation therapy will likely become an important new area of research.
3. *How does the burden of therapy affect self-management?* The temptation to add chronic therapies as they become available is great, especially for individuals with more advanced lung disease. However, there are likely to be diminishing returns as the burden of additional therapies decreases an individual's ability to successfully manage any particular therapy. It is clear that decreased adherence to therapies is associated with an increased risk of exacerbations and diminished lung function (38). What is not known is how different combinations of medications will impact self-management, long-term health, and QOL. Studies of strategies to improve self-management and dissemination of those that prove effective will help maximize health.
4. *What is the optimal approach to administration of inhaled antibiotic therapy?* Individuals infected with *P. aeruginosa* typically administer inhaled antibiotics in 28-day, every-other-month cycles. However, it is unknown if this is the best approach for bacterial suppression. For example, as more antibiotics become available, it will be possible to provide continuous therapy by cycling multiple inhaled antibiotics. Studies to determine the optimal approach to initiating and continuing inhaled antibiotics to enhance lung function and minimize bacterial resistance are needed.

## CONCLUSIONS

These updated guidelines are based on a systematic review of the published literature. However, any therapeutic decisions must be made individually for each patient. We hope that these recommendations will help CF health care professionals, individuals with CF, and their families make informed health care decisions. We anticipate that these recommendations will be revised as new information becomes available.

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