Cystic Fibrosis Pulmonary Guidelines

Treatment of Pulmonary Exacerbations

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The natural history of cystic fibrosis lung disease is one of chronic progression with intermittent episodes of acute worsening of symptoms frequently called acute pulmonary exacerbations. These exacerbations typically warrant medical intervention. It is important that appropriate therapies are recommended on the basis of available evidence of efficacy and safety. The Cystic Fibrosis Foundation therefore established a committee to define the key questions related to pulmonary exacerbations, review the clinical evidence using an evidence-based methodology, and provide recommendations to clinicians. It is hoped that these guidelines will be helpful to clinicians in the treatment of individuals with cystic fibrosis.

Keywords: aminoglycosides; IV antibiotics; drug synergism; *Pseudomonas*; respiratory therapy

Cystic fibrosis (CF) is a complex genetic disease affecting many organs, although 85% of the mortality is a result of lung disease (1). CF lung disease begins early in life with inflammation and impaired mucociliary clearance and consequent chronic infection of the airways (2). There is progressive decline of lung function with episodes of acute worsening of respiratory symptoms, often referred to as “pulmonary exacerbations.” Although a generally applicable prospective definition of a pulmonary exacerbation has not been developed, clinical features of an exacerbation may include increased cough, increased sputum production, shortness of breath, chest pain, loss of appetite, loss of weight, and lung function decline (3). Pulmonary exacerbations have an adverse impact on patients’ quality of life and a major impact on the overall cost of care (4). Identifying optimal treatment methods for these events could produce significant improvements in quality and length of life for patients with CF.

To identify the best treatment practices, the CF Foundation’s Pulmonary Therapies Committee, comprising individuals knowledgeable in all the major facets of CF care, conducted a search of published results of controlled trials of common treatment methods for exacerbations. It is not our intent to define a pulmonary exacerbation, nor to discuss relative severity, but to evaluate the evidence supporting therapies and approaches for the management of a health decline determined by a CF specialist to represent an exacerbation of CF lung disease. This systematic review allowed the Committee to make specific treatment recommendations and to determine areas that need additional study.

The guidelines presented are designed for general use in most individuals with CF, but should be adapted to meet specific needs as determined by the individual, their family, and their health care provider.

METHODS

A systematic review was performed addressing a series of questions related to treatment of pulmonary exacerbations. For each question, the body of evidence was evaluated by the full Committee. Recommendations were drafted using the U.S. Preventive Services Task Force (USPSTF) grading scheme, which provides a mechanism to weigh the quality of evidence and the potential harms and benefits in determining recommendations (Table 1) (5). The complete METHODS and RESULTS can be found in the online supplement. A summary of the questions and the evidence identified for each is provided in Table 2.

RECOMMENDATIONS

Most of the patients included in the studies reviewed were adults. The review was not limited to specific age groups and specific recommendations are not based on patient age. Unfortunately, the pediatrician is often faced with making treatment decisions based on data obtained from adults. The Committee suggests that the CF pediatrician consider these recommendations while allowing for obvious differences, such as effect of body size on drug clearance and effect of age on need for a caregiver.

The Committee determined that there is insufficient information to make a recommendation for many of the questions. Suggestions for clinical studies to investigate these questions have been provided where appropriate. These will not be easy studies as outcome measures must be relevant, immediate (e.g., improvement of symptoms and lung function), and long-term (e.g., time to next exacerbation, rate of decline of lung function).

Site of Treatment

Once a decision has been made to intervene for a pulmonary exacerbation, the clinician must then decide where that treat-
TABLE 1. RECOMMENDATION GRADE DEFINITIONS AND SUGGESTIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Suggestions for Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The Committee recommends the service. There is high certainty that the net benefit is substantial.</td>
<td>Offer/provide this service.</td>
</tr>
<tr>
<td>B</td>
<td>The Committee recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is small.</td>
<td>Offer/provide this service.</td>
</tr>
<tr>
<td>C</td>
<td>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.</td>
<td>Offer/provide this service only if other considerations support offering or providing the service to an individual patient.</td>
</tr>
<tr>
<td>D</td>
<td>The Committee recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harm outweighs the benefits.</td>
<td>Discourage the use of this service.</td>
</tr>
<tr>
<td>I</td>
<td>The Committee concludes that the current evidence is insufficient to compare treatment sites (Table 2) (7). There was only one randomized controlled trial identified, and it demonstrated similar results in most outcome measures for home and hospital settings. Therefore, the Committee felt that the evidence was limited, making the certainty of a recommendation low.</td>
<td></td>
</tr>
</tbody>
</table>

Table adapted from a published U.S. Preventive Services Task Force Recommendation Statement (5).

- **:** Previous recommendations (10, 11).
- *:* Cochrane Review exists on this topic.
- **:** Moderate Small

TABLE 2. EVALUATION OF THE EVIDENCE

<table>
<thead>
<tr>
<th>Question</th>
<th>Studies</th>
<th>N</th>
<th>Certainty</th>
<th>Grade of Recommendation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of treatment*</td>
<td>1 RCT(7)</td>
<td>17</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence that hospital and home treatment are equivalent</td>
</tr>
<tr>
<td>Chronic therapies</td>
<td>**</td>
<td>**</td>
<td>Moderate</td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>Simultaneous use of inhaled and IV antibiotics</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence to recommend for or against simultaneous use</td>
</tr>
<tr>
<td>Airway clearance therapies</td>
<td>**</td>
<td>**</td>
<td>Moderate</td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>Number of antibiotics to treat Pseudomonas*</td>
<td>17 RCT(25–41)</td>
<td>768</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence that a single antibiotic is equivalent to a combination antibiotic</td>
</tr>
<tr>
<td>Aminoglycoside dosing*</td>
<td>4 RCT(29, 51–53)</td>
<td>349</td>
<td>Moderate</td>
<td>Small</td>
<td>C</td>
</tr>
<tr>
<td>Continuous infusion beta-lactam antibiotics</td>
<td>1 RCT(56)</td>
<td>5</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence to recommend continuous infusion</td>
</tr>
<tr>
<td>Duration of antibiotics*</td>
<td>0</td>
<td>0</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence to define optimal duration of antibiotics</td>
</tr>
<tr>
<td>Synergy testing (routine)</td>
<td>1 RCT(24)</td>
<td>132</td>
<td>Low</td>
<td>Zero</td>
<td>D</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>2 RCT(63, 64)</td>
<td>44</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence to recommend use of corticosteroids</td>
</tr>
</tbody>
</table>

Definition of abbreviations: N = number of patients evaluated; RCT = randomized controlled trial; RXO = randomized crossover trial; QRT = quasi-randomized trial; XO = crossover trial.
* Cochrane Review exists on this topic.
** Previous recommendations (10, 11).
whether these observations are correct and clinical studies are necessary to answer this question; however, there are considerable challenges for such studies including: (1) the inability to blind subjects and research team as to intervention, (2) the potential for attrition biasing the intervention groups and (3) the wide diversity in resources for home care at various care centers. Also, at many care centers, treatment is not exclusively delivered in hospital or at home, rather, it is initiated in the hospital and completed at home. Such a study would be appropriate only for those patients who are deemed to be good candidates for home treatment.

**Recommendation:** The CF Foundation recommends against delivery of intravenous antibiotics in a nonhospital setting unless resources and support equivalent to the hospital setting can be assured for the treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation.)

Continuing Chronic Therapies for Maintenance of Lung Health

Recommendations for the use of chronic medications (12) and airway clearance therapies (13) in patients with CF have been made previously by this Committee. Because of the paucity of data related to the use of chronic medications and airway clearance therapies specifically in the setting of an acute exacerbation, the Committee refers to the prior guidelines. Most of the studies reviewed for those guidelines included patients who were treated for an acute exacerbation, and use of the study agent was not stopped during treatment of the acute exacerbation. The Committee found no compelling reason why any recommended chronic therapy should be discontinued during treatment of a pulmonary exacerbation.

In fact, airway clearance therapy has long been considered a crucial aspect of treatment of a pulmonary exacerbation. In general, the Committee believes that airway clearance therapies should be intensified as part of the treatment of an acute exacerbation. This typically means increased time for each treatment as well as an increase in the frequency of treatments. In addition, treatment of an exacerbation should be looked upon as an opportune time to educate the patient further about the various methods of airway clearance.

The use of other chronic therapies, however, may require careful consideration in some situations, such as the use of high-dose nonsteroidal antiinflammatory agents (e.g., ibuprofen) in the setting of IV aminoglycosides due to a potential increased risk of nephrotoxicity (14). Another possible problem involves the use of inhaled antibiotics in conjunction with IV antibiotics during treatment of an exacerbation (15). There are few published data examining the safety or efficacy of this dual therapy, but it has been suggested that such an addition does not result in a better or a faster rate of clinical improvement (16). Although exploiting two delivery routes could enhance antibacterial effect due to improved drug exposure, absorption of the inhaled drug into the circulation could increase risk of toxicity. Further, serum aminoglycoside levels, commonly measured to guide IV dosing, could be difficult to interpret when inhaled and IV aminoglycoside treatments are both used, particularly when dependent upon the relative timing of dosing of the antibiotics. Simple pharmacokinetic studies could answer these questions. Despite these potential problems, inhaled and IV antibiotics are frequently used concomitantly in treatment of an exacerbation. A clinical trial examining the benefits and risks of such a treatment strategy should be considered. Until more evidence is available, the committee suggests that the decision to continue an inhaled antibiotic in conjunction with the same IV antibiotic should be determined on a case-by-case basis.

With these caveats in mind, the Committee makes the following recommendations, based upon prior guidelines (12, 13):

**Recommendation:** The CF Foundation concludes that there is insufficient evidence to recommend for or against continued use of inhaled antibiotics in patients treated with the same antibiotics intravenously for the treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation.)

**Recommendation:** The CF Foundation recommends continuing chronic therapies for maintenance of lung health during treatment of an acute exacerbation of pulmonary disease. (Grade B recommendation.)

**Recommendation:** The CF Foundation recommends that airway clearance therapy be increased as part of the treatment of an acute exacerbation of pulmonary disease. (Grade B recommendation.)

Number of Antibiotics Used to Treat *Pseudomonas aeruginosa*

Because the most common pathogen identified in cultures of the CF airways is *Pseudomonas aeruginosa*, antibiotic choices for treatment of an acute exacerbation are typically directed at this pathogen. In the acutely ill patient without CF, empiric use of two antibiotics is recommended because inadequate coverage (i.e., using a single antibiotic to which the organism is resistant) results in dire outcomes (17). The standard approach to antibiotic treatment of *P. aeruginosa* in patients with CF (18) has been to use two antipseudomonal drugs to enhance activity (17, 19, 20) and reduce selection of resistant organisms (21, 22). However, in patients with chronic infection, where antibiotic susceptibility tests do not predict clinical outcome (23), the question of monotherapy versus combination therapy is a relevant one. Use of a single antibiotic may result in reduced toxicity as well as cost; for a patient who will be treated with antibiotics multiple times throughout life, these are important consequences (24). Further, antibiotic therapy in CF infection generally selects for resistant bacteria (25), so the argument that using combination antibiotic therapy may prevent selection of resistant strains is not sound. Finally, the use of combination antibiotic therapy with synergistic activity *in vitro* has not been shown to result in improved clinical outcomes (26).

The search comparing monotherapy with combination therapy in the treatment of a CF pulmonary exacerbation identified a large number of trials (27–45) (Table 2). However, upon analysis, the committee determined that there remains insufficient evidence addressing this important question, mainly because of methodological limitations and a small number of patients in each trial. Thus, the trials did not demonstrate compelling evidence that the two therapies are equivalent or to support one therapy over the other. It may well be that use of a single antibiotic is an appropriate choice in patients with a milder stage of disease (46), but when there is a more advanced stage of disease, infections may be more complex and combination therapy may prove more successful.

Conducting a definitive trial comparing monotherapy with combination therapy would be challenging. Microbiological outcomes (e.g., decrease in bacterial density, selection for resistance) would be difficult to interpret, and difference in clinical outcomes (e.g., reduced symptoms, time to next exacerbation) may be either so small, or take too long, to appreciate. Nevertheless, the Committee feels the comparison of monotherapy with combination therapy is a question worthy of further investigation.

Although the Committee recognizes that the use of combination antibiotic therapy has not been validated in the treatment of CF lung infections, the standard of care has been to use combination antibiotics as treatment of *P. aeruginosa* in pa-
Dosing of Antibiotics

**Aminoglycoside dosing.** Aminoglycoside antibiotics are commonly used in the treatment of CF pulmonary exacerbations. This class of antibiotic has concentration-dependent effects on bacteria (i.e., increased killing as concentrations are increased), suggesting there is greater efficacy at higher concentrations (47, 48), although the optimum maximum concentration for treatment of lung infections in CF has not been established. Dosing of aminoglycosides, however, is limited by potential for nephrotoxicity, ototoxicity, and vestibular toxicity. Clinicians are hampered by a lack of information on optimum peak and trough concentrations that balance the greatest efficacy with the lowest risk of toxicity. Traditionally, these antibiotics have been dosed on a 3-times-daily schedule (49), but some have suggested that once-daily dosing would allow for a greater peak concentration that would improve efficacy while reducing the overall exposure to the drug, decreasing the risk of toxicity (50). For example, in patients with CF and normal renal function, a dose of 10 mg/kg/d tobramycin given every 24 hours is predicted (51) to produce a peak blood level of 25–35 μg/ml and a 9- to 11-hour period with the drug concentration below detectable levels. A dose of 10 mg/kg/d tobramycin given at 8-hour intervals is predicted to produce a peak blood level of only 7 to 10 μg/ml and with only a 1 to 2-hour period with the drug concentration below detectable levels. (More details on this and other aminoglycoside dosing patterns are provided in Table E3 (see the online supplement). Once-daily dosing could thus reduce toxicity. However, whereas the antipseudomonal effect of aminoglycosides in the period when blood levels are undetectable (i.e., the post-antibiotic effect) is not clear, the greatly increased period of time with undetectable drug could put patients at risk for suboptimal treatment.

A meta-analysis of single versus multiple dose aminoglycosides for the treatment of infection in non-CF patients (52) found that once daily administration of aminoglycosides was as effective as multiple daily dosing, with a lower risk of nephrotoxicity. The committee therefore reviewed the efficacy of once-daily aminoglycoside therapy compared with multiple-dose daily aminoglycoside therapy for the treatment of an acute exacerbation of CF pulmonary disease. We identified five trials that addressed this question (31, 53–56) (Table 2). The results were consistent with studies in non-CF patients. There was comparable efficacy for once-, twice-, and thrice-daily dosing of aminoglycosides. Although no reduction in complications was demonstrated in patients with CF, the Committee felt that the essential pharmacodynamic principles could be the same as for non-CF patients.

It is important to note that all of the trials evaluated here involved a single course of therapy and thus did not assess questions of toxicity due to multiple treatments. The Committee suggests that patients treated with frequent courses of aminoglycosides should receive periodic monitoring of drug concentration, as dosage adjustment may be necessary. Periodic assessments of toxicity such as audiograms and measurement of serum creatinine are also recommended.

**Recommendation:** The CF Foundation recommends that once-daily dosing of aminoglycosides is preferable to 3-times daily dosing for treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation.)

**Beta-lactam antibiotics.** β-Lactam antibiotics demonstrate time-dependent pharmacodynamic properties—that is, maintaining the concentration at a given multiple above the minimum inhibitory concentration for longer portions of the dosing interval is associated with better antibacterial effect, but increasing the concentration above this multiple does not improve the killing effect (47, 57). As a result, there is a growing interest in continuous or extended infusion of β-lactam antibiotics in non-CF infections. A search for evidence demonstrating the effects of longer infusion times in the treatment of CF pulmonary exacerbations identified only one small trial (58) (Table 2), which did not demonstrate a statistically significant difference between continuous and intermittent dosing. The committee felt that there is insufficient information to determine whether this dosing strategy for β-lactam antibiotics is preferable, but well-designed clinical trials with a sufficient number of subjects are needed. These should be able to demonstrate the correlation between pharmacodynamic parameters and clinical outcomes.

**Recommendation:** The CF Foundation concludes that there is insufficient evidence to recommend the continuous infusion of β-lactam antibiotics for treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation.)

**Duration of Antibiotic Treatment**

The duration of antibiotic therapy has been studied in patient groups with conditions or diseases other than CF, such as community-acquired pneumonia (59) and acute exacerbations of chronic bronchitis (60), leading to recommendations for shorter durations of therapy. Analysis of treatment times reported in the CF Foundation Patient Registry (1) revealed considerable variation in practice among CF care centers (see online supplement for details). Our review, however, was unable to identify a single study that addressed this question in treatment of acute exacerbations of CF pulmonary disease.

Because shorter treatment times could reduce toxicity and cost, as well as possibly decrease selection of resistant pathogens (59), the Committee felt that the optimal duration of antibiotic therapy is an important question that should be studied further. Studies of duration of IV antibiotic therapy have been performed for the treatment of ventilator-associated pneumonia (comparing 8–15 d of antibiotic treatment) (61) and such a strategy might be successful for CF exacerbations as well. Key clinical endpoints in such trials would include lung functions, toxicity, selection of antibiotic-resistant pathogens, time to next exacerbation, and health-related quality of life, including treatment burden.

**Recommendation:** The CF Foundation concludes that there is insufficient evidence to recommend an optimal duration of antibiotic treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation.)

**Synergy Testing**

As stated earlier, the standard approach to treatment of *P. aeruginosa* infection has been to use two or more antibiotics. Clinicians typically select antibiotics to which the pathogens are susceptible, but in chronic CF airway infections, it may be impossible to select antibiotics to which all identified pathogens are susceptible. There are now methods of testing the susceptibility of bacteria to combinations of antibiotics. The combination of antibiotics may have no interaction or they may have antagonism or synergism (62). The role for routine synergy testing has been recently debated (63, 64).
The Committee felt that the single study addressing this question was performed rigorously and is unlikely to be duplicated (26) (Table 2). Data from this study do not support routine synergy testing, even for multidrug-resistant bacteria. However, the Committee felt that antibacterial synergism may be relevant in unique clinical settings (e.g., patients awaiting lung transplantation or those with multiresistant pathogens who have failed to respond to antibiotics selected by standard means). The benefit of synergy-guided therapy in such a subpopulation has not been tested.

**Recommendation:** The CF Foundation recommends against the use of synergy testing as part of the routine evaluation of the patient with an acute exacerbation of pulmonary disease and multidrug-resistant bacteria. (Grade D recommendation.)

**Corticosteroids**

The guidelines developed by the Committee for the use of chronic medications to maintain lung health (12) recommend against the routine use of oral or inhaled corticosteroids. Despite a demonstrated benefit of systemic steroids on lung function, the overall harm from side effects outweighed the benefits. However, a short course of systemic corticosteroids may offer benefit in the treatment of an acute exacerbation without the long-term adverse effects, an approach that has been used in the treatment of acute exacerbations in chronic obstructive pulmonary disease (65). Our search identified two trials that examined steroid use in the treatment of pulmonary exacerbations in CF (66, 67) (Table 2), but patient numbers and differences were small. A larger, well-designed clinical trial would be needed to determine the role of steroid treatment during exacerbations.

**Recommendation:** The CF Foundation concludes that there is insufficient evidence to recommend the routine use of corticosteroids in the treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation.)

**CONCLUSIONS**

We have reviewed and evaluated the evidence supporting the therapies used for the treatment of acute pulmonary exacerbations in CF airways disease. We have developed recommendations based on the quality of the published evidence and the estimate of the net benefit demonstrated within those publications. In addition, we have identified important questions for which we lack high-quality data and for which additional studies are needed. This document should be viewed as a guideline for CF care; it is our intent to review these recommendations periodically to address new data. We are hopeful that clinicians will find these recommendations to be useful in their care of patients with CF.

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**Cystic Fibrosis Foundation**

**Project Assistant:** Sarah Waybright, Clinical Programs

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