Cystic Fibrosis Pulmonary Guidelines:

Treatment of Pulmonary Exacerbations

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Project supported by the Cystic Fibrosis Foundation

Running title: CF Pulmonary Exacerbations

Subject Category: 74 (Cystic fibrosis in adults: management)
At A Glance Commentary

Acute exacerbations of pulmonary disease occur commonly in patients with cystic fibrosis. This manuscript represents the efforts by a committee formed by the Cystic Fibrosis Foundation to analyze studies of the efficacy and safety of therapies and approaches commonly used for treatment of pulmonary exacerbations and make recommendations for their use based on the available data.

This article appears in an expanded version online, accessible from this issue's table of content online at www.atsjournals.org
ABSTRACT

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.

Word count: 99

Key words: aminoglycosides, IV antibiotics, drug synergism, *Pseudomonas*, respiratory therapy
List of Abbreviations:

CF - cystic fibrosis; IV – intravenous; QRT – quasi-randomized trial; RCT – randomized controlled trial; RXO – randomized crossover trial; USPSTF - U.S. Preventive Services Task Force; XO – crossover trial
INTRODUCTION

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 version of this manuscript (see this issue’s table of contents at www.atsjournals.org). 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 treatment can best be provided. Because intravenous (IV) antibiotic therapy, an effective component of treatment for pulmonary exacerbations (6), can now often be delivered in the home, the committee asked whether using IV antibiotics outside of the hospital setting is as efficacious and safe as similar treatment in the inpatient setting.

The question assumes that all therapies required for successful treatment can be provided equally in both inpatient and outpatient settings; IV antibiotics are but one part of the treatment of an exacerbation. In cases where outpatient resources cannot match inpatient resources, there is no reason to expect similar outcomes. For example, families of pediatric patients must have the financial resources and time needed to meet treatment goals successfully if the decision is made to treat a pulmonary exacerbation in the outpatient setting. Other necessary resources include reliable utilities (electricity, telephone, and plumbing) and the ability to perform airway clearance therapies.

Home therapy may nevertheless be appropriate for selected patients with CF. The committee therefore examined evidence comparing treatment sites (Table 2) (7). There was only one comparative trial identified, and it demonstrated similar results in most outcome measures for home and hospital setting. Therefore, the committee felt that the evidence was limited, making the certainty of a recommendation low.

If there is any doubt, admission to the hospital is the suggested option. This may be particularly relevant for patients with co-morbidities that complicate care, and for patients with more severe exacerbations, who may be too fatigued or in too much distress to be able to perform the therapies adequately. For example, nutritional needs, elevated in most patients with
CF, are even greater during an exacerbation (8). Patients may demonstrate glucose intolerance during an exacerbation; those patients with CF-related diabetes typically require increased insulin during treatment of an exacerbation (9). An additional concern includes patients with renal dysfunction, who will need close observation for potential deterioration and drug monitoring.

Although they did not meet criteria for this systematic review, there are observational studies that suggest better outcomes for patients treated in a hospital than for those treated at home (10,11). There is significant interest in learning 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 treatment 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 non-hospital setting unless resources and support equivalent to the hospital setting can be assured for the treatment of an acute exacerbation of pulmonary disease. (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 non-steroidal anti-inflammatory 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). While 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 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 risk 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. (I recommendation)

**Recommendation:**
The CF Foundation recommends continuing chronic therapies for maintenance of lung health during treatment of an acute exacerbation of pulmonary disease. (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. (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 2 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 2 anti-pseudomonal 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 vs. 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 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 patients with CF. As such, the committee felt that there is not compelling evidence to change that strategy.

**Recommendation:**

The CF Foundation concludes that there is insufficient evidence to recommend the use of a single antibiotic as being equivalent to the use of more than one antibiotic class for treatment of *Pseudomonas* infection during an acute exacerbation of pulmonary disease. (I recommendation)
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 $\mu$g/ml and a 9-11 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 7-10 $\mu$g/ml and with only a 1-2 hour period with the drug concentration below detectable levels. (More details on this and other aminoglycoside dosing patterns are provided in Table 3, online.) Once daily dosing could thus reduce toxicity. However, while the anti-pseudomonal 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 sub-optimal treatment.
A meta-analysis of single vs. 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 to multiple dose daily aminoglycoside therapy for the treatment of an acute exacerbation of CF pulmonary disease. We identified 5 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. While 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. (C recommendation)

**Beta-lactam antibiotics.** Beta-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 beta-lactam antibiotics in non-CF infections. A search for evidence
demonstrating the effects of longer infusion times in treatment of CF pulmonary exacerbations
identified only one small trial (58) (Table 2), which did not demonstrate statistically significant
difference between continuous and intermittent dosing. The committee felt that there is
insufficient information to determine whether this dosing strategy for beta-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 beta-lactam antibiotics for treatment of an acute exacerbation of pulmonary disease.
(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 manuscript 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 carried out for the treatment of ventilator-associated pneumonia (comparing 8 to 15 days 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. (I recommendation)

Synergy Testing

As stated earlier, the standard approach to treatment of P. aeruginosa infection has been to use 2 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 identified 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 multi-drug 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 multi-resistant 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 multi-drug-resistant bacteria. (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 harms 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 utilized in the treatment of acute exacerbations in chronic obstructive pulmonary disease (65). Our search identified two trials that examined steroid use in 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. (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.
ACKNOWLEDGMENTS

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REFERENCES


Table 1. Recommendation Grade Definitions and Suggestions for Practice*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</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>
</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 moderate to substantial.</td>
</tr>
<tr>
<td>C</td>
<td>The committee recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is moderate or high certainty that the net benefit is small.</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 harms outweigh the benefits.</td>
</tr>
<tr>
<td>I</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>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suggestions for Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer/provide this service</td>
</tr>
<tr>
<td>Offer/provide this service.</td>
</tr>
<tr>
<td>Offer/provide this service only if other considerations support offering or providing the service in an individual patient.</td>
</tr>
<tr>
<td>Discourage the use of this service</td>
</tr>
</tbody>
</table>

*Table adapted from a published U.S. Preventive Services Task Force Recommendation Statement (5)
### Table 2. Evaluation of the Evidence

<table>
<thead>
<tr>
<th>Question</th>
<th>Studies</th>
<th>N</th>
<th>Certainty</th>
<th>Magnitude of Benefit</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></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>
<td>Continue current practices</td>
</tr>
<tr>
<td>Simultaneous use of inhaled and IV antibiotics</td>
<td>0 RCT (^{(25-41)})</td>
<td>0</td>
<td>Low</td>
<td></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>
<td>Continue current practices</td>
</tr>
<tr>
<td>Number of antibiotics to treat <em>Pseudomonas</em></td>
<td>17 RCT (^{(25, 31-33)}) 1 RXO (^{(42)}) 1 QRT (^{(43)})</td>
<td>768</td>
<td>Low</td>
<td></td>
<td>I</td>
<td>Insufficient evidence that single antibiotic is equivalent to combination antibiotics</td>
</tr>
<tr>
<td>Aminoglycoside dosing*</td>
<td>4 RCT (^{(29, 51-53)}) 1 RXO (^{(54)})</td>
<td>349</td>
<td>Moderate</td>
<td>Small</td>
<td>C</td>
<td>Once daily dosing is acceptable for treatment of <em>Pseudomonas</em></td>
</tr>
<tr>
<td>Continuous infusion beta-lactam antibiotics</td>
<td>1 XO (^{(56)})</td>
<td>5</td>
<td>Low</td>
<td></td>
<td>I</td>
<td>Insufficient evidence to recommend continuous infusion</td>
</tr>
<tr>
<td>Duration of antibiotics*</td>
<td>0 RCT (^{(24)})</td>
<td>0</td>
<td>Low</td>
<td></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>
<td>Routine use not recommended</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>2 RCT (^{(63, 64)})</td>
<td>44</td>
<td>Low</td>
<td></td>
<td>I</td>
<td>Insufficient evidence to recommend use of corticosteroids</td>
</tr>
</tbody>
</table>

*Cochrane Review exists on this topic

**Previous recommendations (10, 11)

N = number of patients evaluated

RCT = randomized controlled trial

RXO = randomized crossover trial

QRT = quasi-randomized trial

XO = crossover trial
Cystic Fibrosis Pulmonary Guidelines:

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ONLINE EXPANDED EDITION

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At A Glance Commentary

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ABSTRACT

Cystic fibrosis is an autosomal 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 microbial pathogens from the lung and develop chronic pulmonary infections and inflammation. 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.

Word count: 141

Key words: aminoglycosides, IV antibiotics, drug synergism, Pseudomonas, respiratory therapy
List of Abbreviations:

BMI – body mass index; CF - cystic fibrosis; COPD - chronic obstructive pulmonary disease;
FEV$_1$ - forced expiratory volume in 1 second; FVC - forced vital capacity; IV – intravenous;
MIC - minimum inhibitory concentration; QRT – quasi-randomized trial; RCT – randomized
controlled trial; RXO – randomized crossover trial; USPSTF - U.S. Preventive Services Task
Force; XO – crossover trial
INTRODUCTION

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 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 occur commonly; 38% of all patients seen at CF care centers in the US were treated with intravenous (IV) antibiotics for at least one pulmonary exacerbation during 2007 (4). Thus, pulmonary exacerbations have an adverse impact on patients’ quality of life and a major impact on the overall cost of care (5).

Appropriate care and management of CF lung disease is likely to increase the quality and length of life of individuals with CF. To provide guidance to the clinician who must choose from an ever-expanding arsenal of treatments for chronic CF lung disease, the CF Foundation established the Pulmonary Therapies Committee. This document represents the committee’s recommendations, based on available evidence, for the treatment of pulmonary exacerbations. It is not our intent to define a pulmonary exacerbation, nor to discuss the relative severity of an exacerbation, but to evaluate the evidence supporting commonly used therapies and approaches for the management of health decline determined by a CF specialist to represent an exacerbation of CF lung disease, and to determine areas that need additional study. The guidelines 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

Assessment of Evidence

A meeting of the Pulmonary Therapies Committee (see Acknowledgments) was held in November 2006 to prioritize therapies to be covered in these guidelines. Only those therapies believed to be used with regularity in some patients and for which there was published, peer-reviewed literature were selected for consideration. The committee members developed and refined a series of questions related to these treatments, including: (1) site of treatment (i.e. home vs. hospital); (2) number of antibiotics (one vs. more than one); (3) aminoglycoside antibiotic regimen (once daily vs. multiple-dose daily); (4) beta-lactam antibiotic regimen (continuous infusion vs. intermittent infusion); (5) duration of antibiotics (less than 7 days vs. more than 7 days); (6) choice of antibiotics (i.e. based on standard susceptibility testing vs. synergy testing); (7) use of systemic corticosteroids.

There are other therapies commonly used for acute pulmonary exacerbations that are not addressed here, but are considered elsewhere. These include nutritional support (6) and control of CF-related diabetes (7). Patients with advanced stage lung disease may also benefit from supplemental oxygen or even need ventilatory support, but those therapies are not unique to patients with CF and are not addressed in this document.

Systematic reviews addressing the selected questions were commissioned from Johns Hopkins University. The reviews included English-language reports of controlled trials that described outcomes of lung function, time to next exacerbation, quality of life, nutritional status
(weight), adverse events, or symptom resolution. Searches were conducted of PubMed (June 2007), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (July 2007) databases. We combined controlled vocabulary terms and text words for exacerbations and for cystic fibrosis to create comprehensive search strategies (see Appendix). Reference lists in relevant reviews and eligible articles were also scanned.

Two reviewers independently screened articles for eligibility. Disagreements concerning eligibility were resolved by consensus or by a third reviewer. For each eligible article, two reviewers abstracted information from the published report including study and participant characteristics, outcomes, as well as elements of critical appraisal such as concealment of treatment allocation or masking of outcome assessors. Evidence tables and a qualitative synthesis for each therapy were provided to the committee.

**Process of Drafting Recommendations**

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) (8).

A draft of the recommendations was presented to the CF clinical community in July 2008 in order to solicit public commentary. This input was considered by the committee in preparation of final recommendations.

**RESULTS**
Assessment of Evidence

1. *Existing systematic reviews.* The committee identified 4 relevant Cochrane systematic reviews that addressed site of treatment (9), choice of antibiotics (10), number of antibiotics (11), and aminoglycoside antibiotic regimen (12). Subsequent to this search, the Cochrane review on site of treatment was updated; there were no new citations and no change in the conclusion (13). In addition, 2 new Cochrane reviews were published on duration of antibiotic therapy (14) and combination antimicrobial susceptibility testing (15).

2. *Systematic reviews of original research.* A search identified a total of 739 unique citations. The abstract screening identified 159 citations for further consideration. Citations were deleted during abstract screening (n=581) primarily because: they did not address any of the review questions (n=433); they did not address treatment of acute exacerbations (n=116); they were in abstract form only (n=60); or they did not contain original data (i.e., a review or commentary) (n=40). Reviewers did not need to agree on the reason for deletion. An additional 143 citations were excluded during the full-text review. The most common reasons for exclusion included: they did not address any review questions (n=20); they contained no original data (n=8); or they did not address the treatment of an acute exacerbation (n=11).

The committee identified 28 studies, published between 1977 and 2007, as eligible for inclusion in this review. Figure 1 provides an overview of the searching and screening processes. One study addressed site of treatment (16), 19 addressed number of antibiotics (17-35), 5 addressed aminoglycoside antibiotic regimen (21, 36-39), 1 addressed beta-lactam
antibiotic regimen (40), 1 addressed choice of antibiotics (41), and 2 addressed corticosteroid use (42, 43). No studies were identified addressing duration of antibiotics (Table 2). The most frequent outcomes addressed were lung function and adverse events (Table 2). Only 1 study assessed quality of life (16).

**RECOMMENDATIONS**

**Site of Treatment**

Once a decision has been made to intervene for a pulmonary exacerbation, the clinician must then decide where that treatment can be provided successfully and safely. The plan of care will include many of the therapies discussed here and typically will involve antibiotic therapy, which has been shown to be an effective component of the treatment of a pulmonary exacerbation (44). Indeed, the use of antibiotics has been a chief feature defining an exacerbation in some clinical trials (45-47).

Although many patients are treated with oral antibiotics (e.g. ciprofloxacin, trimethoprim-sulfamethoxasole) for exacerbations that are presumably mild (48), this question addressed the site of treatment when the clinician has elected to use intravenous (IV) antibiotics, which traditionally required admission to the hospital. Advances in treatment options have made the provision of home IV antibiotics increasingly common. In 2007, 25-32% of the total days of IV therapy prescribed for pulmonary exacerbations were given at home (4). The question addressed by the committee was whether using IV antibiotics outside of the hospital setting (e.g. at home) is as efficacious and safe as similar treatment in the inpatient setting. The committee compared the efficacy of outpatient to inpatient treatment of a pulmonary exacerbation in
improving lung function, reducing time to next exacerbation, improving quality of life, improving nutritional status, providing symptom resolution, and reducing adverse events.

A systematic review identified only one randomized controlled trial (17 participants, all adults; 31 admissions) that compared home and hospital antibiotic therapy (16). At both sites, participants received the same antibiotic therapy of IV ceftazidime and tobramycin. There were 10 observational studies which were excluded because they did not fulfill inclusion criteria (49-58).

Lung function. Both home and hospital treatment arms in the study had significant improvements in lung function, but there was no significant difference in forced expiratory volume in 1 second (FEV₁, p=0.27) or forced vital capacity (FVC, p=0.30) between home and hospital treatment arms at both 10 and 21 days.

Time to next exacerbation. Not reported.

Quality of life. The study used the Chronic Respiratory Disease Questionnaire (59) to assess the quality of life among participants. Higher scores indicate better quality of life and mean values are reported here. There were no significant differences between home and hospital arms of the study for dyspnea (p=0.25) and emotional scores (p=0.11). There were differences for changes in fatigue score (home 3.6 vs. hospital 6.8, p=0.04) and mastery score (i.e. feeling of control over the disease; home 2.6 vs. hospital 5.5, p=0.03) favoring hospitalization. Also, the change in total score favored the hospital group (home 16.5 vs. hospital 29.5, p=0.03). However, in terms of disruptions, home-treated participants fared better on family (home 6.2 vs. hospital 4.5, p=0.001), personal (home 5.1 vs. hospital 3.8, p=0.004), sleeping (home 6.0 vs. hospital 4.4, p=0.005) and total disruption scores (home 23.9 vs. hospital 18.3, p<0.001) at day 21.
**Nutritional status.** There was no significant difference in weight gain after treatment in hospital compared to treatment at home (p=0.10).

**Symptom resolution.** Not reported.

**Adverse events.** There were no adverse events reported in either the hospitalized or home-treated group.

A Cochrane systematic review (9) identified the same study that compared home and hospital antibiotic therapy and concluded that in the short term, home therapy is not harmful and, in general, reduces social disruptions.

As stated earlier, there were 10 observational studies which were not included in the review (49-58). In general, these studies reported improvement in lung function for both home and hospital treatment, with greater improvement for those treated in the hospital setting. Although these were not controlled trials, the observation was fairly consistent.

The committee felt that the evidence addressing this question was limited, making the certainty of a recommendation low. The question assumes that the therapies required for successful treatment of the pulmonary exacerbation could be provided equally in both the inpatient and outpatient setting. In those cases where the outpatient resources cannot match the inpatient resources, there is no reason to expect a similar outcome compared to an inpatient treatment. However, home therapy may be appropriate for selected patients with CF. Factors relevant to this decision are provided in the section on Key Points of Discussion.

**Recommendation:**

The CF Foundation recommends against delivery of intravenous antibiotics in a non-hospital setting unless resources and support equivalent to the hospital setting can be assured for the
treatment of an acute exacerbation of pulmonary disease. Certainty of net benefit, low; Grade of recommendation, I.

**Continuing Medications Used Chronically for Lung Health and Airway Clearance**

Recommendations for the use of chronic medications (60) and airway clearance therapies (61) in patients with CF have been made previously by this committee. Many of the studies reviewed for those guidelines included patients who were treated for an acute exacerbation, and use of the study agent was not specifically stopped during treatment of the acute exacerbation. 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, we refer to these prior guidelines. The committee found no compelling reason why any of these recommended chronic therapies would not provide continued benefit.

However, there are situations that may require careful consideration. One example is whether to continue the use of inhaled antibiotics in patients who are receiving the same drug intravenously (e.g. tobramycin, colistin). Inhaled antibiotics are often used in the treatment of an exacerbation (62), but there are no published data showing that this improves the response to the treatment of an exacerbation or increases the risk of aminoglycoside toxicity. Clinicians may also need to consider carefully the use of high dose non-steroidal anti-inflammatory drugs (e.g. ibuprofen) in the setting of IV aminoglycosides due to the potential of increased risk of nephrotoxicity (63).

**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. Certainty of net benefit, low; Grade of recommendation, I.

Recommendation:
The CF Foundation recommends continuing other medications used chronically for maintenance of lung health during treatment of an acute exacerbation of pulmonary disease. Certainty of net benefit, moderate; Magnitude of net benefit, moderate; Consensus recommendation, B.

Recommendation:
The CF Foundation recommends that airway clearance therapy be increased as part of the treatment of an acute exacerbation of pulmonary disease. Certainty of net benefit, moderate; Magnitude of net benefit, moderate; Consensus recommendation, B.

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. The standard approach to antibiotic treatment of P. aeruginosa in patients with CF has been to use 2 drugs with activity against this pathogen (64). This is based upon arguments that the broader coverage: (1) ensures antibacterial activity against potential antibiotic-resistant pathogens (65); (2) reduces selection of resistant organisms (66, 67); and (3) offers synergistic activity against the pathogens (68, 69). However, it is important to note that there are patients
who are treated with oral antibiotics for mild exacerbations and they are typically treated with only one antibiotic (48).

The committee reviewed the efficacy of one antibiotic compared to 2 or more antibiotics for the treatment of an acute exacerbation of pulmonary disease in improving lung function, reducing time to next exacerbation, improving quality of life, improving nutritional status, providing symptom resolution, and reducing adverse events. The search identified 19 studies that addressed this question (17-35).

Lung function. Fourteen of the studies assessed lung function (17-24, 26-28, 31-33) and none reported statistically significant differences between monotherapy and combined therapy.

Time to next exacerbation. Five trials assessed time to next exacerbation. Smith (26) (n=75) reported that the patients receiving azlocillin plus tobramycin had a longer interval before next admission than did those treated with azlocillin alone. This difference reached a peak at 80 days, at which time 30% of the patients on combined therapy had been readmitted compared to 60% of the patients receiving azlocillin alone (p<0.01). The other four trials (n=180) reported no statistically significant difference between monotherapy and combined therapy (21, 30, 32, 34).

Quality of life. Not reported.

Nutritional status. Four trials reported on nutritional status. McCarty (28), Parry (34), and Stack (35) (total n=139) each reported no statistically significant difference between groups but provided no raw data. Gold (31) (n=30) reported an increase in weight for both groups, but there was no difference between them (p>0.05).

Symptom resolution. Three trials assessed symptom resolution. Bosso (27) (n=30) reporting on cough, sputum production, and dyspnea found no difference in the change of scores from baseline between the monotherapy and combined therapy groups (-31.6% monotherapy vs.
-28.6% combination therapy, p>0.05). Gold (31) (n=30) reported no statistically significant difference in the number of patients reporting resolution or change in raw score of symptoms (cough, dyspnea, anorexia scored on 0 to 4 point scale) as assessed by a research nurse. Krause (25) recorded the number of patients reporting resolution (7 for those in monotherapy and 14 for those in combination therapy, no statistical analysis completed).

Adverse events. Thirteen of the studies (n=621) assessed adverse events (17, 21-23, 26-32, 34, 35). No differences are apparent in the number of dropouts caused by adverse events, the total number of events or the type of events reported.

A Cochrane review examining the use of single antibiotic compared to combination therapy identified 8 trials (11). Five were included in our review (21, 26, 28, 32, 34). Three studies were not included in our review: 2 of these were published as abstracts only (70, 71), and 1 was assessed as not specifically addressing treatment of acute exacerbation (72). The committee included 14 studies not included by Elphick: 10 addressed combinations not considered by their review (i.e., A vs (B+C)), (17-20, 23, 27, 30, 31, 33, 35), 1 article was excluded by the Cochrane review as it presented results based on number of courses of antibiotics versus number of patients (29), 1 was excluded on the basis that it was not a randomized trial (25), 1 was excluded as it assessed combinations of colistin (22), and 1 was excluded because it included both anti-staphylococcal and anti-pseudomonal antibiotics (24). The authors of the Cochrane review noted that 6 of their included studies had methodological flaws; they concluded that there was insufficient evidence to determine whether single or combined therapy was more effective in treating exacerbations.

The Pulmonary Therapies Committee agreed that there is insufficient evidence addressing this important question. 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 \textit{P. aeruginosa} in patients with CF. As such, the committee felt that there is not compelling evidence to change that strategy.

\textit{Recommendation:}

The CF Foundation concludes that there is insufficient evidence to recommend the use of a single antibiotic as being equivalent to more than one antibiotic class for treatment of \textit{Pseudomonas} infection during an acute exacerbation of pulmonary disease. Certainty of net benefit, low; Grade of recommendation, I.

\textbf{Dosing of Antibiotics}

There has been a growing literature on optimal dosing of antibiotics using the principles of pharmacodynamics, which integrates the relationship between pharmacokinetics, or how a patient absorbs, distributes and eliminates the antibiotic, and pathogen susceptibility (73). A commonly used measure of \textit{in vitro} activity of an antibiotic is the minimum inhibitory concentration (MIC), which is the lowest concentration of the antibiotic that results in inhibition of growth of the bacteria under standard conditions. Pharmacodynamics describes the effect of antibiotics on the bacteria and how this varies with concentration and time. Antibiotic concentrations at the site of infection are not measured and serum concentrations are often used as their surrogates. Most of these types of studies have shown that it is not a matter of simply dosing antibiotics to exceed the MIC; rather, what matters is by how much the MIC is exceeded (concentration dependent effect) and for how long the MIC is exceeded (time dependent effect).
by the antibiotic concentration at the site of infection. These definitions are based upon eradication of the pathogen, which is not the outcome after treatment of an acute pulmonary exacerbation in patients with CF. For this review, study was limited to concentration-dependent and time-dependent properties of commonly used antibiotics for the treatment of a CF pulmonary exacerbation.

Aminoglycoside dosing

Aminoglycoside antibiotics, which are commonly used in the treatment of CF pulmonary exacerbations, have traditionally been dosed on a 3-times-daily schedule (74). These antibiotics have concentration-dependent effects (i.e. increased killing of bacteria as concentrations are increased) suggesting there is greater efficacy at higher concentrations (73, 75). A dosing strategy for peak gentamicin and tobramycin concentrations of ≥8 µg/ml for Gram-negative bacterial pneumonia in non-CF patients demonstrated better outcomes (76), but this was independent of bacterial MIC values. Peak-concentration (Cmax)/MIC >8:1 for aminoglycosides have been associated with treatment success in non-CF patients (77, 78). The optimum Cmax for treatment of lung infections in CF has not been established.

Dosing of aminoglycosides is limited because of the potential for toxicity, specifically nephrotoxicity, ototoxicity, and vestibular toxicity. Some have suggested that once daily dosing will allow for a greater peak concentration that will result in improved efficacy, and yet reduce the overall exposure to the drug, decreasing the risk of toxicity (79). This is based upon the notion that although the antimicrobial effects are concentration-dependent, the toxicity effects are time-dependent; therefore, dosing patterns that maximize concentration peaks while minimizing time at or above the toxicity saturation threshold will optimize the therapeutic ratio.
A meta-analysis of single vs. multiple dose aminoglycosides for the treatment of infection in non-CF patients (80) 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 to multiple dose daily aminoglycoside therapy for the treatment of an acute exacerbation of pulmonary disease in improving lung function, reducing time to next exacerbation, improving quality of life, improving nutritional status, providing symptom resolution, and reducing adverse events. Five trials were identified that addressed this question (21, 36-39).

**Lung function.** Al Ansari (39) (n=15) reported change in final FEV₁ from baseline (% predicted) for each group, but did not provide any analysis of between group difference (difference from baseline 6.3 for once-daily and 7.2 for thrice-daily). Master (21) and Vic (38) (total n=66) each reported significant differences between baseline and final FEV₁, FVC, and FEF₂₅₋₇₅ (all as % predicted) for both once and thrice daily groups and neither found statistically significant differences between the treatment groups. Whitehead (37) (n=49) reported non-statistically significant (p=0.2) between-group differences for FEV₁ and FEF₂₅₋₇₅, while there was a small difference for FVC (p=0.03) favoring once daily therapy.

Smyth (36) (n=219) reported analyses per protocol and by intention-to-treat. No differences were found in FEV₁ (% predicted) between the once and thrice daily tobramycin groups in either analysis (10.4% for once daily vs. 10.0% for thrice daily, adjusted mean difference 0.4%; 95% confidence interval -3.3 to 4.1%).

**Time to Next Exacerbation.** Master (21) (n=44) reported a mean number of days to next admission of 173 for once daily and 153 for thrice daily treatment groups (p>0.05). Smyth (36)
(n=219) reported 131 days to next course of IV antibiotics for the once daily group compared with 168 days for the thrice daily group (p=0.48).

**Quality of life.** Not reported.

**Nutritional status.** Not reported.

**Symptom resolution.** Not reported.

**Adverse events.** Three trials (n=312) reported adverse events. The number of events was the same in each treatment group in the Smyth (36), Whitehead (37) and Master (21) trials.

A Cochrane review, with an updated search completed in February 2007, identified 4 trials (n=328) that assessed once daily versus thrice daily aminoglycosides. Three of these were included in our review (36-38). The committee excluded one study that the Cochrane review included (81) because it was an abstract only. The Cochrane review excluded two of the studies that were included in our review. Master (21) was excluded from the Cochrane review as the thrice daily group also included an additional antibiotic. The other study was excluded by the Cochrane review due to its crossover design (39). From the four trials, the Cochrane review concludes that there was no evidence of different efficacy for once versus thrice daily regimens (12).

The committee felt that although there are few studies of aminoglycoside dosing in patients with CF, the results of these studies are consistent with what has been demonstrated in similar studies of non-CF patients (80), with comparable efficacy for once, twice, and thrice daily dosing of aminoglycosides. Although no reduction in complications has been demonstrated in patients with CF, the committee felt that the essential pharmacodynamic principles could be the same as for non-CF patients. However, it is important to note that all of the trials evaluated here were with a single course of therapy and they do not assess questions of
toxicity due to multiple treatments. Also, the findings in non-CF patients excluded those patients with renal impairment. To reduce the risk of nephrotoxicity, the committee suggests pharmacokinetic monitoring of all patients who are treated with aminoglycosides.

**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. Certainty of net benefit, moderate; Magnitude of net benefit, small; Grade of recommendation, C.

**Beta-lactam antibiotics**

Beta-lactam antibiotics are commonly used for the treatment of CF pulmonary exacerbations. These antibiotics demonstrate time-dependent pharmacodynamic properties. Maintaining the concentration at a given multiple above the MIC 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; conversely, allowing the concentration to fall below this threshold decreases the effect (73, 82).

The committee reviewed the efficacy of continuous beta-lactam infusion compared to intermittent beta-lactam infusion for the treatment of an acute exacerbation of pulmonary disease in improving lung function, reducing time to next exacerbation, improving quality of life, improving nutritional status, providing symptom resolution, and reducing adverse events. Only one trial was identified (n=5) (40). No Cochrane review was identified that addressed this question.
Lung function. Differences in FEV$_1$ and FVC were assessed at 4 different time spans (i.e., first day versus 4th, versus 10th and versus 24th, and 10th day versus 24th day). No statistically significant differences were found between continuous and intermittent infusion.

Time to next exacerbation. Not reported.

Quality of life. Not reported.

Nutritional status. Not reported.

Symptom resolution. Not reported.

Adverse events. Not reported.

There is a growing interest in continuous infusion of beta-lactam antibiotics in non-CF infections. Alternatively, it may be possible to maximize antimicrobial potential of the drug by administering the same antibiotic dose over an extended infusion time, reducing toxicity and simplifying drug dosing (83). However, the committee felt that there is insufficient information in patients with CF to determine whether this dosing strategy for beta-lactam antibiotics is preferable.

**Recommendation:**

The CF Foundation concludes that there is insufficient evidence to recommend the continuous infusion of beta-lactam antibiotics for treatment of an acute exacerbation of pulmonary disease. Certainty of net benefit, low; Grade of recommendation, I.

**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 (84), ventilator associated
pneumonia (65), and acute exacerbations of chronic bronchitis (85) but our review was unable to identify a single study that addressed this question in treatment of acute exacerbations of CF pulmonary disease. A recent Cochrane study came to the same conclusion (14).

For the treatment of most infections, antibiotics are provided for a duration sufficient to eradicate the infection, a goal unlikely to be achieved by the treatment of an exacerbation of chronic infection in CF. Treatment goals in CF normally include resolution of symptoms (e.g. cough, dyspnea) or restoration of lung function (e.g. FEV₁). Since there were no specific trials assessing optimal duration of therapy, the committee reviewed the CF Foundation Patient Registry (4) to gain an understanding of current practice patterns in the US. These data reveal that there is considerable variation in practice among centers. The median duration (center specific) of IV antibiotics for patients <18 years of age was 14.5 days (range 6.5-22 days) (Figure 2). For those over 18 years of age, the median duration of IV antibiotics was 16.8 days (range 9-27 days) (Figure 3). The committee also evaluated the duration of IV antibiotics for individual patients to look for an effect based on age (Figure 4) and severity of disease (Figure 5). These do not represent controlled studies of proper duration, but reflect current practices. Although peaks occur in all groups examined at ~15 days, and perhaps again at ~22 days, there is substantial spread, consistent with the notion that there is not a systematic approach to treatment durations.

The committee felt that the optimal duration of antibiotic therapy is an important and fundamental question in the treatment of an acute exacerbation of pulmonary disease and should be studied further. Key clinical endpoints in such trials would include lung function improvement, selection of antibiotic resistant pathogens, time to next exacerbation (delaying the next exacerbation being the goal), 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. Certainty of net benefit, low; Grade of recommendation, I.

**Synergy Testing**

As stated earlier, the standard approach to treatment of *P. aeruginosa* infection has been to use 2 or more antibiotics. Antibacterial resistance of organisms is common, especially later in a patient’s life following exposure to multiple courses of 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 (86). The role for routine synergy testing has been recently debated (87, 88). The committee therefore evaluated the efficacy of antibiotic therapy selected on the basis of synergy testing compared to selection of antibiotic therapy by standard means for the treatment of an acute exacerbation of pulmonary disease in improving lung function, reducing time to next exacerbation, improving quality of life, improving nutritional status, providing symptom resolution, and reducing adverse events.

One study was identified, which included 132 patients. Aaron et al. (41) compared treatment with antibiotics chosen through standard practice compared to antibiotic treatment
chosen based on synergy testing (multiple combination bactericidal antibiotic testing). A recent Cochrane review (15) identified the same study.

*Lung function.* No differences were noted between groups in changes in lung function following therapy. The difference from baseline to day 14 in FVC was 0.48 L for the standard selection group and 0.36 L for the synergy-based selection group (p=0.26), while changes in FEV₁ were 0.23 L for standard therapy group and 0.29 L for the synergy-testing group (p=0.35).

*Time to next exacerbation.* The median number of days to next exacerbation was 79 days in the standard therapy group and 84.5 days in the group treated based on synergy testing. The hazard ratio was 0.86 (95% confidence interval 0.60 to 1.23, p=0.40) favoring standard therapy. Adjustment for age, BMI, type of bacteria and type of antibiotic did not appreciably change the hazard ratio.

*Quality of life.* Not reported.

*Nutritional status.* Not reported.

*Symptom resolution.* Not reported.

*Adverse events.* Two patients dropped out of the standard therapy group and no one dropped out of the synergy-testing group. There was a total of 7 adverse events (2 because of respiratory failure, 5 with an allergic rash) in the standard therapy group and 2 adverse events (hepatitis, allergic rash) in the synergy-testing group.

The Cochrane review, assessing the same study, concluded there is insufficient evidence to support the use of synergy testing to guide antimicrobial therapy of CF pulmonary exacerbations (15). The Pulmonary Therapies Committee felt that the study was performed rigorously and is unlikely to be duplicated. Current data do not support routine synergy testing, even for multi-drug resistant bacteria. However, the committee felt that although there were no
differences noted in the study, antibacterial synergism may be relevant in unique clinical settings (e.g. patients awaiting lung transplantation or those with multi-resistant pathogens who have failed to respond to antibiotics selected by standard means). The benefit of synergy-guided therapy in such a sub-population 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 multi-drug-resistant bacteria. Certainty of net benefit, low; Magnitude of net benefit, zero; Grade of recommendation, D.

**Corticosteroids**
The guidelines developed by the CF Foundation Pulmonary Therapies Committee for the use of chronic medications to maintain lung health (60) recommends against the routine use of oral or inhaled corticosteroids. Despite a demonstrated benefit of systemic steroids on lung function, the overall harms 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. Such an approach has been widely adopted in the treatment of patients with chronic obstructive pulmonary disease (COPD) who suffer from an acute exacerbation based on good evidence that corticosteroids have demonstrated benefit (89).

The committee reviewed the efficacy of steroids compared to placebo for the treatment of an acute exacerbation of pulmonary disease in improving lung function, reducing time to next exacerbation, improving quality of life, improving nutritional status, providing symptom
resolution, and reducing adverse events. Two studies were identified. One assessed the use of IV hydrocortisone for 10 days (43). The other study assessed the use of oral prednisone for 5 days (42). In both studies, corticosteroids were added to standard antibiotic therapy. No Cochrane review was identified that addressed this question.

**Lung function.** There was improvement in lung function in both studies (n=44), but there was no statistically significant difference between the steroid and placebo groups on change in FEV₁.

**Time to next exacerbation.** Not reported.

**Quality of life.** Not reported.

**Nutritional status.** Dovey (42) (n=24) reported non-significant changes in weight (1.6 kg vs. 2 kg for placebo vs. oral steroid groups, respectively, p>0.05).

**Symptom resolution.** Dovey (42) (n=24) reported symptoms monitored by patients at 2 days and 14 days. Each group improved at 2 days (difference of 6.9 for placebo group and 8.5 for steroid group). The authors reported that the differences between baseline and day 14 were not significantly different between the groups (no data provided, p=0.94).

**Adverse events.** Dovey (42) (n=24) reported 9 total events in the placebo group compared to 21 in the oral steroid group. Statistically significant differences were reported for glucosuria (1 in placebo vs. 6 in steroid group, p=0.03). Tepper (43) (n=20) reported 3 cases of wheezing in the placebo group and no adverse events in the IV steroid group.

**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. Certainty of net benefit, low; Grade of recommendation, I.

KEY POINTS OF DISCUSSION

There are many questions regarding treatment of pulmonary exacerbations for CF that remain unanswered by existing clinical trials:

1. *Are these recommendations applicable to children and adults alike?* Most of the patients included in the studies noted here are adults. This review was not limited to specific age groups and the committee has not made specific recommendations based on patient age. Unfortunately, the pediatrician is often faced with making treatment decisions based on data obtained from adults. There are, however, certain treatment issues for pediatric patients that may not be the same as for adults. For example, dosing of certain antibiotics may differ between pediatric and adult patients because of differences in drug clearance. The age of the patient may have an impact on the decision of where to treat the patient. Nevertheless, with these caveats and those that follow, the committee suggests that the recommendations in this document are generally applicable to all patients with CF and an acute pulmonary exacerbation.

2. *What factors define an appropriate candidate for home treatment?* There are a number of factors that are relevant to the determination of appropriate candidates for home treatment. First, the severity of the exacerbation must be considered. Patients with milder symptoms may be able to take on the added burden of the therapies discussed
here, but those who are more ill may be too fatigued or in too much distress to be able to perform the therapies adequately. Second, there must be sufficient resources in the home setting. A pediatric patient is not able to take care of himself and will need a caregiver. The patient and family must have the financial resources as well as the time available to meet treatment goals successfully. The availability of improved IV catheters, nursing and pharmacy support has made home treatment a possibility, but it should be made clear that IV antibiotics are but one part of the treatment of an exacerbation. There should be reliable utilities (i.e. electricity, telephone, and plumbing). Third, the ability to perform airway clearance therapies should be considered, as noted above. Fourth, the presence of co-morbidities may need to be addressed. The patient with CF has increased nutrition requirements at baseline, and energy expenditure is increased during an exacerbation (90). Patients may develop glucose intolerance during an exacerbation and those patients with CF-related diabetes typically require increased insulin during treatment of an exacerbation (7). Patients with renal dysfunction will need close observation for potential deterioration and drug monitoring. Although home treatment has been demonstrated to be successful in properly selected patients, it is not appropriate for all patients. If there is any doubt, admission to the hospital is the suggested option. Although they did not meet criteria for this systematic review, there are observational studies that suggest better outcomes for patients treated in a hospital than for those treated at home (91,92). There is significant interest in learning 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 treatment 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.

3. **Is a single antibiotic sufficient to treat Pseudomonas aeruginosa, or is combination therapy necessary?** Combination antibiotic therapy has become the standard approach for treatment of *Pseudomonas* infection. 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 (65). In patients with chronic infection, where antibiotic susceptibility tests do not predict clinical outcome (93), the question of monotherapy vs. 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 (94). Further, antibiotic therapy in CF infection generally selects for resistant bacteria (95) 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.

Although the committee was unable to find compelling evidence to support combination therapy over monotherapy, there was also insufficient evidence to state that monotherapy is equally effective to combination therapy. It may well be that use of a single antibiotic is a rational choice in patients with a milder stage of disease but when
there is a more advanced stage of disease, infections may be more complex and
combination therapy will prove more successful.

The committee feels this is a question worth studying but performing such a study
would be challenging. Microbiological outcomes (e.g. decrease in bacterial density,
selection for resistance) will be difficult to interpret, and difference in clinical outcomes
(e.g. reduced symptoms, time to next exacerbation, adverse events) may be either so
small, or take too long, to appreciate, raising the issue of feasibility.

4. **What can be said about proper aminoglycoside dosing?** Although there is considerable
literature on aminoglycoside dosing in patients with CF, the best dosing strategy is still
unknown. The basic principles of dosing to enhance efficacy and reduce the risk of
toxicity were stated earlier, but the optimum pharmacokinetic parameters (e.g. peak and
trough concentrations) are not known. An initial dose of aminoglycosides commonly
reported in clinical trials are 10 mg/kg/d for tobramycin and gentamicin, and 30 mg/kg/d
for amikacin. The expected pharmacokinetic parameters for patients with CF and normal
renal function for different dosing intervals (96), are shown in Table 3. What should be
evident in this table is that an increase in the dosing interval (e.g. from every 8 hours to
every 24 hours) allows for higher peak concentrations, but at the expense of a potentially
longer period where there is an undetectable concentration of drug. Whereas these drugs
have concentration-dependent effects and their effect on *Pseudomonas aeruginosa* when
the concentration is undetectable (i.e. post-antibiotic effect) is not clear, a longer period
of time with undetectable drug may put patients at risk for sub-optimal treatment with a
less frequent dosing strategy. This time can be reduced by increasing the dose and
raising the peak concentration, but the clinician must decide which dose and dosing
interval is best suited for the patient. The optimum peak and trough concentrations and
time of detectable drug that balances the greatest efficacy with the lowest risk of toxicity
have not been determined. Finally, since many patients with CF are treated with frequent
courses of aminoglycosides, periodic monitoring of drug concentration and dosage
adjustment as needed is suggested, as are periodic assessments of toxicity such as
audiograms and measurement of serum creatinine.

5. *Should an inhaled antibiotic be continued if using the same IV antibiotic?* There are few
studies that have looked at the simultaneous use of inhaled and IV antibiotics, but it has
been suggested that such an addition does not result in a better or a faster rate of clinical
improvement (97). An argument for such a strategy is an enhanced killing effect on
bacteria by improved drug delivery using two delivery routes. Another may be the
reinforcement of a chronic therapy routine, even if there is no measurable acute benefit.
An argument against this strategy includes the potential increased risk of toxicity as some
of the inhaled drug will be absorbed into the circulation. There may also be difficulty in
interpreting serum aminoglycoside levels, which are commonly measured to guide IV
dosing, when inhaled and IV treatments are used concurrently, particularly dependent
upon the relative timing of dosing of the antibiotics. Although the effect of inhaled
medication on serum concentration is small, this may be a relevant concern in some
patients. The committee felt that the decision to continue an inhaled antibiotic in
conjunction with the same IV antibiotic should be determined on a case-by-case basis. It
is believed that this is a question that should and could be answered in simple
pharmacokinetic studies.
6. **What is the optimal airway clearance therapy during treatment of an exacerbation?** An important aspect of the successful treatment of a pulmonary exacerbation is airway clearance therapy. During acute exacerbations, usual methods of airway clearance may not be as effective because the patient is less capable of performing adequate therapy due to fatigue or pain. An alternative form of therapy may prove more effective. 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. Also, treatment of an exacerbation should be looked upon as an opportune time to educate the patient further about the various methods of airway clearance.

7. **What is the optimal duration of antibiotic therapy?** The committee feels that this is an important question that should be answered. Recent studies of antibiotic duration for other respiratory infections have all led to recommendations for shorter durations of therapy. This may reduce toxicity and cost, and could be associated with reduced selection of resistant pathogens, as has been demonstrated in patients with community acquired pneumonia (84). Studies of duration of IV antibiotic therapy have been carried out for the treatment of ventilator-associated pneumonia (comparing 8 to 15 days of antibiotic treatment) (98) 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.
CONCLUSIONS

The CF Foundation Pulmonary Therapies Committee reviewed the evidence supporting the therapies used for the treatment of acute pulmonary exacerbations in CF airways disease. The committee has developed recommendations based on the quality of the published evidence and the estimate of the net benefit demonstrated within those publications. In addition, the committee has identified important questions for which high quality data are lacking 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.
ACKNOWLEDGMENTS

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*Pseudomonas aeruginosa* isolates and clinical response to parenteral antibiotic administration:

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Appendix: Search Strategies

*PubMed*


*CENTRAL*

#1 (cystic fibrosis):ti,ab

#2 MeSH descriptor Cystic Fibrosis explode all trees

#3 (#1 OR #2)

#4 (acute exacerbation*):ti,ab

#5 (pulmonary exacerbation*):ti,ab

#6 (respiratory exacerbation*):ti,ab

#7 (infecti* exacerbation*):ti,ab

#8 (intravenous antibiotics):ti,ab

#9 (vascular access):ti,ab

#10 (#4 OR #5 OR #6 OR #7 OR #8 OR #9)

#11 (review):pt

#12 (#3 AND #10 AND NOT #11)

*EMBASE*

#1 'cystic fibrosis':ti,ab OR 'cystic fibrosis':de

#2 'acute exacerbation$':ti,ab OR 'pulmonary exacerbation$':ti,ab OR 'respiratory
exacerbation$:ti,ab OR 'infective exacerbation$:ti,ab OR 'infectious exacerbation$:ti,ab
OR 'intravenous antibiotics$:ti,ab OR 'vascular access$:ti,ab

#3 #1 AND #2

#4 [english]/lim

#5 #3 AND #4

#6 review:it

#7 #5 NOT #6
Figure Legends

Figure E1. Summary of search and review process. MEDLINE was accessed via PubMed. EMBASE 5 Excerpta Medica database; CENTRAL 5 Cochrane Central Register of Controlled Trials.

Figure E2. Data from the CF Foundation Patient Registry, 2003-2006. The figure shows the median center-specific treatment duration in days (hospitalization and home intravenous therapy) for pulmonary exacerbations in CF patients less than 18 years of age by CF center. The US national median length of treatment (final bar) for a pulmonary exacerbation in children is 14.5 days (range: 6.5 to 22 days).

Figure E3. Data from the CF Foundation Patient Registry, 2003-2006. The figure shows the median center specific treatment duration in days (hospitalization and home intravenous therapy) for pulmonary exacerbations in CF patients greater than or equal to 18 years of age by CF center. The US national median length of treatment (final bar) for a pulmonary exacerbation in adults is 16.0 days (range: 9 to 27 days).

Figure E4. Duration of intravenous antibiotic therapy used in patients with CF, presumably for treatment of an acute pulmonary exacerbation. Data are derived from the CF Foundation Patient Registry during the year 2007. Note that primary peak frequency occurs around 15 days with a second peak at 23 days, but there is substantial spread.
Figure E5. Duration of intravenous antibiotic therapy used in patients with CF, presumably for treatment of an acute pulmonary exacerbation. Data are derived from the CF Foundation Patient Registry during the year 2007. Data are divided into 4 groups based on percent predicted FEV$_1$ achieved (<40%, 40-69%, 70-90%, and >90%), as a measure of severity of lung disease. Note that primary peak frequency occurs in all groups around 15 days with a second peak at 23 days, but there is substantial spread.
**Table E1. 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 moderate to substantial.</td>
<td>Offer/provide this service.</td>
</tr>
<tr>
<td>C</td>
<td>The committee recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is moderate or high certainty that the net benefit is small.</td>
<td>Offer/provide this service only if other considerations support offering or providing the service in 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 harms outweigh 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 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>Read clinical considerations section of the recommendations. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.</td>
</tr>
</tbody>
</table>

*Table adapted from a published U.S. Preventive Services Task Force Recommendation Statement (8)*
### Table E2. Evaluation of the Evidence

<table>
<thead>
<tr>
<th>Question</th>
<th>Studies</th>
<th>N</th>
<th>Certainty</th>
<th>Magnitude of Benefit</th>
<th>Grade of Recommendation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of Treatment*</td>
<td>1 RCT(^{(10)})</td>
<td>17</td>
<td>Low</td>
<td></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>
<td>Continue current practices</td>
</tr>
<tr>
<td>Simultaneous use of inhaled and IV antibiotics</td>
<td>0 0</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence to recommend for or against simultaneous use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Airway clearance therapies</td>
<td>**</td>
<td>**</td>
<td>Moderate</td>
<td>Moderate</td>
<td>B</td>
<td>Continue current practices</td>
</tr>
<tr>
<td>Number of antibiotics to treat <em>Pseudomonas</em></td>
<td>17 RCT(^{(17-24, 26-28, 30-35)}) 1 RXO(^{(29)}) 1 QRT(^{(25)})</td>
<td>768</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence that single antibiotic is equivalent to combination antibiotics</td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside dosing*</td>
<td>4 RCT(^{(21, 36-38)}) 1 RXO(^{(39)})</td>
<td>349</td>
<td>Moderate</td>
<td>Small</td>
<td>C</td>
<td>Once daily dosing is acceptable for treatment of <em>Pseudomonas</em></td>
</tr>
<tr>
<td>Continuous infusion beta-lactam antibiotics</td>
<td>1 XO(^{(40)})</td>
<td>5</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence to recommend continuous infusion</td>
<td></td>
</tr>
<tr>
<td>Duration of antibiotics*</td>
<td>0 0</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence to define optimal duration of antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synergy testing (routine)</td>
<td>1 RCT(^{(41)})</td>
<td>132</td>
<td>Low</td>
<td>Zero</td>
<td>D</td>
<td>Routine use not recommended</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>2 RCT(^{(42-43)})</td>
<td>44</td>
<td>Low</td>
<td>I</td>
<td>Insufficient evidence to recommend use of corticosteroids</td>
<td></td>
</tr>
</tbody>
</table>

*Cochrane Review

**Previous recommendations (60, 61)

N = number of patients evaluated
RCT = randomized controlled trial
RXO = randomized crossover trial
QRT = quasi-randomized trial
XO = crossover trial
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Initial dose (mg/kg/d)</th>
<th>Predicted Peak (µg/ml)</th>
<th>Predicted Trough (µg/ml)</th>
<th>Predicted Time Below Level of Detection (hrs)</th>
<th>Predicted Peak (µg/ml)</th>
<th>Predicted Trough (µg/ml)</th>
<th>Predicted Time Below Level of Detection (hrs)</th>
<th>Predicted Peak (µg/ml)</th>
<th>Predicted Trough (µg/ml)</th>
<th>Predicted Time Below Level of Detection (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>10</td>
<td>25-35</td>
<td>&lt;0.5</td>
<td>9-11</td>
<td>10-16</td>
<td>&lt;0.5</td>
<td>3-4</td>
<td>7-10</td>
<td>&lt;0.5</td>
<td>1-2</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>10</td>
<td>25-35</td>
<td>&lt;0.5</td>
<td>9-11</td>
<td>10-16</td>
<td>&lt;0.5</td>
<td>3-4</td>
<td>7-10</td>
<td>&lt;0.5</td>
<td>1-2</td>
</tr>
<tr>
<td>Amikacin</td>
<td>30</td>
<td>30-45</td>
<td>&lt;5</td>
<td>9-11</td>
<td>15-20</td>
<td>&lt;5</td>
<td>3-4</td>
<td>10-13</td>
<td>&lt;5</td>
<td>1-2</td>
</tr>
</tbody>
</table>

These values are based upon population pharmacokinetics assuming a volume of distribution of 0.25 L/kg and a half life of 2.5 hours. Standard assays for drug concentrations have a lower level of detection of 0.5 µg/ml (96).
Figure E1. Summary of Search and Review Process

Electronic Databases
MEDLINE® – 558
EMBASE – 238
CENTRAL – 186

Hand Searching - 121

Retrieved 982

Duplicates – 317

Abstract Review 786

Excluded – 605

Full-Text Screen 181

Excluded – 153
Not in English - 4
Meeting abstract only - 5
Does not include/ address CF- 2
No original data- 12
Does not address treatment of acute exacerbation- 11
Does not address any review questions- 20
Does not address any outcomes of interest- 9
Other- 64
Not an RCT or cross-over study- 13
Addressed questions not included in the review-11
Unable to retrieve- 2

Eligible Articles 28
Figure E2. Center-specific Median Duration of Treatment of Pediatric Patients with Acute Exacerbations
Figure E3. Center-specific Median Duration of Treatment of Adult Patients with Acute Exacerbations
Figure E4. Duration of Intravenous Antibiotic Treatment by Age Group
Figure E5. Duration of Intravenous Antibiotic Treatment by Severity of Disease