Current opinion in pulmonary medicine – Treatment of pulmonary exacerbations in cystic fibrosis

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Structured abstract

Purpose of review:

This review will discuss the challenges of defining a pulmonary exacerbations in cystic fibrosis (CF) and the key pathogens which contribute. It will discuss the treatment options currently available and the importance of preventing pulmonary exacerbations.

Recent findings:

The basis for treatment of pulmonary exacerbations remains unchanged over the past 15 years and whilst there have been trials exploring alternative antibiotics, there has been little change. However, there are ongoing studies that are expected to establish a platform for identifying best practices. Chronic CF therapies have been shown to reduce pulmonary exacerbations. In the era of new CFTR (CF transmembrane conductance regulator) modulator therapies, the number of pulmonary exacerbations are expected to be even fewer. However, it is unclear whether the other chronic therapies can be discontinued without losing their benefits in reducing exacerbations.

Summary:

Although there is no universal definition of a pulmonary exacerbation in CF, proposed definitions have many similarities. We have outlined the current recommendations for treatment of pulmonary exacerbations, including the duration and location of treatments. We have also summarised the key therapies used for prevention of pulmonary exacerbations in CF.

Keywords:

Cystic fibrosis; pulmonary exacerbations; treatment

1 Introduction

Pulmonary exacerbations are common events and contribute to progression of airways disease and considerable morbidity in patients with cystic fibrosis (CF).[1] Many events lead to treatment with intravenous antibiotics, which are costly and associated with a reduced quality of life. This review will focus on the prevention of pulmonary exacerbations in CF and current recommendations for their management.

2 Defining a pulmonary exacerbation

The CF Foundation defines a pulmonary exacerbation as an "acute worsening of respiratory symptoms" requiring medical treatment.[2] Extra-pulmonary symptoms, such as weight loss, are commonly seen and there are important differences in presentation between adults and children with CF. Although there is a lack of universal agreement on a pulmonary exacerbation definition, there is a broad consensus on the type of respiratory signs and symptoms to be included (Table 1); none of the definitions have been validated as an instrument for use in clinical research studies. A standardized definition is desirable as it could allow for better comparison of trials and could be used in the study of therapies intended to reduce exacerbation frequency.[3] However, these scoring methods assume that all clinicians would come to the same conclusion and ignore the clinician's historical experience with an individual patient, differences that occur with age, and psychosocial factors that may influence the decision to treat. Treatment trials typically take a pragmatic approach by not questioning the clinician's diagnosis.

Table 1. Summary table of the proposed definitions of a pulmonary exacerbation in CF

Criterion	**Reference**					
	Fuchs 1994 [4]	Rosenfeld 2001[5]	Treggiari 2009[6]	Kraynack 2011[7]	Bilton 2011[8]	Regelmann 2013[9]
Change in sputum	✓	✓	✓ (minor)		✓	✓
Haemoptysis	✓		✓ (major)			
Increased cough	✓	✓	✓ (minor)		✓	✓
Increased dyspnoea or work of breathing	✓		✓ (minor)		✓	
Increased malaise	✓				✓	
Temperature over 38°C	✓					
Decreased appetite or weight loss	✓	✓	✓ (minor)		✓	✓
Sinus pain	✓					
Change in sinus discharge	✓					

Change in chest examination	✓	✓	✓ (minor)			✓
Reduced pulmonary function by 10% or more	✓		✓ (major)		✓	
Low oxygen saturation			✓(major)			
Radiographic changes	✓		✓(major)		✓	
Decreased exercise tolerance		✓	✓ (minor)			
School or work absenteeism		✓				
Diagnosis of pulmonary exacerbation	New antibiotics AND 4/12 signs/symptoms	Score >2.6 based on a scoring system and the selected criterion	At least 1 major criteria OR 2 minor criteria with ≥5 day duration / significant symptom severity	Treatment with oral or intravenous antibiotics	Antibiotics AND 2 of the selected criterion	All the selected criterion

4 Management

The primary aims of pulmonary exacerbation treatment reported by patients and clinicians are to relieve symptoms and recover loss of lung function, respectively.[10]

4.1 Antibiotics

4.1.1 Anti-bacterials

A key feature of CF airways disease is persistent infection and exaggerated inflammation. Given the symptoms typically associated with exacerbations (i.e. cough and sputum production), infection is often invoked as a likely cause or contributor to the condition, and antibiotics are recommended as part of the disease management. Many bacterial species have been identified as potential contributors, including *Staphylococcus aureus, Hemophilus influenzae, Pseudomonas aeruginosa, and Burkholderia complex*.[11] *S. aureus* is the most commonly isolated pathogen in CF, with the highest prevalence in children; *P. aeruginosa* is more prevalent in older children and adults.[1]

Antibiotics are frequently used to treat a pulmonary exacerbation and sputum microbiology is typically used to guide antibiotic selection.[2] Since information from a sputum culture collected at the time of intervention will not be available for several days, clinicians often use prior sputum culture data and previous experience with the patient to guide initial antibiotic selection.[12] While some pathogens (e.g. *S. aureus*) are often treated with a single antibiotic, others (e.g. *P. aeruginosa*

or *B. cepacia*) are more often treated with a combination of antibiotics. This practice may be driven by concerns for antimicrobial resistance, but there is a disconnect between antibiotic susceptibility test results and clinical outcomes.[13] Efforts to overcome this discordance have included use of antibiotics selected by synergy testing [14] and microbiome analysis to enhance individualised antibiotic therapy [15] but these have not been successful..

Since the information provided by sputum culture and susceptibility testing are limited in their value, at least for predicting outcomes for CF pulmonary exacerbations, consensus recommendations have been provided.[12] Anti-bacterials should be selected based on bacterial species isolated in previous respiratory cultures and on previous treatment outcomes. Changes to the antibiotics are more often guided by clinical response than by susceptibility test results.

4.1.2 Anti-virals

Viruses are often identified in respiratory samples collected at the time of a pulmonary exacerbation, and so viruses are often implicated as a potential cause of the event. The most commonly identified viral pathogen is human rhinovirus but others include respiratory syncytial virus (RSV), Influenza types A and B, and parainfluenza.[10, 11] RSV may promote growth of *P. aeruginosa* biofilms through modulation of the immune response and pathogen iron metabolism while rhinovirus has been shown to promote the free movement of P. aeruginosa from biofilms. [12, 13] All people with CF are advised to receive the annual *Influenza* vaccine to reduce their risk of a pulmonary exacerbation during the flu season. For those patients who have an influenza infection, treatment with neuraminidase inhibitors are frequently used, although there are no substantive clinical trials to support this treatment.[16] There are no other specific antiviral therapies beyond supportive care. Preliminary data suggest that very few CF patients have had a severe respiratory illness during the recent COVID-19 pandemic.[17]

4.1.3 Anti-fungals

The role for fungi in the pathogenesis of CF airways disease has long been debated and there are no current recommendations to treat fungi isolated in respiratory cultures. However, there is a greater incidence of allergic bronchopulmonary aspergillosis (ABPA) and pulmonary exacerbations in patients with CF may be due wholly, or in part, to ABPA. There are no randomised controlled trials evaluating the treatment of ABPA in CF, but a combination of systemic corticosteroids and antifungal treatment is recommended in treatment guidelines.[18]

4.2 Duration of treatment

Optimal duration of intravenous antibiotic therapy is still not established and practices vary according to the care site.[1] Durations vary from 4-21 days in paediatric programs to 4-23.5 days in adult programs.[1] An observational study of patients admitted to the hospital for treatment of pulmonary exacerbations showed a mean duration of intravenous antibiotics were 15.9 days. [3] A retrospective study showed improvement in lung function plateaus after 8-10 days of intravenous therapy suggesting that shorter durations of antibiotics might be adequate to treat a pulmonary exacerbation and the time to next exacerbation was unchanged with this shorter antibiotic course.[19]

There is great importance to determining an optimal duration of antibiotic treatment. Too short a course could result in inadequate treatment leading to recurrence of the exacerbation; indeed intravenous antibiotic courses <9 days have been associated with a greater risk of retreatment within the next 30 days.[20] An antibiotic course longer than is necessary is associated with greater

cost and could be associated with a greater risk of complications. The ongoing Standardized Treatment of Pulmonary Exacerbations 2 (STOP2) study is evaluating courses of 10, 14, and 21 days of treatment based on initial clinical response and should provide some insight when completed.[10]

4.3 Location of treatment

Reports comparing site of therapy, inpatient vs home intravenous therapy, are mainly observational and retrospective. The one randomized trial found no difference in outcomes.[21] More recently, analysis of the Epidemiologic Study of Cystic Fibrosis dataset looked at 4500 exacerbations and found that inpatient treatment with IV antibiotics was more likely to result in recovery of lung function than at-home treatment.[22] Another single centre study of 54 CF patients showed in-hospital treatment to be superior to home treatment, as indicated by better improvement of FEV_1 in patients with CF-related complications and weight gain.[23] Conversely, a large (>1500 patients) retrospective study comparing inpatient vs at home intravenous antibiotics showed no difference in long term FEV_1 recovery and time to next exacerbation.[19] Consequently, there are conflicting data as to the ideal site of treatment. Obviously the assumption must be that the potential for care would be similar, but it would be impossible to do a properly conducted study. There are important biases in any such study that would be difficult to overcome (e.g. clinician equipoise, subject willingness to be randomized]. The guidelines on pulmonary exacerbations recommend that the decision should be based on the ability to provide sufficient care as the patient's clinical status should dictate the needs (and therefore may dictate the location) of treatment.

5 Recovery and sequelae

Pulmonary exacerbations are associated with loss of lung function (FEV_1), decreased survival, and worsened quality of life.[3] A cohort study using the CF registry showed that up to 25% of patients failed to recover baseline FEV_1.[24] A challenge in such analyses is knowledge of what can be defined as baseline. In a study using registry data to define baseline (i.e. best lung function in previous 6 months) the best lung function was at the time of admission in nearly 25% of patients.[3] Nonetheless, a more rigorous analysis of the impact of exacerbations on lung function, using a baseline defined as the previous lung function measured as part of a clinical trial, found that patients returned to baseline lung function only half the time, and this was not improved with a CFTR modulator.[25] Multiple factors may contribute to the lack of complete recovery from a pulmonary exacerbation, including: aetiology, host response, and treatment. The eICE trial was designed to assess whether earlier identification of events could improve outcomes. Whilst it showed that home monitoring of lung function led to identifying more patients with pulmonary exacerbations, the trial did not demonstrate a difference in FEV_1 after one year of monitoring.[26] However, it could be hypothesized that failure to treat with best practices would not be expected to realize such an improvement; the exacerbations identified in the home monitoring arm were more likely to receive oral antibiotics and less likely to be treated with hospitalisation.

6 Prevention

Given the low rate of recovery of lost lung function, then prevention of pulmonary exacerbations becomes a much more important strategy. There are some therapies that have demonstrated clear benefit while some still lack good evidence.

Airway Clearance Therapies

Airway clearance therapies are considered the most basic and essential of CF treatments. Augmentation of airway clearance using agents such as dornase alfa, hypertonic saline, and mannitol have shown benefits in CF patient by improving mucous clearance.[27] A recent Cochrane systematic

review of dornase alfa for CF confirmed its role in improving lung function and decreasing exacerbations. [28] Hypertonic saline (HS) is an osmotic agent that is routinely used and a Cochrane systematic review confirmed that use HS reduced frequency of exacerbation but with a limited effect on lung function. [29] Guidelines from US, Europe and UK all suggest using dornase alfa as 1st choice mucoactive agent for older CF patients. They suggest using dornase alfa and HS in children under 5 years on an individual basis but more robust data are required. More recently, mannitol (an osmotic agent like HS) has been shown to significantly improve FEV_1 and reduce pulmonary exacerbations.[30] This effect was initially thought to be applicable for adults only but a subsequent study in children between 6-17 years showed similar results.[31] Both HS and mannitol are irritants and require pre-treatment with bronchodilator. Direct head to head trials between dornase alfa and the other hyperosmolar agents are not sufficiently robust to conclude one's superiority over the other.

Prophylactic antibiotics

Macrolide antibiotics like azithromycin have been beneficial to CF patients likely due to their dual effect on infection and inflammation. The recent Optimize trial confirmed previous reviews that patients treated with azithromycin were less likely to have pulmonary exacerbations.[32, 33] Recently, a retrospective cohort study using the CFF patient registry reported a reduction in the average rate of annual decline of FEV_1 (over 3 years) in patients with *P. aeruginosa* and receiving azithromycin.[34]

Inhaled antibiotics have proven benefits in CF patients by reducing pulmonary exacerbations and improving lung function. [35] While intermittent therapy (28 day on/off) is the labelled regimen, continuous daily therapy is increasingly recommended.[18] A study of continuous alternating inhaled antibiotic therapy (CAT) for chronic *P. aeruginosa* infection was halted early because of feasibility challenges, leaving the study underpowered; however, the CAT regimen seemed to reduce exacerbation rates (by 25%).[36] This approach has become increasingly popular—especially among patients with greater impairment in lung function or greater frequency of acute pulmonary exacerbations.[1]

Inhaled glucocorticoids and bronchodilators

Both inhaled glucocorticoids and bronchodilators (beta-2 agonists and muscarinic antagonist) are used with great frequency as maintenance therapy in CF patients.[1] Recent Cochrane reviews for both have shown no significant improvement in lung function and the time until the first exacerbation with these interventions.[37, 38]

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators

CFTR modulators treat the underlying cause of the disease and have improved clinical outcomes in patients with CF. A consistent finding among the various CFTR modulator combinations have demonstrated a consistent finding of reduction in pulmonary exacerbations of between 30% and 63%.[39, 40] [41] Since the impact appears to be greater with the more potent CFTR modulator combinations, it is expected that patients treated with them will see a marked improvement in their overall health. However, it is likely that conventional preventative and treatment strategies for pulmonary exacerbations will still be needed in the era of CFTR modulators. Trials previously evaluating CFTR modulators included chronic therapies and therefore it is unknown whether CFTR modulators alone will reduce the number of pulmonary exacerbations. Newer trials such as SIMPLIFY, which review stopping some chronic medications, are important research areas.[42]

7 Conclusion

Acute pulmonary exacerbations in CF are common events and a main cause of morbidity and mortality in CF. Although we lack a specific clinical definition for an exacerbation, there are common features that have been used in practice. These events are often associated with acute loss of lung function that does not fully recover, and so there is great need to use therapies to prevent exacerbations and to determine best practices for treatment of them.

There are guidelines based upon sound evidence for a number of therapies to reduce the frequency of pulmonary exacerbations. A systematic review performed to develop guidance on treatments of exacerbations found a paucity of evidence, but there are ongoing studies that should provide greater evidence for best practices.[43]

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This important clinical trial aimed to describe the clinical presentations of patients admitted for intravenous antibiotics and understand the treatment goals of physicians. It showed that nearly half of patients admitted to hospital already received oral or inhaled antibiotics and had a decline in their FEV1 in the preceding 12 months. The primary objectives of physicians were lung function recovery and symptom resolution.

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This is a well-designed observational study with aims to evaluate antibiotic treatment durations for pulmonary exacerbations. The results are yet to be published.

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This is an important trial which investigates inadequate pulmonary exacerbation treatments. It showed that 5.7% of patients had intravenous antibiotic treatment failure and therefore required retreatment. Those who had initially received <9 days or ≥23 days were shown to have a significantly increased risk (1 to 4 days: $p<0.001$; 5 to 8 days: $p=0.002$, ≥23 days: $p=0.005$) of needing retreatment.

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This is an important study that could influence the location of pulmonary exacerbation treatments. It showed that across 75 sites, there was a significant positive response in return of FEV1 for inpatient treatments compared to at-home treatments. However, this could also be a result of different patient populations and disease progression in the 2 groups.

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This is an important study evaluating the use of azithromycin in children with CF and early P. aeruginosa infection. It showed that the use of azithromycin 3 times a week can reduce the risk of a pulmonary exacerbation by 44% (hazard ratio 0.56, confidence interval 0.37-0.83, p=0.004).

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