

Pulmonary exacerbation: Towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials

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Abstract

Pulmonary exacerbations represent a key outcome variable in clinical trials of cystic fibrosis (CF). As there is variation in the trigger for use of intravenous antibiotics compared to the use of oral antibiotics or new nebulised therapy for treatment of exacerbations, the consensus view is that use of intravenous antibiotics cannot be regarded as the key defining character for an exacerbation on its own. The consensus view is that the clinical need for additional treatment as indicated by a recent change in clinical parameters provides the best definition of an exacerbation. Which parameters to include as well as the problems associated with the use of scoring systems and symptom clusters are being discussed.

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1. Introduction

Pulmonary exacerbations are a key outcome measure in clinical trials because:

- i Pulmonary exacerbations exhibit a strong contribution in a well validated survivorship model. Each acute pulmonary exacerbation had a negative impact on 5 year survival equal to subtracting 12% of FEV₁ [1]
- ii Pulmonary exacerbations have been shown to have a profound negative impact on health related quality of life [2]
- iii Pulmonary exacerbations have been a key secondary endpoint in landmark studies of new therapies for cystic

fibrosis (CF), including RhDNase [3], Tobramycin (TOBI) [4], Azithromycin [5] and hypertonic saline [6]

- iv There are significant costs associated with the requirement for intravenous antibiotic therapy at home or in hospital
- v As a result of i–iv above, reduction in pulmonary exacerbations can be considered an important endpoint independent of change in lung function.

There is consensus that pulmonary exacerbations represent a key outcome variable in clinical trials of CF.

2. Definition of pulmonary exacerbation

2.1. Physician defined requirement to treat

The simplest definition of pulmonary exacerbation is a physician defined requirement to intervene with new antibiotic therapy, either oral or intravenous. This definition is open to

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variability depending on clinician preference and threshold for treatment. However, this simple definition was used effectively in the Azithromycin study [5] when exacerbations were defined as the use of intravenous anti-*Pseudomonas* antibiotics or oral quinolones for seven or more days. In the TOBI trial [4], use of intravenous antibiotics and hospitalisation were used to characterise exacerbations and revealed significant benefit in favour of the active treatment.

This definition is not recommended as a EuroCareCF consensus as there may be variation in the prescription of intravenous antibiotics and access to inpatient treatment in different countries.

As there is variation in the trigger for use of intravenous antibiotics compared to the use of oral antibiotics or new nebulised therapy for treatment of exacerbations, the consensus view is that use of intravenous antibiotics cannot be regarded as the key defining character for an exacerbation on its own.

2.2. Symptom defined requirement to treat

Exacerbations can be usefully defined by a cluster of symptoms and signs as defined by Fuchs et al. [3].

Clinical need for intravenous antibiotics as indicated by presence of at least 4 of 12 possible signs or symptoms:

- Change in sputum volume or colour
- New or increased haemoptysis
- Increased cough
- Increased dyspnoea
- Increased malaise, fatigue or lethargy
- Temperature over 38°C
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical findings on examination of the chest
- Decrease in pulmonary function by 10% or more
- Radiographic changes

This definition has proven useful in the landmark DNase study [3] and the large trial of hypertonic saline [6].

The criteria of Fuchs et al. [3] i.e.: symptom defined (4 out of 12) can be applied regardless of treatment. It is clear from the hypertonic saline study that there is a significant difference in exacerbations defined as per the original criteria of Fuchs et al. [3] and an analysis involving symptoms identified by Fuchs et al. [3] (hereafter termed Fuchs symptoms) regardless of treatment.

The Fuchs symptoms defined exacerbation with or without requirement for treatment have shown utility in clinical trials for both children and adults with CF. We recommend that this definition is adopted for future clinical trials in Europe.

The consensus view is that the clinical need for additional treatment as indicated by a recent change in clinical parameters provides the best definition of an exacerbation. The clinical parameters used should be those of the criteria of Fuchs et al. [3].

The European Consensus Group wishes to validate modified criteria of Fuchs et al. [3] as follows:

An exacerbation will be defined as the need for additional antibiotic treatment as indicated by a recent change in at least two of the following:

- Change in sputum volume or colour
- Increased cough
- Increased malaise, fatigue or lethargy
- Anorexia or weight loss
- Decrease in pulmonary function by 10% or more / Radiographic changes
- Increased dyspnoea

2.3. Scoring system to define exacerbation

Several studies have addressed the possibility of standardising a symptom defined exacerbation score. However, these are subject to the difficulty of deciding on the gold standard for validation. If the gold standard is the physician's opinion then variability is likely to be introduced. An Australian survey highlighted this problem [7]. Rosenfeld et al. [8] developed two scores which were validated in the intervention arm of the TOBI trial. One score included lung function as a variable. The second had no requirement for lung function. The utility of this is obvious in terms of pan-European studies and the algorithm produces a score where the critical value of 2.6 or above represents a physician defined exacerbation. The problem with this score is that it does not necessarily correlate with a new treatment or intervention.

2.4. Symptom cluster that defines need for treatment

Rabin et al. [9] examined patient registry data in order to predict the factors that were associated with new treatment. The scoring system developed by Rabin et al. [9] defines separate criteria for different age groups and in particular includes a definition of exacerbations for under 6 year olds. The scoring system of Rabin et al. [9] appears easy to apply in clinical studies, but does not have a track record in clinical trials.

The consensus view is that the scoring system of Rosenfeld et al. [8] should not be used for European studies as the defining score does not always correlate with a change in treatment. The scoring system developed by Rabin et al. [9] could be used, but because it has no track record in clinical trials we do not recommend it for current use. Future trials could incorporate a validation of the scoring system of Rabin et al. [9] particularly in studies of children under 6 years of age.

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Conflict of interest

None declared.

References

- [1] Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001;153(4):345–52.
- [2] Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest* 2002;121(1):64–72.
- [3] Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994;331(10):637–42.
- [4] Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999;340(1):23–30.
- [5] Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. *JAMA* 2003;290(13):1749–56.
- [6] Elkins MR, Robinson M, Rose BR, et al. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006;354(3):229–40.
- [7] Dakin C, Henry RL, Field P, Morton J. Defining an exacerbation of pulmonary disease in cystic fibrosis. *Pediatr Pulmonol* 2001;31(6):436–42.
- [8] Rosenfeld M, Emerson J, Williams-Warren J, et al. Defining a pulmonary exacerbation in cystic fibrosis. *J Pediatr* 2001; 139(3):359–65.
- [9] Rabin HR, Butler SM, Wohl ME, et al. Pulmonary exacerbations in cystic fibrosis. *Pediatr Pulmonol* 2004; 37(5):400–6.