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Original Article

Pulmonary exacerbations in CF patients with early lung disease

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Abstract

Background: Current definitions of pulmonary exacerbation (PE) in cystic fibrosis are based on studies in participants with significant lung disease and may not reflect the spectrum of findings observed in younger patients with early lung disease.
Methods: We used data from a recent trial assessing the efficacy of azithromycin in children to study signs and symptoms associated with PEs and related changes in lung function and weight.
Results: While increased cough was present in all PEs, acute weight loss and reduction in oxygen saturation were not observed. Changes in lung function did not differ between subjects who did experience a PE and those who were exacerbation-free.
Conclusions: Cough was the predominant symptom in CF patients with early lung disease experiencing a PE. There was no significant difference in mean 6-month change in lung function or weight among subjects with one or more exacerbations and those without an exacerbation.

Keywords: Pulmonary exacerbation; *Pseudomonas aeruginosa*; Chronic; Infection; Cystic fibrosis; Azithromycin; Mild; Lung function; Weight

1. Introduction

Pulmonary exacerbations (PEs) occur commonly in patients with cystic fibrosis (CF) across all age groups and severity of lung disease. PEs in CF usually present with a constellation of symptoms such as cough, shortness of breath, and fever and signs such as weight loss, increased crackles on exam and decline in lung function [1]. PEs are primarily treated with intensification of airway clearance therapies along with oral or intravenous (IV) antibiotics, depending on their severity and the spectrum of pathogens detected in respiratory cultures [2].

PEs in CF patients have been associated with increased health care cost [3], reduced quality of life [4,5], and persistent decline in lung function in approximately 25% of patients [6,7]. PEs also serve as important outcome measures in clinical trials in CF [8,9], but there is currently no standardized definition for pulmonary exacerbations. Practitioners' response to a change in signs and symptoms varies widely among care providers and CF centers [10].

Pulmonary exacerbations in cystic fibrosis have largely been defined in two ways based on: 1. treatment with antibiotics (IV,

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inhaled, or oral) [11,12] and 2. clinical signs and symptoms [13–15]. Studies describing the symptom constellation and impact of PEs have largely examined exacerbations in CF patients requiring treatment with IV antibiotics [6,7,13,16]. Only limited data are available on the nature and impact of PEs in CF patients with mild lung disease not infected with *Pseudomonas aeruginosa* who are likely to be treated with oral antibiotics for a PE. In a recently conducted randomized controlled study of azithromycin in children with CF uninfected with *P. aeruginosa* [17] an operational *a priori* definition for exacerbations was utilized which was also utilized in the EPIC trial [18]. We have utilized this dataset to characterize the spectrum of signs and symptoms of PEs in CF patients with milder lung disease not infected with *P. aeruginosa* and to explore the association between the occurrence of a PE and changes in two key clinical status measures (lung function and weight) in this study population [19].

2. Methods

The details of the 6-month randomized control trial to assess the efficacy of azithromycin in CF children uninfected with *P. aeruginosa* have been published elsewhere [20]. Only details relevant to the aims of these analyses are summarized below:

The study was conducted as a multicenter, randomized, double-blind placebo-controlled trial in 40 CF care centers in the United States and Canada. Eligibility criteria included documented diagnosis of CF, weight ≥18 kg, age 6–18 years, FEV_1 ≥ 50% predicted, and negative respiratory tract cultures for *P. aeruginosa* for at least one year. Exclusion criteria included a positive respiratory tract culture for *P. aeruginosa* in the year prior to screening or at screening; relative decrease in FEV_1 % predicted ≥ 20% between screening and randomization; use of antibiotics or "high dose" systemic steroids within 14 days of screening (defined as ≥1 mg/kg/day if participant's weight <20 kg or ≥20 mg/day if participant's weight ≥20 kg); initiation of dornase alfa, ibuprofen, aerosolized antibiotics or hypertonic saline within 30 days of screening; a positive respiratory culture for *Burkholderia cepacia* complex or non-tuberculous mycobacteria (NTM) within 1 year of screening.

In this study, we used an *a priori* case definition for PEs based on signs and symptoms characterized as major criteria or minor criteria (Table 1) [18] This definition was developed by a working group of CF clinicians and was also used in another clinical trial of infants and children with CF, the Early *Pseudomonas* Infection Control (EPIC) trial [18]. In the current study, we used a shorter duration of symptoms for the minor criteria when compared to the PE definition used in the EPIC trial (3 *versus* 5 days), which the principal investigators felt was more reflective of current antibiotic practice in the patient group being studied.

At the initiation of each new antibiotic, site investigators completed an electronic case report form and indicated the presence or absence of signs and symptoms comprising the PE definition that prompted antibiotic treatment. However, the decision to utilize antibiotics was not dependent on whether or not the protocol definition for PE was met. Study site investigators made treatment decisions for management of PEs including specific antimicrobial agents, the route of administration (IV, oral, and/or inhaled agents) and non-antibiotic therapies (*e.g.*, steroids, mucolytic agents, nutritional supplements).

Table 1
Pulmonary exacerbation definition.
Adapted from Treggiari MM, Rosenfeld M, Mayer-Hamblett N, et al. Early anti-pseudomonal acquisition in young patients with cystic fibrosis: rationale and design of the EPIC clinical trial and observational study. Contemporary clinical trials 2009; 30:256–268.

The presence of a pulmonary exacerbation is established by the following: At least one of the major criteria or two of the minor signs/symptoms and fulfillment of symptom duration.
Major criteria: (One finding alone establishes the presence of a pulmonary exacerbation)
(1) Decrease in FEV_1 of ≥10% from best baseline within past 6 months, unresponsive to albuterol (in participants able to reproducibly perform spirometry)
(2) Oxygen saturation <90% on room air *or* ≥5% decline from previous baseline
(3) New lobar infiltrate(s) or atelectasi(e)s on chest radiograph
(4) Hemoptysis (more than streaks on more than one occasion in past week)
Minor signs/symptoms: (Two minor signs/symptoms are required with duration criteria in the absence of major criteria)
(1) Increased work of breathing or respiratory rate
(2) New or increased adventitial sounds on lung exam
(3) Weight loss ≥5% of body weight or decrease across 1 major percentile in weight percentile for age in past 6 months
(4) Increased cough
(5) Decreased exercise tolerance or level of activity
(6) Increased chest congestion or change in sputum
Signs/symptom duration: (Required with two minor signs/symptoms in absence of major criteria)
(1) Duration of sign/symptoms ≥3 days or significant symptom severity

2.1. Statistical analysis

The proportion of subjects experiencing protocol-defined PEs and the number and proportion of total exacerbations triggered by major and minor symptoms are summarized by treatment group. The frequency of signs and symptoms comprising exacerbations is also summarized. Descriptive summaries are provided to explain the type of antibiotic treatment (IV, oral, or inhaled) received at the time of an exacerbation. More than one type of antibiotic could be prescribed for an individual event; therefore antibiotic treatment categories are not mutually exclusive.

The 6-month mean change from baseline in FEV_1 (liters and % predicted) and weight (kg and percentile) and corresponding 95% confidence intervals were calculated by treatment group among those subjects that experienced at least one PE and those remaining exacerbation-free throughout the study. Associations between the occurrence of a pulmonary exacerbation and six month changes in baseline FEV_1 and weight were tested using a two-sided 0.05 level t-test. Analyses were performed using R statistical package version 2.14.0 (R Foundation for Statistical Computing, Vienna, Austria).