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Original Article

Pulmonary exacerbations and acute declines in lung function in patients with cystic fibrosis☆,☆☆

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Abstract

Background: Patients with cystic fibrosis (CF) who experience acute declines in percent predicted FEV_1 ($ppFEV_1$ decreased ≥10% relative to baseline) are often not treated with antibiotics for pulmonary exacerbations (PEx), whereas other patients are treated even when they have not experienced a decline in lung function.
Methods: We analyzed 2 patient cohorts using 3 years of Epidemiologic Study of CF data. Cohort 1 (12,837 patients) experienced a ≥10% acute decline in $ppFEV_1$ (n = 22,898) and Cohort 2 (10,416 patients) had a clinician-diagnosed PEx (n = 20,731).
Results: 70.7% of ≥10% decline events were treated with antibiotics; with intravenous antibiotics used 67.1% of the time. 32.0% of clinician-diagnosed PEx declined <10%; with intravenous antibiotics used 36.9% of the time.
Conclusions: A clinician's decision to diagnose a PEx and treat with antibiotics often is not defined by measured lung function: a ≥10% FEV_1 decline is not considered an absolute indication of a PEx and the lack of a decline does not contraindicate a PEx. Clinicians appear to use the history of prior PEx plus other variables as factors for diagnosing PEx.

Keywords: Cystic fibrosis; Pulmonary exacerbations; Lung function

1. Introduction

Patients with cystic fibrosis (CF) endure repeated pulmonary exacerbations (PEx) and progressive loss of lung function [1]. However, a standard definition for a PEx has long eluded the medical community [2,3]. Currently the most frequent approach to study PEx is to use a clinician's decision to treat with antibiotics [4]. Thus, the initiation of antibiotics to treat changing respiratory signs or symptoms is used in both epidemiologic and clinical trial analyses of PEx. However, these analyses often differ as to which antibiotics are included and whether they are administered as intravenous (IV), inhaled, or oral. In addition, particularly for clinical trials, the definition often combines this clinical decision with some assessment of clinical criteria, such as specific signs or symptoms [5].

One reason why PEx are considered important is that frequently they involve an acute reduction in lung function, and often this reduction is not recovered following treatment [6–8]. Furthermore, there is an association between PEx and long-term loss of lung function and decreased survival in patients with CF [9–11]. Lung function is not the only criterion used by clinicians to decide when

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to diagnose a PEx [12]. Often clinicians diagnose a PEx when there is little or no acute change in lung function [4]. Conversely, when patients experience a substantial acute decline in lung function they are sometimes not treated for a PEx [13]. This lack of treatment for declines in lung function is despite the fact that treatment, and especially IV treatment, is associated with better recovery [14].

We previously reported an association between acute decline events not being treated with antibiotics and long term loss of lung function [14]. To better understand this association, the objectives of this study were to: (1) analyze factors associated with antibiotic treatment or not for events where patients experienced an acute decline in lung function (≥10% relative decline in percent of predicted forced expiratory volume in 1 s ($ppFEV_1$)), and (2) analyze factors associated with clinician-diagnosed PEx where patients did or did not have a coincident acute decline in lung function.

2. Methods

The Epidemiologic Study of CF is a multicenter, prospective, encounter based, longitudinal study of therapy and the natural history of CF in North America [15]. Informed consent was obtained based on decisions by local human subject review boards. This analysis was approved by the University Hospitals Cleveland Medical Center Institutional Review Board (Cleveland, OH). Data from 2003 to 5 included information specific to the diagnosis and treatment of PEx and for this analysis was used to identify clinical events in patients who either: 1) had a relative acute decline of ≥10% in $ppFEV_1$[calculated using Global Lung Initiative reference values] [16] compared to the best value in the baseline year (defined as 31–365 days prior to the index FEV_1), or 2) were treated with antibiotics (oral, inhaled, or IV) for a PEx (diagnosed by the patient's clinician). Although clinicians were allowed to make their own diagnosis of a PEx, the study instructions included this definition: *"Pulmonary Exacerbation" is defined as a new prescription of antibiotics for treatment of a new increase in respiratory symptoms or clinical worsening of pulmonary status*.

Two separate analyses, involving overlapping but not identical groups of events, were undertaken. *First*, events involving a ≥10% relative decline in $ppFEV_1$ were used to compare antibiotic treated versus not treated [Note that only the treated events would be considered a PEx given the above definition]. Treatment was defined as any new oral, inhaled, or IV antibiotic within 180 days following the $ppFEV_1$ decline. Subsequent $ppFEV_1$ decline events for individual patients were included if they occurred at least 180 days following the previous decline event. *Second*, events defined by the clinician as a PEx were compared based on the size of $ppFEV_1$ decline, which was calculated as the best $ppFEV_1$ in the previous year to the worst $ppFEV_1$–30 to +3 days of the start of antibiotic treatment. We compared PEx events with ≥10% relative $ppFEV_1$ decline to those with <10% relative $ppFEV_1$ decline. Subsequent PEx events for these patients were included if there was at least 30 days after the end of antibiotic treatment before a new PEx was diagnosed. Throughout the study, individual patients could experience multiple clinical events and the analyses were based on events and not patients.

With these two groups of events defined (i.e. FEV_1 decline events with/without treatment and PEx events with/without a coincident FEV_1 decline), logistic regression was used to identify statistically significant predictor variables. Each variable was considered alone (univariate analysis) and as part of a multivariate analysis. In order to make the two analyses comparable, predictors were retained in both multivariate models if statistically significant at the 0.05 level in either analysis.

The candidate variables were: age, sex, race/ethnicity (non-Hispanic white vs. other), genotype (F508del homozygous, F508del heterozygous, other, unknown), Medicaid status (yes vs. no), number of PEx treated with IV antibiotics in the prior year (excluding the 31 days prior to the event), height-for-age (HFA) *z*-score, weight-for-age (WFA) *z*-score, body mass index (BMI) *z*-score, best $ppFEV_1$ in the prior year (categorized <40, 40–<70, 70–<100, and ≥100), clinical symptoms (daily cough, daily sputum production), clinical signs (clubbing, crackles, wheeze), co-morbidities (pancreatic insufficiency as indicated by use of pancreatic enzymes, hemoptysis, sinusitis, diabetes as indicated by the use of insulin), and microbiology (aspergillus, atypical mycobacteria, *Burkholderia cepacia*, *Haemophilus influenza, Pseudomonas aeruginosa, Staphylococcus aureus, Stenotrophomonas maltophilia,* or no culture recorded).

SAS version 9.4 (SAS Institute, Cary NC) was used for all statistical calculations. To account for multiple events for the same patient, the logistic regression was evaluated using generalized estimating equations methods using the GENMOD procedure in SAS.

3. Results

Univariate results are shown in Tables 1 and 2. These results were used to develop the multivariate model used for both analyses and included: age, sex, race/ethnicity, genotype, Medicaid status, number of PEx treated in the prior year, BMI, best $ppFEV_1$, daily cough, daily sputum production, clubbing, crackles, wheeze, hemoptysis, sinusitis, atypical mycobacteria, *Burkholderia cepacia*, *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Stenotrophomonas maltophilia* (Fig. 1A and B).

3.1. Events with ≥10% $ppFEV_1$ decline and were treated vs. not treated (Table 1 and Fig. 1A)

During the 3 years of data collection there were 22,898 events recorded involving a ≥10% relative $ppFEV_1$ decline. Of these events, 16,183 (70.7%) across 8108 patients were treated and 6715 (29.3%) across 4729 patients were not treated with antibiotics. Only oral antibiotics were used 21.0% of the time, inhaled antibiotics (with or without oral antibiotics) 11.9% of the time, and IV antibiotics (with or without oral or inhaled antibiotics) 67.1% of the time. Antibiotics were started a median 2 days (interquartile range −6 to +23 days) following the ≥10% $ppFEV_1$ decline.

Univariate, but not multivariate, analysis showed that not having a culture recorded reduced the chance of treatment (Table 1). Treatment was significantly associated with older age, pancreatic insufficiency, poor nutrition (lower HFA, WFA,

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