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Original Article

Standardized Treatment of Pulmonary Exacerbations (STOP) study: Physician treatment practices and outcomes for individuals with cystic fibrosis with pulmonary Exacerbations

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Abstract

Background: Pulmonary Exacerbations (PEx) are associated with increased morbidity and mortality in individuals with CF. PEx management practices vary widely, and optimization through interventional trials could potentially improve outcomes. The object of this analysis was to evaluate current physician treatment practices and patient outcomes for PEx.
Methods: The Standardized Treatment of Pulmonary Exacerbations (STOP) observational study enrolled 220 participants ≥12 years old admitted to the hospital for PEx at 11 U.S. CF centers. Spirometry and daily symptom scores were collected during the study. Physicians were surveyed on treatment goals and their management practices were observed. Treatment outcomes were compared to stated goals.
Results: The mean (SD) duration of IV antibiotic treatment was 15.9 (6.0) days. Those individuals with more severe lung disease (<50% FEV_1) were treated nearly two days longer than those with >50% FEV_1. Physician-reported FEV_1 improvement goals were 10% (95% CI: 5%, 14%) lower for patients with 6-month baseline FEV_1 ≤50% predicted compared with those with 6-month baseline FEV_1 >50% predicted. There were clinically and statistically significant improvements in symptoms from the start of IV antibiotic treatment to the end of IV antibiotic treatment and 28 days after the start of treatment. The mean absolute increase in FEV_1 from admission was 9% predicted at end of IV antibiotic treatment, and 7% predicted at day 28. Only 39% fully recovered lost lung function, and only 65% recovered at least 90% of lost lung function. Treatment was deemed successful by 84% of clinicians, although 6-month baseline FEV_1 was only recovered in 39% of PEx.

Abbreviations: CF, cystic fibrosis; CFFPR, Cystic Fibrosis Foundation Patient Registry; CFRSD-CRISS, Cystic Fibrosis Respiratory Symptom Diary-Chronic Respiratory Infection Symptom Score Questionnaire; CI, confidence interval; FEV_1, forced expiratory volume at 1 second; IV, intravenous; LOCF, last observation carried forward; MCID, minimal clinically important difference; Pa, *Pseudomonas aeruginosa*; PEx, pulmonary exacerbation; SD, standard deviation; STOP, Standardized Treatment of Pulmonary Exacerbations

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Conclusions: In this prospective observational study of PEx, treatment regimens and durations showed substantial variation. A significant proportion of patients did not reach physician's treatment goals, yet treatment was deemed successful.

Keywords: Cystic fibrosis; Pulmonary Exacerbations; Physician treatment practices; Antibiotic therapy

1. Introduction

Pulmonary Exacerbations (PEx) occur frequently in individuals with cystic fibrosis (CF), and are associated with loss of lung function (forced expiratory volume over one second [FEV_1]), decreased survival, and worsened quality of life [1–9]. A systematic review of PEx found insufficient evidence upon which to base recommendations on duration of antibiotic therapy, number of antibiotics to use, use of systemic corticosteroids, and site of treatment (home versus hospital) [10–12]. The current practices for treatment of PEx vary widely for key treatment decisions such as these [9,10,13–16]. In the US, the median duration of treatment with intravenous (IV) antibiotics for a PEx is 13.1 days for individuals <18 years old and 14.0 days for those >18 years old [11]. However, there is a wide variation, with the median duration at individual centers varying from 4.0 to 21.0 days across pediatric programs, and 4.0–23.5 days across adult programs [11]. An acute or sub-acute drop in lung function is a typical feature of a PEx and a significant proportion of patients do not fully recover lost lung function following treatment [1,9,17–19]. A delayed or suboptimal treatment is one possible explanation for the lack of complete recovery. The wide variance in the current treatment practices presents an opportunity to determine which practices are most efficacious.

The Standardized Treatment of Pulmonary Exacerbations (STOP) in patients with cystic fibrosis study (clinicaltrials.gov: NCT02109822) was performed with the purpose of identifying clinical endpoints that could be used in future investigation of treatments for PEx. The objective of this analysis was to describe the treatment practices for patients with CF admitted to the hospital for a PEx, and the outcomes associated with this treatment. In addition, we identified the a priori goals of the admitting clinician [20] and compared outcomes at the end of treatment according to the initial physician treatment goals in order to identify optimal treatment regimens.

2. Methods

STOP was an observational cohort study that enrolled 220 participants with CF from 11 centers that were admitted to the hospital for treatment of PEx from January 2014 to January 2015. A complete description of the study methods are described elsewhere [20]. Patients were ≥12 years of age and currently hospitalized for treatment of a PEx with IV antibiotics. Complete inclusion/exclusion criteria and physician surveys are listed in the online supplement. Duration and choice of IV antibiotics were determined by the treating physician and observed. A survey was performed on day 1 that captured whether the treating physician's primary goal was to recover lung function or to improve symptoms, and a target FEV_1 that would constitute a treatment success was recorded. Spirometry was assessed at admission, day 7, end of IV treatment, and at 28 days after the start of IV treatment. FEV_1% predicted was calculated using Global Lung Initiative equations [21]. Symptoms were assessed daily using the Cystic Fibrosis Respiratory Symptom Diary and Chronic Respiratory Infection Symptom Score (CFRSD-CRISS), with total scores ranging from 0-100, where a higher score indicates greater symptom severity [22]. A change of 11 units is considered clinically significant [23]. At day 28, we asked clinicians if they considered the treatment a success (though we did not designate a definition of success) to evaluate the durability of treatment. This study design is unique in combining this prospective data with data from the Cystic Fibrosis Foundation Patient Registry (CFFPR), which was accessed to obtain retrospective data.

Descriptive statistics were used to summarize demographics, symptom duration and distribution, and spirometry at the time of enrollment. FEV_1% predicted was compared to historical values recorded in the CFFPR. Change from historical baseline (best in a 6 or 12-month period) and admission assessment were calculated at completion of IV therapy and day 28, and then compared to clinical characteristics, treatment practices, and treatment goals defined by the admitting clinician. T-tests were used to compare continuous variables by treatment goals and demographic values at baseline. Proportions were compared via Fisher's exact test with corresponding 95% confidence intervals (CIs) derived using the Newcombe–Wilson method. For sensitivity analyses, missing visit 3 data were imputed using last observation carried forward (LOCF) method to estimate effects of missing data on change from admission outcomes. Analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, 2013), and R (versions 3.2.1, The R Foundation for Statistical Computing, Vienna, Austria, 2015). This study was approved by each of the participating center's Institutional Review Board and all participants or guardians provided written informed consent and assent where required.

3. Results

3.1. Baseline demographics

Key demographic data, duration of symptoms, presenting PEx features, and historic lung function are described elsewhere [20]. Briefly, 220 patients were enrolled (56% female), with a mean (SD) age 26.3 (9.5) years, 19% of which were adolescents (12–17 years old).