Journal of Cystic Fibrosis 16 (2017) 592 – 599

www.elsevier.com/locate/jcf

Original Article

Standardized Treatment of Pulmonary Exacerbations (STOP) study: Observations at the initiation of intravenous antibiotics for cystic fibrosis pulmonary exacerbations☆

Don B. Sanders [a,*,1], George M. Solomon [b], Valeria V. Beckett [c], Natalie E. West [d], Cori L. Daines [e], Sonya L. Heltshe [c,f], Donald R. VanDevanter [g], Jonathan E. Spahr [h], Ronald L. Gibson [f], Jerry A. Nick [i], Bruce C. Marshall [j], Patrick A. Flume [k], Christopher H. Goss [c,f,l] on behalf of the STOP Study Group [2]

[a] *Department of Pediatrics, University of Wisconsin-Madison, Madison, WI, USA*
[b] *Department of Medicine, Gregory Fleming James Cystic Fibrosis Center, University of Alabama at Birmingham, Birmingham, AL, USA*
[c] *Cystic Fibrosis Foundation Therapeutics Development Network Coordinating Center, Seattle Children's Research Institute, Seattle, WA, USA*
[d] *Department of Medicine, Johns Hopkins University, Baltimore, MD, USA*
[e] *Department of Pediatrics, University of Arizona, Tucson, AZ, USA*
[f] *Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, USA*
[g] *Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH, USA*
[h] *Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*
[i] *Department of Medicine, National Jewish Health, Denver, CO, USA*
[j] *Cystic Fibrosis Foundation, Bethesda, MD, USA*
[k] *Departments of Medicine and Pediatrics, Medical University of South Carolina, Charleston, SC, USA*
[l] *Department of Medicine, University of Washington, Seattle, WA, USA*

Received 30 September 2016; revised 7 March 2017; accepted 4 April 2017
Available online 29 April 2017

Abstract

Background: The Standardized Treatment of Pulmonary Exacerbations (STOP) program has the intent of defining best practices in the treatment of pulmonary exacerbations (PEx) in patients with cystic fibrosis (CF). The objective of this analysis was to describe the clinical presentations of patients admitted for intravenous (IV) antibiotics and enrolled in a prospective observational PEx study as well as to understand physician treatment goals at the start of the intervention.

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis; CFFPR, CF Foundation Patient Registry; CFRSD-CRISS, CF Respiratory Symptom Diary–Chronic Respiratory Infection Symptom Score; CI, confidence interval; FEV_1, forced expiratory volume at 1 s; IV, intravenous; NTM, non-tuberculous mycobacteria; PEx, pulmonary exacerbation; STOP, Standardized Treatment of Pulmonary Exacerbations

☆ Contributors: PAF, CHG, DBS, SLH, VVT and DRV contributed to the study design. All authors participated in data analysis/interpretation and critical review and revision of the manuscript. PAF and CHG participated in project management. SLH and VVT participated in data management and statistical analysis. All authors approved the final draft for submission.

* Corresponding author at: Riley Hospital for Children, 705 Riley Hospital Dr, ROC 4270, USA.
E-mail address: dbsand@iu.edu (D.B. Sanders).

[1] Dr. Sanders is currently a faculty member in the Department of Pediatrics, Indiana University, Indianapolis, IN, USA.

[2] See Supplemental Appendix for STOP Study Group.

http://dx.doi.org/10.1016/j.jcf.2017.04.005

Methods: We enrolled adolescents and adults admitted to the hospital for a PEx treated with IV antibiotics. We recorded patient and PEx characteristics at the time of enrollment. We surveyed treating physicians on treatment goals as well as their willingness to enroll patients in various study designs. Additional demographic and clinical data were obtained from the CF Foundation Patient Registry.
Results: Of 220 patients enrolled, 56% were female, 19% were adolescents, and 71% were infected with *P. aeruginosa*. The mean (SD) FEV_1 at enrollment was 51.1 (21.6)% predicted. Most patients (85%) experienced symptoms for ≥7 days before admission, 43% had received IV antibiotics within the previous 6 months, and 48% received oral and/or inhaled antibiotics prior to IV antibiotic initiation. Forty percent had ≥10% FEV_1 decrease from their best value recorded in the previous 6 months, but for 20% of patients, their enrollment FEV_1 was their best FEV_1 recorded within the previous 6 months. Physicians reported that their primary treatment objectives were lung function recovery (53%) and improvement of symptoms (47%) of PEx. Most physicians stated they would enroll patients in studies involving 10-day (72%) or 14-day (87%), but not 7-day (29%), treatment regimens.
Conclusions: Based on the results of this study, prospective studies are feasible and physician willingness for interventional studies of PEx exists. Results of this observational study will help design future PEx trials.

Keywords: FEV_1; Symptoms; *Pseudomonas aeruginosa*

1. Introduction

Patients with cystic fibrosis (CF) develop chronic lung infections and suffer from recurrent acute pulmonary exacerbations (PEx), generally described as a worsening of respiratory signs and symptoms that are typically treated with antibiotics [1]. PEx are associated with considerable morbidity and increased healthcare costs [2–5]. There is often loss of lung function that is not fully recovered following treatment [6,7]. It is possible that some PEx treatment decisions may account for poorer outcomes [8,9]; for example, in the US, treatment with IV antibiotics for less than 9 days and treatment entirely outside of the hospital have both been associated with an increased risk of retreatment with IV antibiotics within 30 days of PEx treatment completion, despite similar patient characteristics at IV antibiotic initiation [9].

There were more than 17,000 events treated with IV antibiotics recorded in the US CF Foundation Patient Registry (CFFPR) in 2014 [10]. Despite this being such a common event, there is a paucity of evidence upon which to develop PEx treatment guidelines [11] and substantial variation in therapeutic decisions surrounding PEx [8,10,12–15]. Identifying best practices and evidence to guide treatment decisions offers the potential to improve the treatment of, and outcomes after, PEx.

To design a study to begin to define optimal treatment strategies, several questions need to be addressed. The PEx treatment guidelines highlighted several questions that might warrant investigation [11], but it is not known whether clinicians and patients would be willing to participate in such trials. Additionally, there are several endpoints that might be relevant for a PEx intervention study, including FEV_1, symptom recovery, and time to next exacerbation. Understanding physician goals at the time they initiate IV antibiotics is necessary to select a clinical efficacy endpoint that will be accepted in practice. To formally power a study in CF PEx, a better understanding is needed regarding the magnitude of treatment effect and variance for these measures, in addition to the optimal timing of the endpoint assessment. A better understanding is also needed regarding which factors might confound a clinical trial in PEx (e.g., inpatient vs outpatient setting, airway clearance techniques, antibiotic selection and dosing); delineating the impact of these potential confounders is essential to designing any future clinical trial in PEx.

A careful review of the literature found the answers to these questions lacking. Thus, the Standardized Treatment of Pulmonary Exacerbations (STOP) study (clinicaltrials.gov NCT02109822) was performed to gather additional information to define key clinical endpoints, their magnitude of response, and their variance in order to guide future interventional trials to optimize PEx therapy and outcomes. In addition, we sought input from treating clinicians on treatment goals and willingness to enroll patients in various potential PEx study designs. We describe herein the methods for the STOP study, the clinical presentations of these patients, and the results of a physician survey that will inform future study design.

2. Methods

STOP was an observational study conducted at eleven US CF centers between January 2014 and January 2015. Centers were recruited based on their willingness to participate, and their ability to enroll study subjects efficiently. 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.

To be eligible for STOP, patients had to have a confirmed diagnosis of CF and be admitted to the hospital for treatment of a PEx with IV antibiotics. Because the characteristics of patients treated with IV antibiotics are generally similar whether they are admitted or not [9], we excluded patients whose IV antibiotics were initiated outside of the hospital in order to collect early response data during the most aggressive interventions. The diagnosis of PEx was determined by the treating physician. Patients were recruited within 24 h of the start of IV therapy. Inclusion and exclusion criteria are included in the online supplement. Demographic and clinical data were collected at the time of enrollment and extracted from the CFFPR, including: age, sex, race/ethnicity, genotype, spirometry, respiratory microbiology, CF-related complications, pancreatic status, and history of previous PEx treatment. Additional data were collected