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Study design considerations for the Standardized Treatment of Pulmonary Exacerbations 2 (STOP2): A trial to compare intravenous antibiotic treatment durations in CF☆

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ABSTRACT

Background: Pulmonary exacerbations (PEx) in cystic fibrosis (CF) are common and contribute to morbidity and mortality. Duration of IV antibiotic therapy to treat PEx varies widely in the US, and there are few data to guide treatment decisions.

Methods: We combined a survey of CF stakeholders with retrospective analyses of a recent observational study of CF PEx to design a multicenter, randomized, prospective study comparing the efficacy and safety of different durations of IV antibiotics for PEx to meet the needs of people with CF and their caregivers.

Results: IV antibiotic duration was cited as the most important PEx research question by responding CF physicians and top concern among surveyed CF patients/caregivers. During PEx, forced expiratory volume in 1 s (FEV_1% predicted) and symptom responses at 7–10 days of IV antibiotics identified two distinct groups: early robust responders (ERR) who subsequently experienced greater FEV_1 improvements compared to non-ERR (NERR). In addition to greater FEV_1 and symptom responses, only 14% of ERR patients were treated with IV antibiotics for > 15 days, compared with 45% of NERR patients.

Conclusions: A divergent trial design that evaluates subjects' interim improvement in FEV_1 and symptoms to tailor randomization to IV treatment duration (10 vs. 14 days for ERR, 14 vs. 21 days for NERR) may alleviate physician and patient concerns about excess or inadequate treatment. Such a study has the potential to provide evidence necessary to standardize IV antibiotic duration in CF PEx care –a first step to conducting PEx research of other treatment features.

1. Introduction

Pulmonary exacerbations (PEx) in cystic fibrosis (CF) are a major cause of morbidity linked to disease progression [1,2] and diminished survival [3,4]. They are common and recurring [5], typically treated with antibiotics and increased airway clearance [6]. A systematic review of the literature found scant evidence upon which to base treatment recommendations [7]. Analysis of the CF Foundation (CFF) Patient Registry (CFFPR) demonstrates wide variation in treatment parameters [5] making it difficult to determine optimal practice [6]. This is particularly important as analysis of the CFFPR suggested a lack of recovery of lung function to previous baseline [8]. There are many reports of risk factors for PEx outcomes but nearly all are based on either observational data subject to indication bias [9,10,11,12], or

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[1] See Data Supplement Appendix A for STOP Study Group.

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small single center randomized studies with inconclusive findings [13,14,15,16,17].

Identification of best PEx treatment practices is hindered by multiple logistic barriers, including variability of presenting signs and symptoms [18], diverse physician and patient objectives for treatment [19], and the range of treatment combinations currently utilized [12]. Ideally, PEx treatment practices could be optimized by conducting a series of randomized controlled studies comparing differences in a single parameter (e.g., treatment durations, home vs. hospital treatment). It has been suggested that studying differences in treatment duration may be the 'most logical' parameter for initial PEx treatment studies [20].

The Standardized Treatment of Pulmonary Exacerbations (STOP) study was an observational pilot study of individuals with CF who were admitted to the hospital for intravenous (IV) antibiotics for treatment of a PEx. STOP gathered PEx presentation characteristics, physician goals and treatment choices, physician willingness to enroll patients in hypothetical trials, and clinical response [18,19,21], with the ultimate objective of leveraging results to design future controlled interventional trials standardizing aspects of CF PEx treatment. While STOP identified a general willingness of CF physicians participating in the study to participate in standardized PEx studies, it was necessary to get broader input from other CF clinicians, patients and families to understand prioritization of PEx treatment questions and clinical response measures, and specific concerns regarding the design of randomized prospective studies in PEx.

We describe the survey results and report retrospective analyses of the STOP study to rationalize and design a multicenter, randomized, prospective study comparing the clinical efficacy and safety of different durations of IV antibiotic treatment.

2. Materials and methods

2.1. Stakeholder surveys

Two surveys were developed to gauge PEx experiences, perceptions, and research importance among 1) CF patients/caregivers, and 2) CF physicians/providers [Appendices B,C in the data supplement]. The patient/caregiver questionnaire was distributed via email to 150 patients and caregivers in the CFF-organized Adult and Patient Family Advisory group (AFA) and conducted via secure, anonymous, electronic data capture using online REDCap database services [22] hosted at the University of Washington. Similarly, a link to the REDCap physician survey was emailed to all CFF Care Center Program Directors (81 adult and 88 pediatric programs) for secure, anonymous completion.

2.2. STOP study

STOP (clinicaltrials.govNCT02109822) was an observational pilot study conducted at eleven adult and pediatric CFF Therapeutic Development Network sites between 2014 and 2015 [18,19,21]. In brief, CF patients 12 years and older admitted to the hospital for a PEx were assessed for spirometry and patient-reported signs and symptoms throughout treatment and to Day 28. Human subjects approval was granted at all sites by their institutional review boards and written informed consent was obtained from all subjects.

2.3. Variables and statistical methods

Spirometry was conducted according to ATS standards [23] and forced expiratory volume in 1 s (FEV_1) is expressed as percent predicted [24]. Absolute changes in FEV_1% predicted from admission to Day 7–10, end of IV antibiotic treatment, and Day 28 were calculated. The CF Respiratory Symptom Diary (CFRSD) was scored according to the Chronic Respiratory Infection Severity Score (CRISS), where 100 is the most severe, and 0 the least. Changes in CRISS and FEV_1% predicted from admission to Day 7–10, end of IV, and Day 28 were summarized. We examined response defined as 'early robust response' (ERR) if absolute FEV_1 and CRISS improvements from admission to Day 7–10 exceeded specific, candidate thresholds. For FEV_1, we assessed response ranges from 5% to 10% predicted; for the CRISS we used the minimal clinically important response of 11 units [25]. Patients not meeting the thresholds at Day 7–10 were considered non-ERR (NERR). Candidate ERR thresholds were cross-tabulated with IV treatment duration and subsequent response at end of IV and Day 28. Means, standard deviations and 95% confidence intervals were used to calculate sample sizes and superiority/non-inferiority margins for a future study. All analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, 2013), and R (version 3.2.1, The R Foundation for Statistical Computing, Vienna, Austria, 2015).

3. Results

3.1. Physician and patient/caregiver (AFA) surveys

102 of 169 CF physicians (60.4%) responded to the survey in July 2015: 44% were pediatric providers, 45% were adult providers, and 11% providing care to both, with even distribution across US regions. A majority (73%) of respondents had > 10 years' experience in CF care and most (78%) worked at centers with > 100 patients. Just over one third (n = 52) of the AFA completed the patient/caregiver survey in June 2015: 49% were persons with CF and 51% were parents, spouses, or partners of persons with CF; 37% of the surveyed CF population was < 18 years of age. Nearly all (92%) reported IV antibiotic treatment of PEx for the person with CF at some time in the past. Detailed responses to questions regarding current PEx practices, interest in future studies, and clinical endpoints are in the online data supplement (Tables E1, E2). Key findings include: (1) both groups expressed high interest in studies of management of PEx (Table 1); (2) clinicians reported (80%) and patients/caregivers assumed (85%) that antibiotics are selected based on recent culture and susceptibility testing; and (3) there were differences between clinicians and patients/families regarding most important treatment response measures: change in FEV_1 (47% clinicians vs. 17% patient/caregivers, respectively) and improvement in symptoms (32% clinicians vs. 77% patient/caregivers). Both groups also offered additional comments (Tables E3, E4) with concerns expressed about too short a treatment duration, resulting in incomplete treatment, but also concern for receiving too long of a treatment.

3.2. Influence of survey results on STOP2 study design

STOP2 is a prospective comparison of different IV antibiotic treatment durations because both clinician and patient/caregiver surveys identified treatment duration as high-priority PEx management question (Table 1). Because the majority of those enrolled in the STOP pilot

Table 1
Ranking of clinical trial questions for improving treatment of pulmonary exacerbations.

Rank	Clinician responses	Higher priority[a]	Patient/family responses	Higher priority[a]
1	Antibiotic treatment duration	73%	Site of treatment (home, hospital)	51%
2	1 vs. 2 antibiotics for *Pa*[b]	48%	When to start antibiotics	51%
3	Continuous infusion of β-lactam	38%	Antibiotic route(s)	43%
4	Site of treatment (home, hospital)	35%	Antibiotic treatment duration	40%
5	Use of corticosteroids	32%	Use of corticosteroids	20%

[a] Proportions of respondents identifying topic as 1st or 2nd highest priority to study.
[b] *Pseudomonas aeruginosa* airway infection.