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Oral antibiotic prescribing patterns for treatment of pulmonary exacerbations in two large pediatric CF centers

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Abstract

Introduction: Oral antibiotics are frequently prescribed for outpatient pulmonary exacerbations (PEx) in children with cystic fibrosis (CF). This study aimed to characterize oral antibiotic use for PEx and treatment outcomes at two large U.S. CF centers.

Methods:Retrospective, descriptive study of oral antibiotic prescribing practices among children with CF ages 6- 17 years over one year. The care setting for antibiotic initiation(clinic or phone encounter) was determined and outcomes were compared.

Results: 763 oral antibiotic courses were prescribed to 312 patients ages 6-17 years (77% of 403 eligible patients) with a median of 2 courses per year (range 1-10). Fifty-eight percent of prescriptions were provided over the phone. Penicillin was the most commonly prescribed antibiotic class (36% of prescriptions) but differences in antibiotic class prescriptions were noted between the two centers. Hospitalizations occurred within 3 months following 19% of oral antibiotic courses. FEV_1 recovered to within 90% of prior baseline within 6 months in 87% of encounters; the mean (SD) % recovery was 99.6% (12.1%) of baseline. Outcomes did not differ between phone and clinic prescriptions.

Conclusions:Phone prescriptions, commonly excluded in studies of PEx, made up more than half of all oral antibiotic courses. Heterogeneity in prescribing patterns was observed between the two centers. Most patients had improvement in FEV_1 returning to near their

prior baseline, but hospitalizations occurred in one-fifth following oral antibiotic treatment. Efforts to optimize PEx treatment must consider care that occurs over the phone; this is particularly important as the use of telemedicine increases.

Introduction

Pulmonary exacerbations (PEx) are frequent causes of morbidity for patients with cystic fibrosis (CF) and are characterized by an increase in respiratory symptoms above baseline including increased cough, sputum production and decreased exercise tolerance. While people with CF diagnosed with a PEx may require hospitalization for intravenous antibiotics, more than 70% of PEx are treated with oral antibiotics, and in children and those with milder lung disease the likelihood of oral antibiotic treatment is even higher[1,2]. Oral antibiotics are frequently prescribed over the phone in pediatric centers, but the extent to which this is done has not been characterized. Despite the routine use of outpatient oral antibiotics, there are limited data describing the prescribing patterns of oral antibiotics (e.g. whether antibiotics are prescribed in clinic or over the phone, the type of antibiotics used, treatment duration) and subsequent treatment outcomes[3-6]. As the use of remote monitoring for CF patients including phone calls and telehealth visits increases due to the COVID-19 pandemic, a better understanding of phone-treated PEx is warranted.

Guidelines for oral antibiotic treatment of PEx are lacking although individual CF centers have developed local clinical care guidelines in an attempt to standardize decreases in forced expiratory volume in 1 second (FEV_1) measurements and outpatient PEx treatment[7]. However, treatment guidelines often do not consider remote monitoring

for PEx and their treatment when objective measurements including FEV_1 are lacking. The COVID-19 pandemic has resulted in a rapid shift in CF care with more remote monitoring including telehealth visits and phone calls. It is likely that this shift will remain in the short term and may result in more permanent changes in the way that we approach CF care. Studies of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators have demonstrated a reduction in hospitalizations related to exacerbations and a shift towards more outpatient treatment[8-12]. It is also possible that with improvements in exacerbation frequency/severity and overall lung health that there will be shift towards more remote treatment of PEx for pediatric patients.

We aimed to evaluate the heterogeneity of oral antibiotic treatment between two large pediatric CF centers and to characterize oral antibiotic prescribing patterns for PEx in children at two large CF centers. Secondarily, we sought to evaluate if there is a difference in PExoutcomes between those in which oral antibiotics were prescribed in clinic vs. over the phone. We hypothesized that there would be differences in antibiotic prescribing patterns between the two centers given the absence of standardized treatment guidelines for outpatient PEx. Additionally, we hypothesized that antibiotic prescriptions over the phone would be frequent in our clinic populations and be associated with a lower risk of subsequent hospitalization and better lung function recovery. We based this on the assumption that patients receiving antibiotics over the phone were recognizing symptoms and being treated earlier than those being seen in clinic.

Methods

Study Population and Design

Children between the ages of 6 and 17 years of age with a diagnosis of CF[13], and at least one PEx treated with oral antibiotics during the study period at Children's Hospital Colorado (Aurora, CO) and Riley Hospital for Children (Indianapolis, IN) were included. All antibiotics prescribed fromJuly 2016-June 2017 were reviewed. A PEx treated with oral antibiotics was defined as a prescription of an acute course of oral antibiotics for worsening respiratory symptoms and/or signs.. Chronic oral and inhaled antibiotics were excluded. For each antibiotic prescription, the antibiotic prescribed and its duration and prescribing setting (clinic versus over the phone) were recorded. Demographic data, clinical characteristics and symptoms at the time of PEx, as well as outcomes of hospitalization during the subsequent 3 months and lung function measurements during the subsequent 6 months were obtained. All data were extracted from electronic medical records.

Statistical Analysis

Descriptive statistics included the median and range and simple proportions, as applicable. The percent of antibiotics prescribed in each antibiotic class were compared between centers using a multinomial regression model with a random subject effect and a fixed center effect. Percent-predicted FEV_1 was calculated using the Wang-Hankinson[14,15] reference equations.

Differences in outcomes between antibiotic prescriptions provided in clinic versus over the phone were measured by the proportion of patients hospitalized in the three months following an oral antibiotic prescription and recovery of baseline forced

expiratory volume in 1 second (FEV_1) within 6 months. The risk of hospitalizations in the three months following an oral antibiotic course was estimated between those with antibiotics prescribed in clinic versus over the phone using a logistic regression model with a random subject effect.

Baseline FEV_1 (defined as highest FEV_1 in the 6 months prior to the antibiotic course) were compared to the best FEV_1 within 6 months following antibiotic treatment. For patients receiving antibiotics in clinic, the FEV_1 at the time of antibiotic initiation was also obtained. To determine the percent of patients who returned to baseline in the 6 months following the PEx, defined as 90% of baseline or higher[16], logistic regression with a random subject effect was utilized. In addition, the percent of baseline FEV_1 recovered was determined by comparing the ratio of best FEV_1 in the 6 months after treatment to the best FEV_1 in the 6 months prior to treatment across groups using a linear mixed model.

Based on observed differences in outcomes for the penicillin antibiotic class compared to other classes, a follow-up propensity score analysis was performed to reduce the impact of treatment-selection bias and estimate the effect of prescriptionsof different antibiotic classes on risk of hospitalization. Subjects were matched one-to-one using a Mahalanobis distance on the propensity score[17] that was estimated using CF Center, care setting for treatment initiation (phone or clinic visit), highest FEV within 6 months prior and Stenotrophomonas culture result in a logistic regression using prescribed penicillin as the outcome.

The Colorado Multiple Institutional Review Board and Indiana University Institutional Review Board approved this study. Consent was waived and HIPAA standards were maintained during the study.

Results

Demographics

Over a one-year period, 312/403 (77%) 6- to 17-year-old children with CF at Children's Hospital Colorado (CHCO) and Riley Hospital for Children (RHC) were prescribed at least one oral antibiotic course for an acute pulmonary exacerbation. A total of 763 oral antibiotic courses (437 CHCO, 326 RHC, E-Table 1) were prescribed with a median of two antibiotic courses per patient (range 1-10). Demographic data and clinical characteristics of the 312 subjects who received an antibiotic course are listed in Table 1. Baseline FEV_1 was similar to the overall pediatric CF population at each center. Significant differences were noted in the culture results between the two centers, with RHC having a higher proportion of patients who were MRSA positive and a lower proportion positive for H. influenzae ($p < 0.01$ for both).

Antibiotic Prescribing Patterns

Overall, 58% of antibiotics were prescribed over the phone, but differences existed between the two centers. Phone prescriptions were more common at CHCO compared to RHC (62% versus 52%, $p<0.01$, E-Table 2). There were 199 subjects (64% of cohort) between the two centers who received more than 1 antibiotic course; approximately half of these patients were prescribed antibiotics both in clinic and over the phone.

At both centers combined, the vast majority (90%) of antibiotic courses were prescribed for 14-21 days. At CHCO, 3.2% of antibiotic courses were prescribed for <14 days compared to 16% at RHC. There was no difference in antibiotic prescription duration between phone and clinic antibiotic prescriptions when compared within site. The most common antibiotic prescribed differed between the two centers: amoxicillin-clavulanic acid at CHCO (48%) and trimethoprim-sulfamethoxazole (38%) at RHC (Figure 1). There was no difference in the antibiotic class prescribed between clinic and phone encounters (E-Table 2) with the exception of infrequently prescribed antibiotics (<8% of total antibiotic courses). Additionally, there were no differences in age, gender, microbiology history or baseline FEV_1 between phone and clinic prescriptions. Overall, antibiotic prescriptions were more common in the fall/winter months (October-March, 430 prescriptions) compared to the spring/summer months (April-September, 333 prescriptions, Figure 2).

Reported signs and symptoms

The most common symptom at the time of antibiotic prescription was an increase in cough (90%), followed by increased sputum (39%), fatigue (16%) and shortness of breath (11%). There were significant differences in reports of cough, increased sputum production, shortness of breath and fatigue between clinic and phone encounters (E-Image 1, E-Table 3). Cough alone was recorded in 216 (28%) encounters. Multiple symptoms were reported in 478 (63%) encounters. The most common combination was increased cough, wet cough and change in sputum, which occurred in 108 (23%) of these encounters. There were 583 encounters that had symptom duration information; the median (IQR) duration was 5 (3-7) days. Clinic encounters had longer reported symptom

duration compared to phone encounters (7 versus 4 days, p<0.01, E-Table 3). Chest exams were recorded in 306 (95%) of the clinic encounters. Abnormal breath sounds were noted in 32% of the clinic encounters. Of those with abnormal breath sounds, crackles (64%) were the most common finding followed by wheezing (20%) and rhonchi (13%).

Hospitalizations

Hospitalization occurred within 3 months following 143 oral antibiotic prescriptions (18.7% of encounters) for a total of 110 discrete hospitalizations; 86 hospitalizations occurred after 1 oral antibiotic course, 16 hospitalizations occurred after 2 oral antibiotic courses and 7 and 1 hospitalizations occurred after 3 and 4 courses, respectively. There was no difference in the odds of hospitalization between clinic and phone encounters (p=0.82). Subjects who cultured positive for *Stenotrophomonasmaltophilia* any time over the one-year study period were more likely to be hospitalized (p-value=0.01, E-Table 4). There was no association between hospitalization and symptom duration in the subset of encounters (n=509) in which this information was documented. Those subjects who had higher baseline FEV_1 % predicted or received treatment with penicillins (almost all amoxicillin-clavulanic acid) were less likely to be hospitalized (p < 0.01, E-Table 4). The association with reduced hospitalization and treatment with penicillin class antibiotics remained after performing a follow-up analysis using propensity score matching to better balance factors associated with penicillin prescriptions (E-Table 5).

There were 232 subjects who did not have a hospitalization within 3 months of any oral antibiotic treatment; the median (IQR) number of oral antibiotic courses for the non-hospitalized group was 2 (1-3). This was significantly lower than for the 80 subjects who did experience a hospitalization, with a median (IQR) of 3 (2-4) antibiotic courses during the one-year study period ($p<0.01$).

Lung function recovery and changes in pulmonary function

Median (IQR) baseline lung function (defined as highest FEV_1 % predicted within the prior 6 months) was 96% (82, 107) predicted in the overall cohort with no significant difference between the two centers, nor between phone and clinic encounters. FEV_1 recovered to within 90% of baseline in 87% of encounters and >100% of baseline in 44% of encounters. The mean (sd) recovery of FEV_1 was 99.6% (12.2%) and did not differ between clinic and phone encounters (E-Image 2, E-Table 6). Percent FEV_1recovery was not different between those who were hospitalized within 3 months following an oral antibiotic course(98.8% [13.7]) and those who were not (99.8% [11.8], p=0.42). There was no association between antibiotic class prescribed and percent FEV_1 recovery, but older age and higher baseline FEV_1 were associated with worse recovery (E-Table 7).

In the subset of encounters where antibiotics were prescribed in clinic (n=361), 173 included FEV_1 measurements at baseline (highest value within the past 6 months), at the clinic visit and within 6 months after antibiotics. The mean (sd) decrease in FEV_1 from the 6-month baseline to the start of antibiotics was -7.5% (11.8) predicted, with no significant difference between sites (E-Table 8), and the mean increase to the highest FEV_1 within 6 months was 7% (9.6)predicted (Figure 3). Out of 173 clinic encounters

with FEV1 values at the start of the antibiotic course, 92 (53%) had FEV_1% >90% of baseline. Among the encounters at which antibiotics were prescribed but no symptoms recorded (11.5%), the mean (sd) drop in FEV_1 from baseline was -9.8% (9.1) predicted.

Discussion

This study demonstrates that greater than 75% of school-aged children at two large pediatric CF centers experienced at least one PEx treated with oral antibiotics over one year. Previous registry-based studies have demonstrated that those with milder lung function and younger age are more likely to receive oral antibiotics versus IV antibiotics[1]. Therefore, it remains important to characterize exacerbations treated with oral antibiotics and their associated outcomes as this is a mainstay of treatment for pediatric patients.

We hypothesized that the majority of antibiotic prescriptions would be over the phone and that those events would have improved outcomes based on earlier recognition and treatment. We found that 58% were indeed treated over the phone, and these PEx had a shorter duration of symptoms prior to treatment (4 vs 7 days). We did not detect difference in hospitalization rate or FEV_1 recovery by treatment care setting in this retrospective, electronic health record-based study.

Prescribing patterns between these two centers were heterogeneous; significant differences were noted in the antibiotic class prescribed, the proportion of phone versus clinic prescriptions and subsequent hospitalizations. Specifically, at CHCO, the most common antibiotic was amoxicillin-clavulanic acid, while at RHC it was trimethoprim-sulfamethoxazole (TMP-SMX). This is likely due to the higher rate of MRSA within the cohort from RHC as well as differences in provider prescribing patterns. Of note, CHCO

has an oral antibiotic guideline for treatment of outpatient PEx that recommends the use of amoxicillin-clavulanic acid as first line treatment for both MSSA and *Haemophilusinfluenzae.* Heterogeneity in IV antibiotic choice for CF pulmonary exacerbations has also been demonstrated for pediatric patients despite existing national guidelines for PEx treatment[18]. Antibiotic prescriptions over the phone were more common at CHCO, perhaps related to the large and mountainous geographic region it serves.

Hospitalizations occurred following almost 20% of oral antibiotic courses in our cohorts. There are limited data on the risk of hospitalization following treatment with oral antibiotics. In a prospective study of IV antibiotics, half of adults and 75% of adolescents received oral antibiotics prior to hospitalization[19]. In a retrospective analysis of a cohort of pediatric and adult patients with CF performed over 1 year, 27% of PEx prescribed oral antibiotics were subsequently treated with IV antibiotics[4], slightly higher than that observed in our cohort. This difference may be explained by the inclusion of both pediatric and adult patients and a lower average baseline FEV_1 (~79%) in the prior study[4]. We also found that the risk of hospitalization following a PEx treated with antibiotics in the penicillin class was reduced compared to other antibiotics classes. It is unclear if this is related to the underlying CF pathogen or the antibiotic. Prospective studies are needed to better understand this finding.

Despite the frequency of oral antibiotic use in the pediatric population and those with milder lung disease[1], there are limited studies describing FEV_1 outcomes following this treatment[3-6]. The average drop in lung function at the time of a PEx (-7.5%) was similar to the decreases observed in other studies[3,5]. The majority of patients in our cohort

recovered to within 90% of their FEV_1 baseline, suggesting that oral antibiotics are effective for most but there is likely a subgroup that do not respond well and need more aggressive therapy. Stanojevic and colleagues performed a large retrospective cohort study of adult and pediatric patients over a five-year period and evaluated the effect of oral antibiotic treated pulmonary exacerbations on short-term clinical outcomes[5]. They determined that lung function was lower in those who had an exacerbation treated with oral antibiotics in the previous year than those who did not, and that lung function decline over the five-year study period was greater in those that experienced more frequent exacerbations[5]. Almost 20% of subjects in the Toronto cohort treated with oral antibiotics did not return to within 90% of baseline at follow-up (within 3 months)[5], higher than in our cohort. The timing of follow up lung function measurements and the inclusion of adults within the Toronto cohort may have contributed to this difference.

In this study, recovery to baseline FEV_1within 6 months was less likely in those who were older and had a higher baseline FEV_1 which contrasts with prior studies showing older patients[3,20] and those with higher baseline FEV_1[3] were more likely to recover following exacerbation treatment. However, these differences may be related to the timing of FEV_1 measurements and longer-term (within six month) versus shorter-term recovery. In children, higher baseline lung function is a risk factor for FEV_1 decline[21],and it may be that inadequate recognition and/or insufficient treatment of PEx contribute to disease progression.

The main strengths of this study are, for the first time, evaluation of PEx treated over the phone (which accounted for over half of all PEx), and inclusion of two large pediatric CF centers. Data collection occurred over a year to prevent any seasonality bias

related to PEx outcomes and treatment. There are several limitations that must be noted. First, the study was retrospective and based on the electronic health record at the CF center, potentially leading to under-ascertainment of exacerbations, incomplete description of symptoms and exam findings and residual confounding by unmeasured characteristics. It is unlikely that there were a significant number of antibiotic courses prescribed at alternate locations based on the clinical practices at our centers. Additionally, we did not record whether patients were instructed to be seen in clinic based on their symptoms reported over the phone; if this occurred often, it would have biased the clinic group towards more severe PEx. We were also unable to assess adherence to oral antibiotic treatment and did not capture if patients were concomitantly treated with steroids or inhaled antibiotics. Furthermore, PEx symptoms treated without oral antibiotics (e.g., with increased frequency of airway clearance alone) were not assessed, limiting our ability to ascribe FEV_1 improvements to the oral antibiotic prescriptions. Some individuals may have received more than one oral antibiotic course for a single PEx. Therefore, the changes observed may not be reflective of a single antibiotic course for a PEx but the repeated measures analysis did account for the fact that these were not independent observations. Additionally, we did not account for any antibiotics received shortly before or after the on-year study period.

There is an urgent need to better understand remote monitoring of PEx, especially in the era of the COVID-19 pandemic and the rapid shifts in CF care to include more telemedicine visits and phone calls. This study highlights that there are several areas for future research including prospective evaluations of PEx treated remotely, identifying patients at risk for hospitalization or failure to recover to baseline lung function and

determining the optimal timing of antibiotic initiation. Future studies of outpatient PEx management should include antibiotics prescribed over the phone, especially as the role of telemedicine expands[22].

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Figures

Figure 1: **Antibiotic prescriptions by class.**Frequency of antibiotic class prescriptions prescribed at Children's Hospital Colorado (CHCO) and Riley Hospital for Children (RHC). The asterisks represent the antibiotic classes in which a significant difference was noted in the proportion of prescriptions between the two centers.

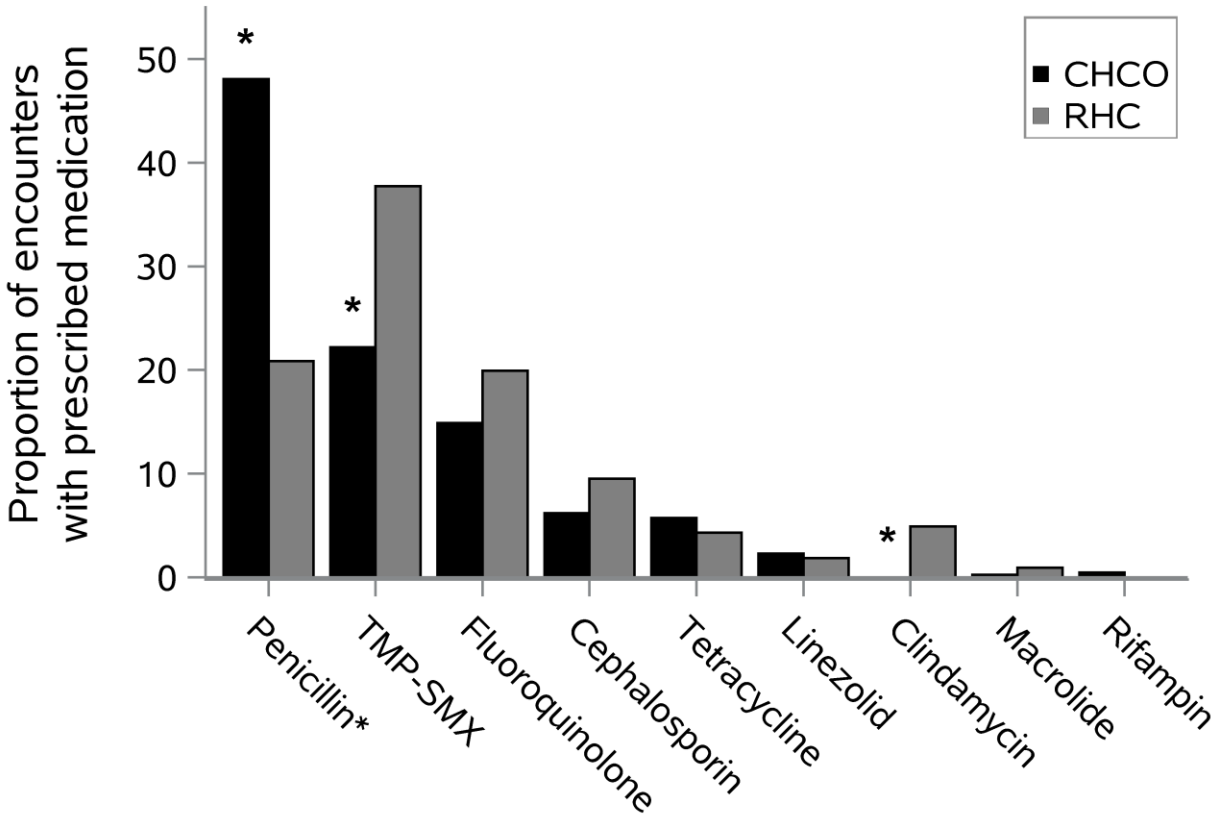


Figure 2: **Antibiotic prescriptions by month.** a) The number of antibiotic prescriptions by month prescribed in clinic and over the phone at the two centers combined. b) The proportion of the total prescriptions by month prescribed over the phone at CHCO and RHC.

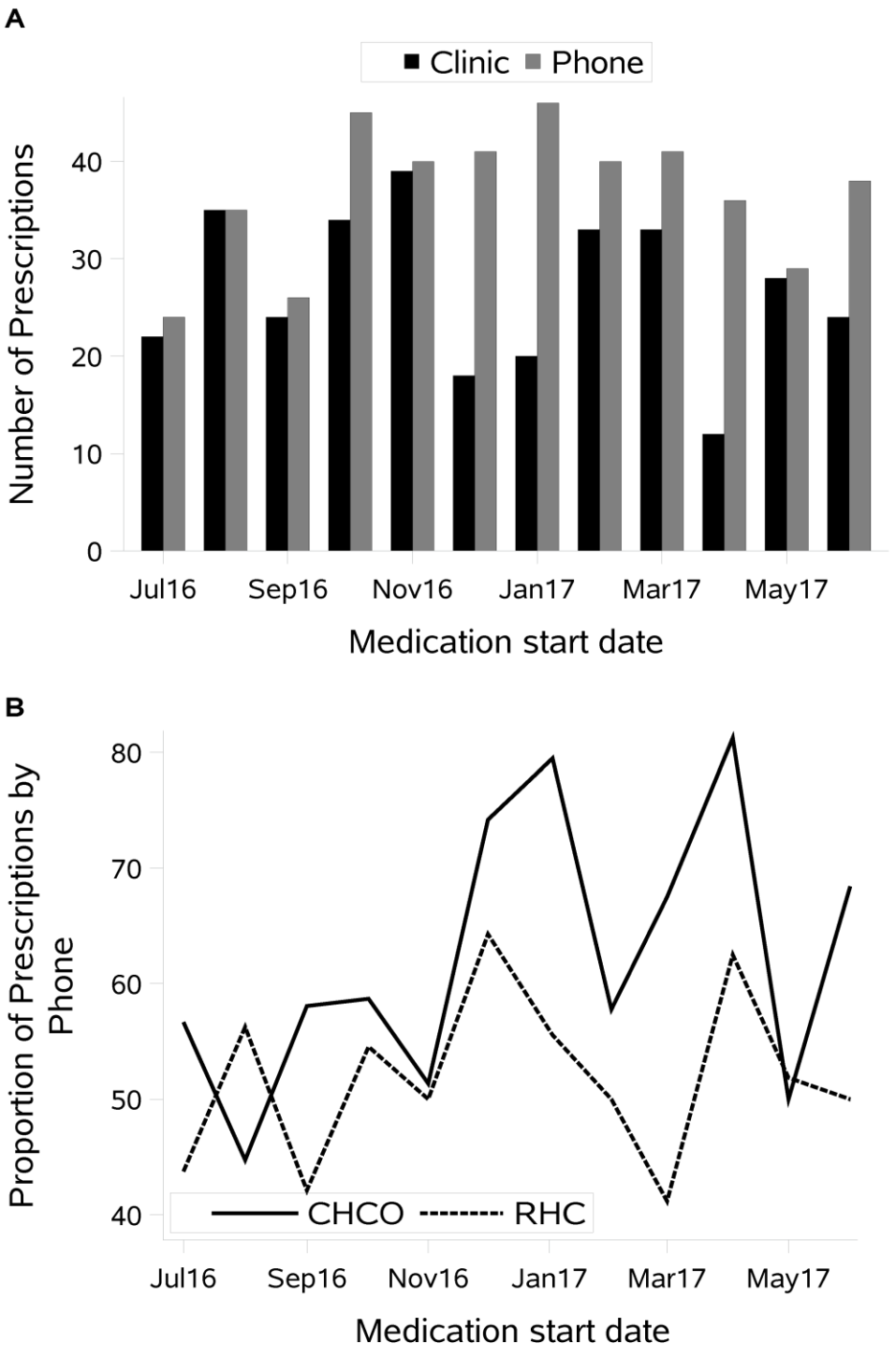
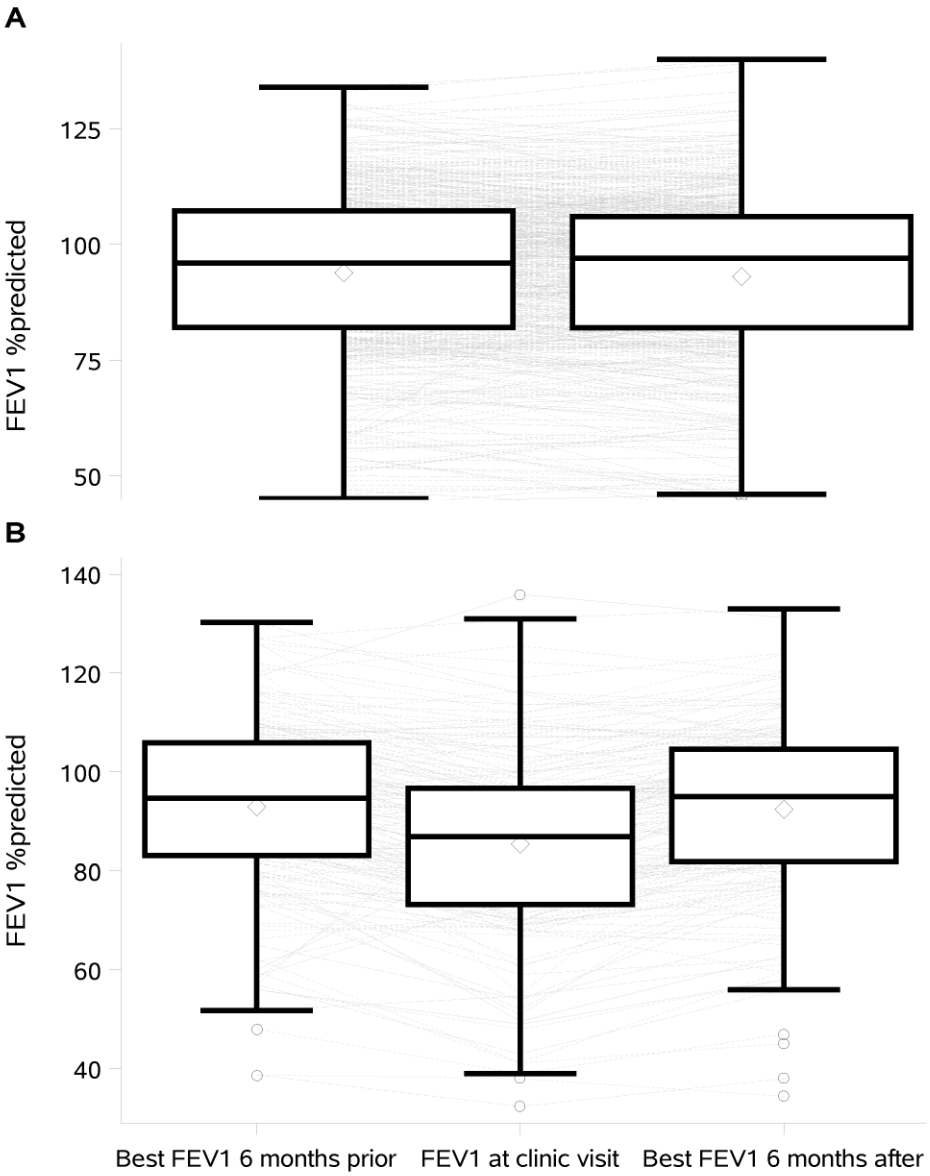


Figure 3: **Pulmonary function outcomes.** Changes in FEV_1 % predicted around antibiotic treatment are shown for a) the overall cohort (n = 670 encounters) and b) the subset of those prescribed antibiotics in clinic with FEV_1% predicted available at all three time points (n = 173). ◊ indicates mean values; boxes represent 25^{th}-75^{th} percentiles; the horizontal line represents the median value; the whiskers represent the 95^{th} percentile.



Table

Table 1: Demographics

	Children's Hospital Colorado	Riley Hospital for Children	Combined	p-value[d]
Number of subjects (% of total CF center population 6-17 years)	180 (77%)	132 (78%)	312	
Female sex, n (%)	94 (52%)	67 (51%)	161 (52%)	0.80
Age in years, median (IQR)[a]	11 (9, 14)	12 (9, 15)	12 (9, 14)	0.36
Caucasian race	171 (95%)	125 (95%)	296 (95%)	0.90
Hispanic ethnicity	25 (14%)	4 (3%)	29 (9%)	**<0.01**
Genotype:				
F508/F508	93 (52%)	81 (61%)	174 (56%)	0.23
F508/Other	72 (40%)	43 (33%)	115 (37%)	
Other/Other	15 (8%)	8 (6%)	23 (7%)	
Microbiology[b]				
Pseudomonas aeruginosa	51 (28%)	39 (30%)	90 (29%)	0.82
MSSA	131 (73%)	83 (63%)	214 (69%)	0.06
MRSA	22 (12%)	41 (31%)	63 (20%)	**<0.01**

H. influenza	60 (33%)	6 (5%)	66 (21%)	<**0.01**
Stenotrophomonas maltophilia	33 (18%)	20 (15%)	53 (17%)	0.46
Baseline FEV_1 % predicted,[c] median (IQR)	96 (85, 108) (n = 166)	98 (86, 106) (n = 117)	97 (85, 107)	0.94
Number of oral antibiotic courses, median (range)	2 (1, 9)	2 (1, 10)	2 (1, 10)	0.87

[a] age of subject on July 1, 2016 (start of study)
[b] from cultures within one year prior to first oral antibiotic treatment (not mutually exclusive)
[c] highest FEV_1 % predicted 6 months prior to first oral antibiotic treatment
[d] p-values compare demographics between sites using either chi-square or Wilcoxon rank sum