



Jordana Hoppe ORCID iD: 0000-0002-1588-4852

Daniel Hinds ORCID iD: 0000-0002-1291-741X

Wayne Morgan ORCID iD: 0000-0002-6346-8140

Edith Zemanick ORCID iD: 0000-0002-7507-9337

Don Sanders ORCID iD: 0000-0001-6265-6249

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

Jordana E. Hoppe MD^a, Daniel M. Hinds MD^{a,b}, Adrienne Colborg MD^a, Brandie D Wagner PhD^{a,c}, Wayne J. Morgan MD^d, Margaret Rosenfeld MD^{e, f}, Edith T. Zemanick MD^a, Don B. Sanders MD^b

^aDepartment of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora CO USA; ^bDepartment of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children, Indianapolis IN USA; ^cDepartment of Biostatistics and Informatics, University of Colorado School of Public Health, Aurora CO USA; ^dDepartment of Pediatrics, University of Arizona College of Medicine, Tucson AZ USA; ^eDepartment of Pediatrics, University of Washington School of Medicine, Seattle WA USA; ^fDivision of Pulmonary Medicine, Seattle Children's Hospital, Seattle, WA USA

Corresponding author:

Jordana E. Hoppe, MD

Children's Hospital Colorado

13123 E 16th Avenue, B-395

Aurora CO 80045

Phone: 720-777-6181; Fax: 720-777-7284

jordana.hoppe@childrenscolorado.org

Sources of Support: This work was supported by the Cystic Fibrosis Foundation (SANDERS18A1, HOPPE16A0)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ppul.25092.

This article is protected by copyright. All rights reserved.

Conflicts of Interest: No conflicts of interest reported by the authors

Keywords: Pulmonary exacerbation, antibiotic, pulmonary function testing, hospitalization, cystic fibrosis

Abbreviated Title: Oral antibiotic prescribing patterns for CF PEx

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. FEV₁ 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 FEV₁ returning to near their

This article is protected by copyright. All rights reserved.

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 outcomes³⁻⁶. 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 (FEV₁) measurements and outpatient PEX treatment⁷. However, treatment guidelines often do not consider remote monitoring

for PEx and their treatment when objective measurements including FEV₁ 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 treatment⁸⁻¹². 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. Secondly, we sought to evaluate if there is a difference in PEx outcomes 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 CF¹³, 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 from July 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 FEV₁ 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 higher¹⁶, 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 prescriptions of different antibiotic classes on risk of hospitalization. Subjects were matched one-to-one using a Mahalanobis distance on the propensity score¹⁷ 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 FEV₁ 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.

Accepted Article

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 FEV₁ 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 *Stenotrophomonas maltophilia* 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 FEV₁ % 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 FEV₁ % 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. FEV₁ recovered to within 90% of baseline in 87% of encounters and >100% of baseline in 44% of encounters. The mean (sd) recovery of FEV₁ was 99.6% (12.2%) and did not differ between clinic and phone encounters (E-Image 2, E-Table 6). Percent FEV₁ recovery 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 FEV₁ recovery, but older age and higher baseline FEV₁ were associated with worse recovery (E-Table 7).

In the subset of encounters where antibiotics were prescribed in clinic ($n = 361$), 173 included FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁% >90% of baseline. Among the encounters at which antibiotics were prescribed but no symptoms recorded (11.5%), the mean (sd) drop in FEV₁ 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 antibiotics¹. 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 FEV₁ 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 *Haemophilus influenzae*. Heterogeneity in IV antibiotic choice for CF pulmonary exacerbations has also been demonstrated for pediatric patients despite existing national guidelines for PEx treatment¹⁸. 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 hospitalization¹⁹. 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 antibiotics⁴, 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 FEV₁ (~79%) in the prior study⁴. 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 disease¹, there are limited studies describing FEV₁ outcomes following this treatment³⁻⁶. 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 FEV₁ 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 outcomes⁵. 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 exacerbations⁵. 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 FEV₁ within 6 months was less likely in those who were older and had a higher baseline FEV₁ which contrasts with prior studies showing older patients^{3,20} and those with higher baseline FEV₁³ were more likely to recover following exacerbation treatment. However, these differences may be related to the timing of FEV₁ measurements and longer-term (within six month) versus shorter-term recovery. In children, higher baseline lung function is a risk factor for FEV₁ decline²¹, 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 FEV₁ 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 expands²².

References

1. Wagener JS, Rasouliyan L, VanDevanter DR, Pasta DJ, Regelman WE, Morgan WJ, Konstan MW, Investigators, Coordinators of the Epidemiologic Study of Cystic F. Oral, inhaled, and intravenous antibiotic choice for treating pulmonary exacerbations in cystic fibrosis. *Pediatric pulmonology* 2013;48:666-73.
2. Sanders DB, Ostrenga JS, Rosenfeld M, Fink AK, Schechter MS, Sawicki GS, Flume PA, Morgan WJ. Predictors of pulmonary exacerbation treatment in cystic fibrosis. *Journal of cystic fibrosis: official journal of the European Cystic Fibrosis Society* 2019.
3. Hoppe JE, Wagner BD, Accurso FJ, Zemanick ET, Sagel SD. Characteristics and outcomes of oral antibiotic treated pulmonary exacerbations in children with cystic fibrosis. *J Cyst Fibros* 2018;17:760-8.
4. Briggs EC, Nguyen T, Wall MA, MacDonald KD. Oral antimicrobial use in outpatient cystic fibrosis pulmonary exacerbation management: a single-center experience. *Clin Respir J* 2012;6:56-64.
5. Stanojevic S, McDonald A, Waters V, MacDonald S, Horton E, Tullis E, Ratjen F. Effect of pulmonary exacerbations treated with oral antibiotics on clinical outcomes in cystic fibrosis. *Thorax* 2016.
6. Ratjen F, Waters V, Klingel M, McDonald N, Dell S, Leahy TR, Yau Y, Grasemann H. Changes in airway inflammation during pulmonary exacerbations in patients with cystic fibrosis and primary ciliary dyskinesia. *The European respiratory journal* 2016;47:829-36.
7. Schechter MS, Schmidt HJ, Williams R, Norton R, Taylor D, Molzhon A. Impact of a program ensuring consistent response to acute drops in lung function in children with cystic fibrosis. *J Cyst Fibros* 2018;17:769-78.
8. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, Griese M, McKone EF, Wainwright CE, Konstan MW, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *The New England journal of medicine* 2011;365:1663-72.
9. Rowe SM, Heltshe SL, Gonska T, Donaldson SH, Borowitz D, Gelfond D, Sagel SD, Khan U, Mayer-Hamblett N, Van Dalfsen JM, et al. Clinical mechanism of the cystic

fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. *American journal of respiratory and critical care medicine* 2014;190:175-84.

10. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, Colombo C, Davies JC, De Boeck K, Flume PA, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *The New England journal of medicine* 2015;373:220-31.
11. Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, Wang LT, Ingenito EP, McKee C, Lu Y, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *The New England journal of medicine* 2017;377:2013-23.
12. Middleton PG, Mall MA, Drevinek P, Lands LC, McKone EF, Polineni D, Ramsey BW, Taylor-Cousar JL, Tullis E, Vermeulen F, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *N Engl J Med* 2019;381:1809-19.
13. Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, Howenstine M, McColley SA, Rock M, Rosenfeld M, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *J Pediatr* 2017;181S:S4-S15 e1.
14. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG, Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol* 1993;15:75-88.
15. Hankinson JL, Kinsley KB, Wagner GR. Comparison of spirometric reference values for Caucasian and African American blue-collar workers. *J Occup Environ Med* 1996;38:137-43.
16. Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Respir Crit Care Med* 2010;182:627-32.
17. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265-81.
18. Cogen JD, Oron AP, Gibson RL, Hoffman LR, Kronman MP, Ong T, Rosenfeld M. Characterization of Inpatient Cystic Fibrosis Pulmonary Exacerbations. *Pediatrics* 2017;139.
19. Sanders DB, Solomon GM, Beckett VV, West NE, Daines CL, Heltshe SL, VanDevanter DR, Spahr JE, Gibson RL, Nick JA, et al. Standardized Treatment of Pulmonary Exacerbations (STOP) study: Observations at the initiation of intravenous antibiotics for cystic fibrosis pulmonary exacerbations. *J Cyst Fibros* 2017;16:592-9.

20. Morgan WJ, Wagener JS, Pasta DJ, Millar SJ, VanDevanter DR, Konstan MW, Scientific Advisory Group I, Coordinators of the Epidemiologic Study of Cystic F. Relationship of Antibiotic Treatment to Recovery after Acute FEV1 Decline in Children with Cystic Fibrosis. *Annals of the American Thoracic Society* 2017;14:937-42.

21. Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, Stokes DC, Wohl ME, Wagener JS, Regelman WE, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr* 2007;151:134-9, 9 e1.

22. Compton M, Soper M, Reilly B, Gettle L, List R, Bailey M, Bruschwein H, Somerville L, Albon D. A Feasibility Study of Urgent Implementation of Cystic Fibrosis Multidisciplinary Telemedicine Clinic in the Face of COVID-19 Pandemic: Single-Center Experience. *Telemed J E Health* 2020.

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.

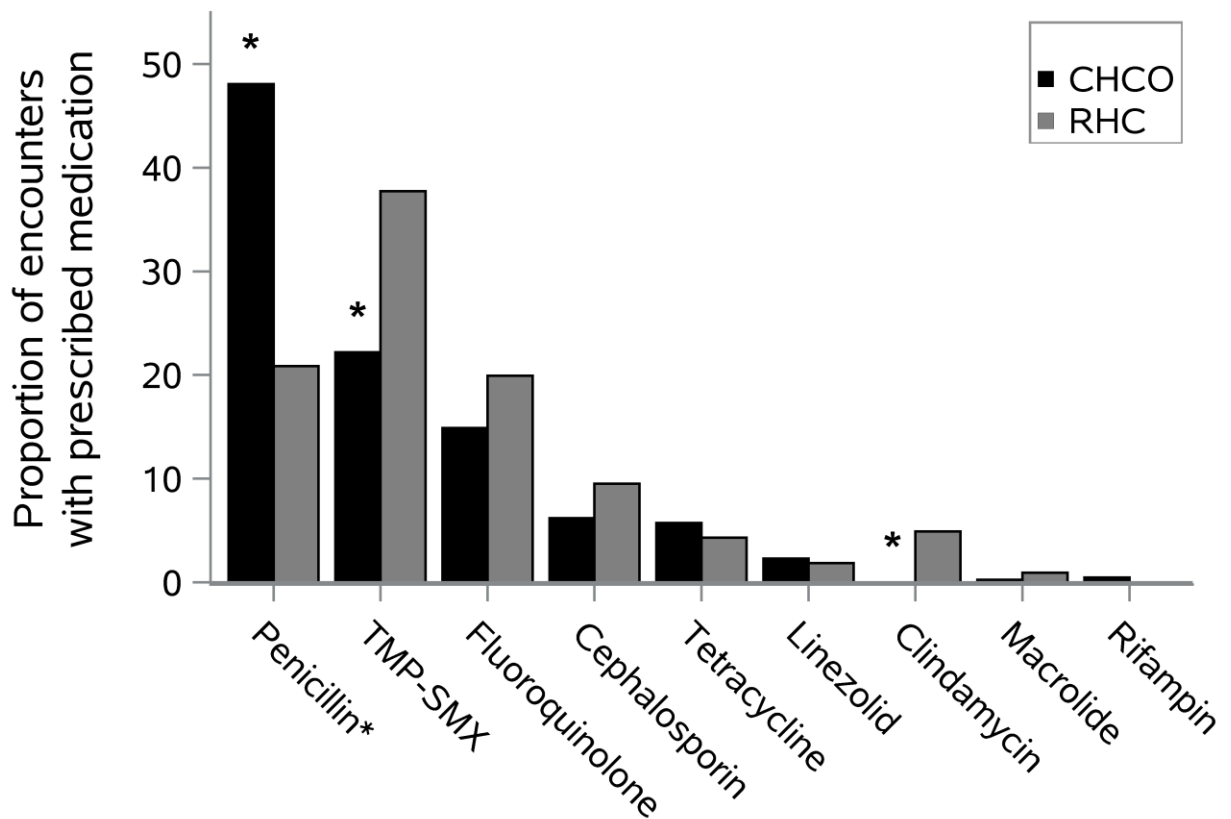


Figure 2: **Antibiotic prescriptions by month.** a) The number of antibiotic prescriptions by month prescribed in clinic and over the phone at the two centers combined. b) The proportion of the total prescriptions by month prescribed over the phone at CHCO and RHC.

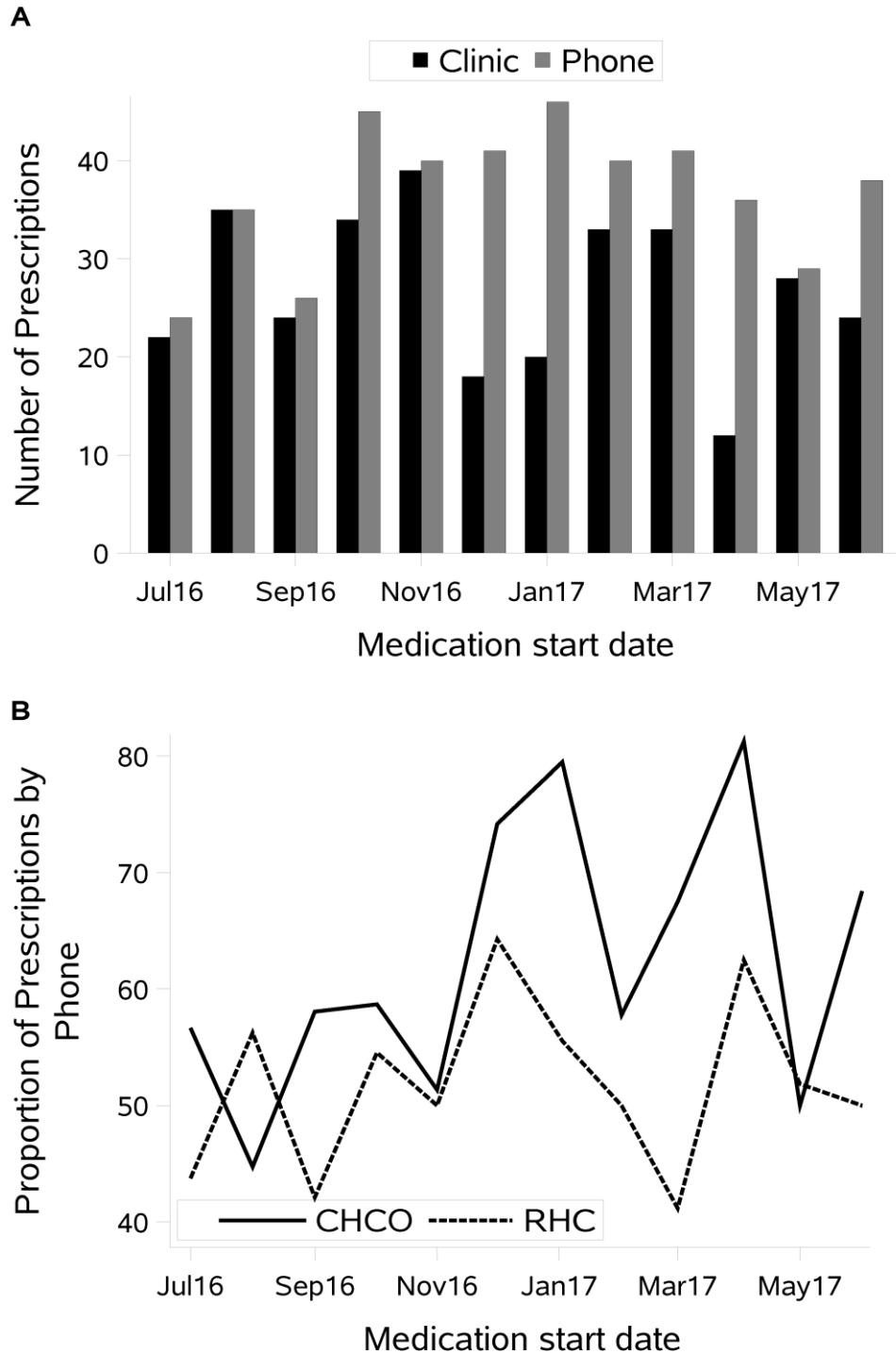
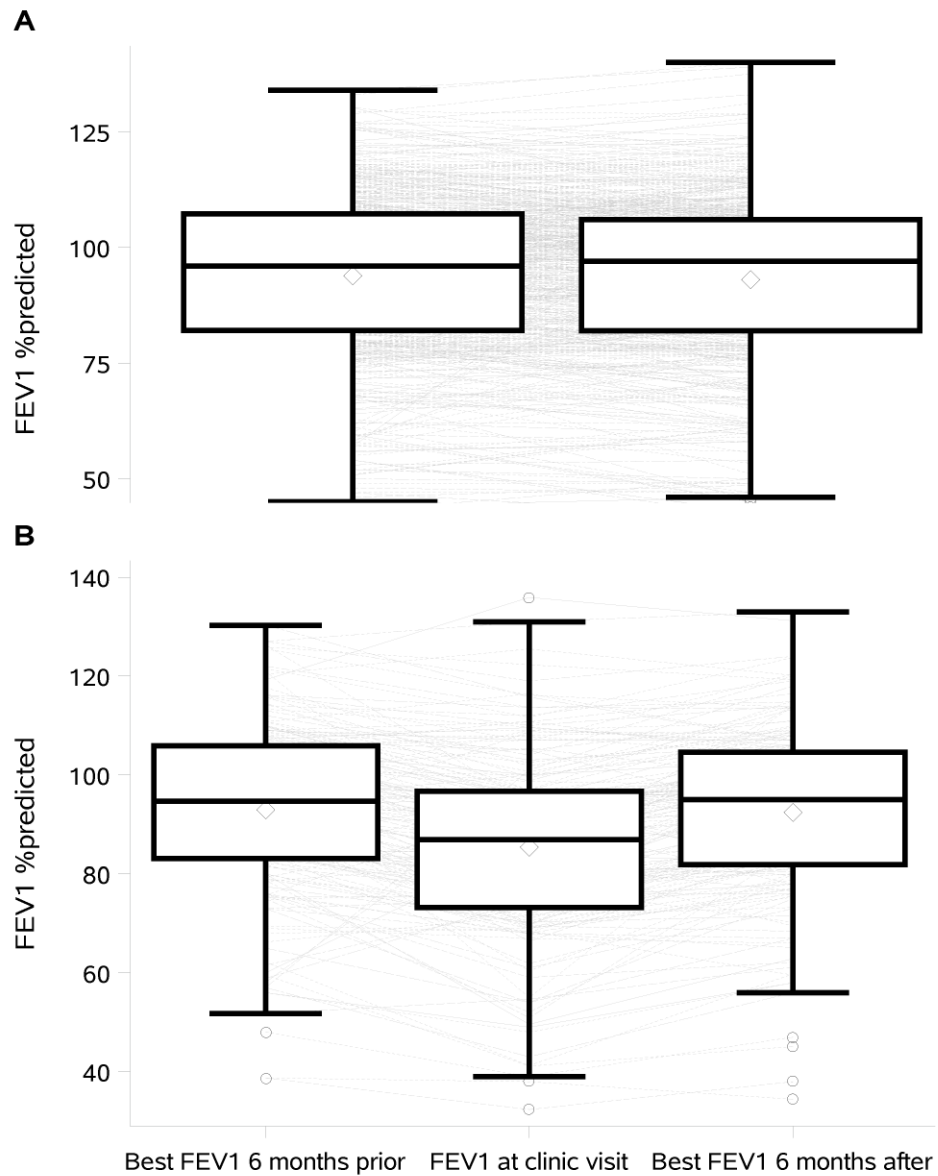


Figure 3: **Pulmonary function outcomes.** Changes in FEV₁ % predicted around antibiotic treatment are shown for a) the overall cohort (n = 670 encounters) and b) the subset of those prescribed antibiotics in clinic with FEV₁% predicted available at all three time points (n = 173). \diamond indicates mean values; boxes represent 25th-75th percentiles; the horizontal line represents the median value; the whiskers represent the 95th 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				
<i>Pseudomonas aeruginosa</i>	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 FEV₁ % predicted 6 months prior to first oral antibiotic treatment

^d p-values compare demographics between sites using either chi-square or Wilcoxon rank sum