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Measuring the impact of an empiric antibiotic algorithm for pulmonary exacerbation in children and young adults with cystic fibrosis

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Abstract

Background: Antimicrobial stewardship is a systematic effort to change prescribing attitudes that can provide benefit in the provision of care to persons with cystic fibrosis (CF). Our objective was to decrease the unwarranted use of broad-spectrum antibiotics and assess the impact of an empiric antibiotic algorithm using quality improvement methodology.

Methods: We assembled a multidisciplinary team with expertise in CF. We assessed baseline antibiotic use for treatment of pulmonary exacerbation (PEx) and developed an algorithm to guide empiric antibiotic therapy. We included persons with CF admitted to Children's National Hospital for treatment of PEx between January 2017 and March 2020. Our primary outcome measure was reducing unnecessary broad-spectrum antibiotic use, measured by use consistent with the empiric antibiotic algorithm. The primary intervention was the initiation of the algorithm. Secondary outcomes included documentation of justification for broad-spectrum antibiotic use and use of infectious disease (ID) consult.

Results: Data were collected from 56 persons with CF who had a total of 226 PEx events. The mean age at first PEx was 12 (SD 6.7) years; 55% were female, 80% were white, and 29% were Hispanic. After initiation of the algorithm, the proportion of PEx with antibiotic use consistent with the algorithm increased from 46.2% to 79.5%. Documentation of justification for broad-spectrum antibiotics increased from 56% to 85%. Use of ID consults increased from 17% to 54%.

The data from this manuscript has been presented at the following meetings: 1. Kennedy C, Greenberg I, Perez G, Chaney H, Sami I, Ogunlesi F, Koumbourlis AC, Hammer B, Hamdy R, Cogen J, Payne A, Hahn A. Measuring the Impact of an Empiric Antibiotic Algorithm for Pulmonary Exacerbation in Children and Young Adults with Cystic Fibrosis. Oral presentation at the American Federation for Medical Research Eastern Regional Meeting, April 2, 2021, Washington DC. 2. Kennedy C, Greenberg I, Perez G, Chaney H, Sami I, Ogunlesi F, Koumbourlis AC, Hammer B, Hamdy R, Cogen J, Payne A, Hahn A. Measuring the Impact of an Empiric Antibiotic Algorithm for Pulmonary Exacerbation in Children and Young Adults with Cystic Fibrosis. e-Poster presentation at the American Thoracic Society Meeting May 14–19, 2021.

Conclusion: Antimicrobial stewardship initiatives are beneficial in standardizing care and fostering positive working relationships between CF pulmonologists, ID physicians, and pharmacists.

KEYWORDS
antibacterial agents, cystic fibrosis, pediatrics, quality improvement

1 | INTRODUCTION

Cystic fibrosis (CF), an autosomal recessive disease affecting more than 30,000 individuals in the United States,[1] is characterized by a dysfunctional ATP-gated chloride channel in the airways, pancreas, and other organs.[2] Pulmonary disease, presenting with increasing respiratory symptoms and eventual respiratory failure, remains the major cause of morbidity and mortality for persons with CF.[2] Lung function decline is exacerbated by recurrent episodes of lung infection and inflammation referred to as pulmonary exacerbations (PEx), which are often treated with antibiotic therapy.[3,4] Despite the ubiquitous and repetitious nature of PEx, there is not a universal, standardized definition to diagnose these events although most definitions include an increase in respiratory symptoms and/or an acute decrease in lung function.[5,6] PEx treatment goals typically include recovery of lost lung function and improvement of PEx symptoms.[5,7]

Antibiotic therapy has long been the mainstay of PEx treatment, and national consensus guidelines recommend an anti-pseudomonal beta-lactam and tobramycin for PEx treatment among people with CF and chronic *Pseudomonas aeruginosa* endobronchial infection.[3] Guidance for bacterial infections beyond *P. aeruginosa* or polymicrobial infections are often based on the intrinsic susceptibility of those organisms.[8] As current consensus supports the use of bacterial species but not specifically susceptibility data in selecting antibiotic therapy,[9] this would not support the use of frequent broad-spectrum antibiotic courses unless a person with CF has not responded to narrow-spectrum antibiotics in the recent past. Furthermore, while early infection with *P. aeruginosa* can be eradicated,[10] chronic infection can predispose to the development of increased antibiotic resistance due to strong selective pressure.[11] In prior studies, the treatment of antibiotic-resistant bacteria with resistant antibiotics has still led to overall improvement in the respiratory symptoms/pulmonary function of persons with CF, as cultured antibiotic resistance has been demonstrated to be less predictive in persons with CF with chronic infections,[12,13] leading to further difficulty in establishing clear guidelines for PEx treatment in persons with CF.

Despite a national consensus guideline for antibiotic treatment, prior research and systematic reviews have repeatedly demonstrated a long-standing lack of sufficient evidence for empiric antibiotic therapy recommendations.[3,14,15] This has led to significant variation in prescribing practices across CF care centers in the United States.[7,16] At our institution we also identified a wide array of antibiotics selected to treat PEx, reflecting a lack of standardized PEx treatment guidelines on optimal antibiotic selection.[17] Using the framework of antimicrobial stewardship, we developed an empiric antibiotic algorithm as a quality improvement initiative to develop a consistency amongst providers in prescribing empiric intravenous (IV) antibiotic therapy for PEx events. The aim of this quality improvement project was to decrease the unwarranted use of broad-spectrum antibiotics for treatment of PEx in persons with CF.

2 | MATERIALS AND METHODS

2.1 | Context

This quality improvement project was conducted at the Children's National Hospital, a tertiary-care hospital with an accredited CF center that serves the metropolitan Washington, DC, area. Pediatric patients and young adults up to age 26 are admitted to our free-standing children's hospital. IRB approval for routine collection of demographic and clinical data around the time of PEx in persons with CF was obtained from Children's National Hospital (Pro6781, December 8, 2015). Participants ≥18 years old provided written consent, and written parental consent was obtained for patients <18 years old. Assent was obtained from children between the ages of 11 and 17 years. This data repository was used to assess baseline antibiotic use and the impact of our quality improvement initiative on IV antibiotics used for PEx treatment between January 1, 2017 and March 31, 2020. Demographics to describe the population were taken at the time of the first pulmonary exacerbation. Disease stage was determined by the participant's best percent predicted. forced expiratory volume in one second ($ppFEV_1$) in the 6 months before their first pulmonary exacerbation during the project period.[18]

2.2 | Intervention

We assembled a multidisciplinary team of pulmonologists, infectious disease (ID) physicians, and pharmacists with expertise in CF at Children's National Hospital to develop the empiric antibiotic algorithm beginning in July 2017. This working group developed an algorithm that provided antibiotic recommendations for microbial species frequently seen in persons with CF, specifically *P. aeruginosa*, *Staphylococcus aureus* (both methicillin-sensitive, MSSA, and methicillin-resistant, MRSA), *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and *Burkholderia cepacia* complex (Figure 1). The resulting algorithm was the product of discussion and compromise amongst key stakeholders, influenced by

expertise, current practices,[19] and evidence-based literature review.[3,8,20–25] A preference for antibiotics without broad-spectrum anaerobic activity (hereafter referred to as "narrow-spectrum" and previously defined by our group[26]) was designated by listing beta-lactam antibiotics to be used in order of preference, with indications for the use of broad-spectrum antibiotics noted to include resistance to narrow-spectrum antibiotics on prior respiratory cultures and/or history of prior infection with *A. xylosoxidans* or *B. cepacia* complex based on previously published reviews.[8] The algorithm was based on anti-pseudomonal beta-lactams as the backbone of treatment,[24] with the addition of other antibiotics as necessary for coverage of multiple organisms identified in culture. The algorithm alluded to a preference of more narrow-spectrum beta-lactam therapy by listing the beta-lactams in order of preference and supported double coverage of more resistant and difficult to treat gram-negative infections. As an example, the preferred backbone therapy for child with *P. aeruginosa* was ceftazidime + tobramycin. If there was also a history of MRSA, vancomycin would be added to this regimen. Combination antibiotic therapy was also recommended for *Stenotrophomonas*, *Achromobacter*, and *Burkholderia* infections. This algorithm was presented to and approved by the Children's National Hospital Antimicrobial Subcommittee of Pharmacy and Therapeutics in June 2018 and was thereafter posted to our local formulary and intranet in July 2018. Additional events that took place on and around that date included creation of a dedicated CF ID consult service (April 2018) and restriction of carbapenem antibiotics by the Antimicrobial Stewardship Program (March 2019).

2.3 | Study of the intervention

This project utilized a subset of the study population from the data repository described above, initially totaling 120 persons with CF (Figure S1). Those persons in our data repository who did not meet the definition for CF (positive sweat test and/or positive genotype) during the entire study period were excluded. We then filtered the data set to identify those persons with CF prescribed IV antibiotics in both the inpatient and outpatient settings. As the intervention was based on education and repeated interactions with pediatric CF providers, persons treated by adult CF providers through a separate multidisciplinary outpatient clinic at our campus were excluded. Additionally, persons with CF who were hospitalized for indications other than a PEx (e.g., bowel

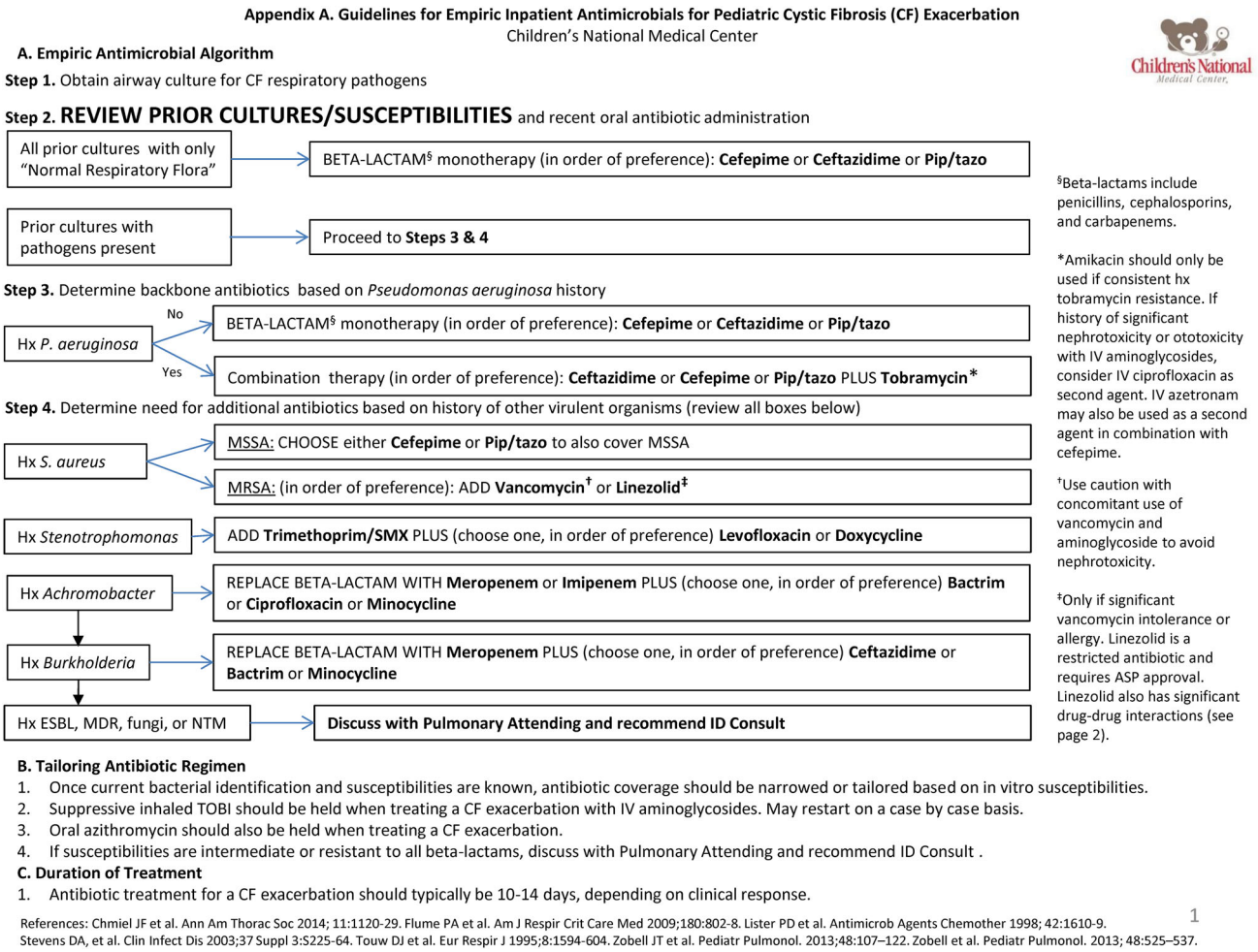

FIGURE 1 Empiric antibiotic algorithm. This empiric antibiotic algorithm was focused on inpatient intravenous antibiotic therapy and was in effect from July 2018 through June 2021 [Color figure can be viewed at wileyonlinelibrary.com]

obstruction) were also excluded. Finally, persons with CF who received treatment for microorganisms not included within the parameters of the empiric algorithm (e.g., nontuberculous mycobacteria) were excluded. Bacteria identified in culture in the 6 months before the PEx were considered as the reference point to which empiric antibiotic selection in alignment with the algorithm was compared. The algorithm did not specify a time frame for review of prior cultures to allow for provider autonomy. The 6-month time point was selected as it was assumed most providers would have used that information in their decision-making.[9] To address the fact that some providers would have based their antibiotic selection on more distant cultures, history of all prior bacterial infections were also noted for secondary analyses.

2.4 | Outcome measures, process metrics, and balancing measures

The primary outcome measure was the proportion of broad-spectrum antibiotics used for PEx treatment in persons with CF for each PEx event. Each antibiotic therapy was determined to be either narrow- or broad-spectrum based on the use of IV beta-lactam therapy and its spectrum of activity against anaerobic bacteria.[26] Narrow-spectrum beta-lactams included ceftazidime, cefepime, ceftriaxone, and oxacillin, while broad-spectrum beta-lactams included piperacillin/tazobactam, meropenem, imipenem/cilastatin, ceftaroline, and meropenem/vaborbactam. If a patient did not start on a beta-lactam therapy, the treatment was considered narrow-spectrum for the purposes of categorization ($n = 9$ of 226). Secondary outcome measures included the total length of hospital stay, total antibiotic duration, and occurrence of acute kidney injury (AKI) while on antibiotic therapy. AKI was defined as a serum creatinine value that either increased from baseline by 150% within 7 days or had an absolute increase by 0.3 mg/dl within 48 h.[27] We also assessed the proportion of antibiotic courses where the antibiotics were changed from the empiric antibiotics selected and how long the empiric antibiotics were given. Process metrics included the proportion of PEx events prescribed empiric therapy consistent with the empiric antibiotic algorithm and the proportion of persons with CF who received an ID consult (which was additionally guided by the algorithm for persons with CF with multi-drug resistant infections). We also assessed, as a process metric, the documentation of justification of broad-spectrum antibiotic use when prescribed for one of the following reasons: resistant organism on prior culture, prior allergic reaction, prior drug toxicity, or prior clinical failure. Balancing measures included hospital days, antibiotic days, the proportion of PEx events where the person with CF received greater than 15 days of antibiotic therapy and the proportion of PEx events where the person with CF required readmission to a hospital within 30 days of treatment completion for another PEx event. These balancing measures served as a proxy for treatment failure. We also assessed the proportion of PEx events where the person with CF had a ppFEV$_1$ within 90% of their best value in the preceding 6 months at the end of antibiotic therapy for treatment of PEx.

2.5 | Analysis

Statistical process control charts tracked outcome measures over time and were created by using QI Macros for Excel. The impact of the intervention was studied retrospectively. Special cause variation was identified by standard criteria.[28] The baseline period assessed was from January 2017 through June 2018, and the intervention period assessed was July 2018 through March 2020. P-charts were used for the monthly outcome measures of the following: broad-spectrum antibiotic use; frequency of the empiric antibiotic treatment that was in line with the Empiric Antibiotic Algorithm; and proportion of PEx events with an ID consult. Descriptive statistics were reported for secondary outcome measures (hospital days, antibiotic days, and AKI), process measures (documentation of justification for broad-spectrum antibiotics), and balancing measures (antibiotic therapy >15 days and hospital readmission within 30 days). Descriptive statistics were also reported for demographics, PEx characteristics, bacteria grown in CF respiratory culture, antibiotic use, and pulmonary function testing results. All studies were obtained at the discretion of the primary pulmonologist, including pulmonary function tests. These were typically obtained at hospital admission and between days 10 and 14 before stopping antibiotic therapy but were not always obtained on the last day of antibiotic therapy. If treatment courses were continued for longer than 14 days, the last pulmonary function test obtained before stopping antibiotic therapy was used.

3 | RESULTS

3.1 | Demographics

The quality improvement project assessed the antibiotic treatment courses for 226 PEx episodes in 56 persons with CF. Twenty-five were prescribed in the outpatient setting only (10 in the baseline period and 15 during the intervention). The remaining courses were all initially prescribed in the inpatient setting. The mean age at first PEx during the project was 12 years (range 3 months to 26 years), 55% were female, 80% were white, and 71% were non-Hispanic (Table 1). Forty-three percent of study participants were F508del homozygous and 37.5% were F508del heterozygous. Disease stage (based on baseline ppFEV$_1$) was also assessed at the time of first PEx (Table 1).[18] For each person, there was an average of 3.96 PEx, with a range of 1–21 PEx events during the project period. Age, BMI, CF transmembrane conductance regulator gene (CFTR) modulator use, and inhaled antibiotic use remained steady across the baseline and intervention periods (Table S1).

3.2 | Impact of the intervention

A monthly P-chart to assess broad-spectrum antibiotic use found no shifts in use from the baseline period following the initiation of an empiric algorithm (Figure 2A). When looking at individual antibiotics, piperacillin/tazobactam was the most frequent broad-spectrum

TABLE 1 Description of the population

	Total cohort ($n = 56$)
Race (n, %)	
White	45 (80%)
Black	9 (16%)
Other	2 (4%)
Ethnicity (n, %)	
Hispanic	16 (29%)
Non-Hispanic	40 (71%)
Sex (n, %)	
Female	31 (55%)
Male	25 (45%)
CFTR Genotype (n, %)	
F508del homozygous	24 (43%)
F508del heterozygous	21 (38%)
Other	11 (20%)
CF-related co-morbidities (n, %)	
CF-related diabetes	11 (20%)
CF-related liver disease	4 (7%)
Pancreatic Insufficiency	50 (89%)
Age[a] *(n, %)*	
0–5 years	12 (21%)
6–11 years	19 (34%)
12–17 years	12 (21%)
18–26 years	13 (23%)
Disease stage[b] *(n, %)*	
Early ($ppFEV_1 \geq 70\%$)	4 (7%)
Intermediate ($ppFEV_1 < 70\%$ and >40%)	27 (48%)
Advanced ($ppFEV_1 \leq 40\%$)	16 (29%)
N/A	9 (16%)

[a]At first pulmonary exacerbation during the project period.

[b]Determined by their best $ppFEV_1$ in the 6 months before their first pulmonary exacerbation during the project period.

antibiotic selected and its use decreased from 24% in the baseline period to 16% following the intervention (Table S2).

3.3 | Assessment of process measures

Adherence to the empiric antibiotic algorithm based on 6-month culture history increased from 46.2% to 79.5% assessed by a monthly P-chart (Figure 2B). The most common reason for non-adherence fell into the "Other" category ($n = 51$ of 104 empiric antibiotic courses; 49%), which was most often due to using a non-preferred beta-lactam in the absence of antibiotic resistance (e.g., meropenem + tobramycin for a susceptible *P. aeruginosa*) or a bug-drug mismatch (e.g., meropenem + tobramycin with a history of MRSA and *Stenotrophomonas*). This decreased during the intervention compared to the baseline period (37% vs. 57%, Table 2). The next most common reasons for non-adherence were treatment of antibiotic-resistant organisms (33%) followed by targeted antibiotic therapy against (a) specified organism(s) (22%) and antibiotic therapy directed against (an) organism(s) in remote cultures (18%). While there was a >10% decrease in treatment of target organisms during the intervention compared to the baseline period (15% vs. 27%), the other reasons remained steady across the study.

As variability in culture results occurs over time and 78% of patients had a remote history of other infectious pathogens (defined as occurring >6 months in the past), we also evaluated adherence to the empiric antibiotic algorithm based on the history of all prior organisms in culture. Adherence to the empiric antibiotic algorithm was much lower when using this comparative metric at 21% ($n = 178$ of 226 antibiotic courses) and was similar in the baseline period and following the intervention (19% vs. 23%). The most common reason for non-adherence to the empiric antibiotic algorithm based on remote culture data was targeted therapy against (a) specified organism (s) (70%) and was steady between the baseline period and the intervention (66% vs. 75%, Table 2).

The proportion of persons with CF receiving an ID consult increased from 17% to 54% when assessed by a monthly P-chart (Figure 2C). Documentation of justification for using empiric broad-spectrum antibiotic therapy was also evaluated and included history of antibiotic resistance ($n = 42$ of 81), prior clinical failure ($n = 14$ of 81), or prior drug allergy ($n = 3$ of 81). These reasons were more frequently documented following the intervention (56% vs. 85%, Table 3).

3.4 | Balancing measures

Persons with CF were hospitalized for a mean of 9 days and had a mean total antibiotic course of 17 days, and this remained steady (Table 3). Likewise, the proportion of persons with CF who experienced AKI was 2% and remained steady. Forty-two percent of persons with CF received antibiotic therapy for more than 15 days and 22% were readmitted for PEx within 30 days. This also remained steady from the baseline period through the intervention period.

As a 22% readmission rate seemed higher than expected, we performed a sub-analysis of clinical characteristics associated with readmission. Important differences between those requiring readmission ($n = 49$) and those that did not ($n = 117$) included the following: a higher frequency of intermediate or advanced disease stage (70% vs. 21%), a past history of MRSA infection (45% vs. 21%), antibiotic use in the preceding 30 days (78% vs. 53%), narrow-spectrum antibiotics selected empirically (75% vs. 60%), change in antibiotics during the treatment period (63% vs. 35%), and an ID consult during the hospitalization (51% vs. 27%).

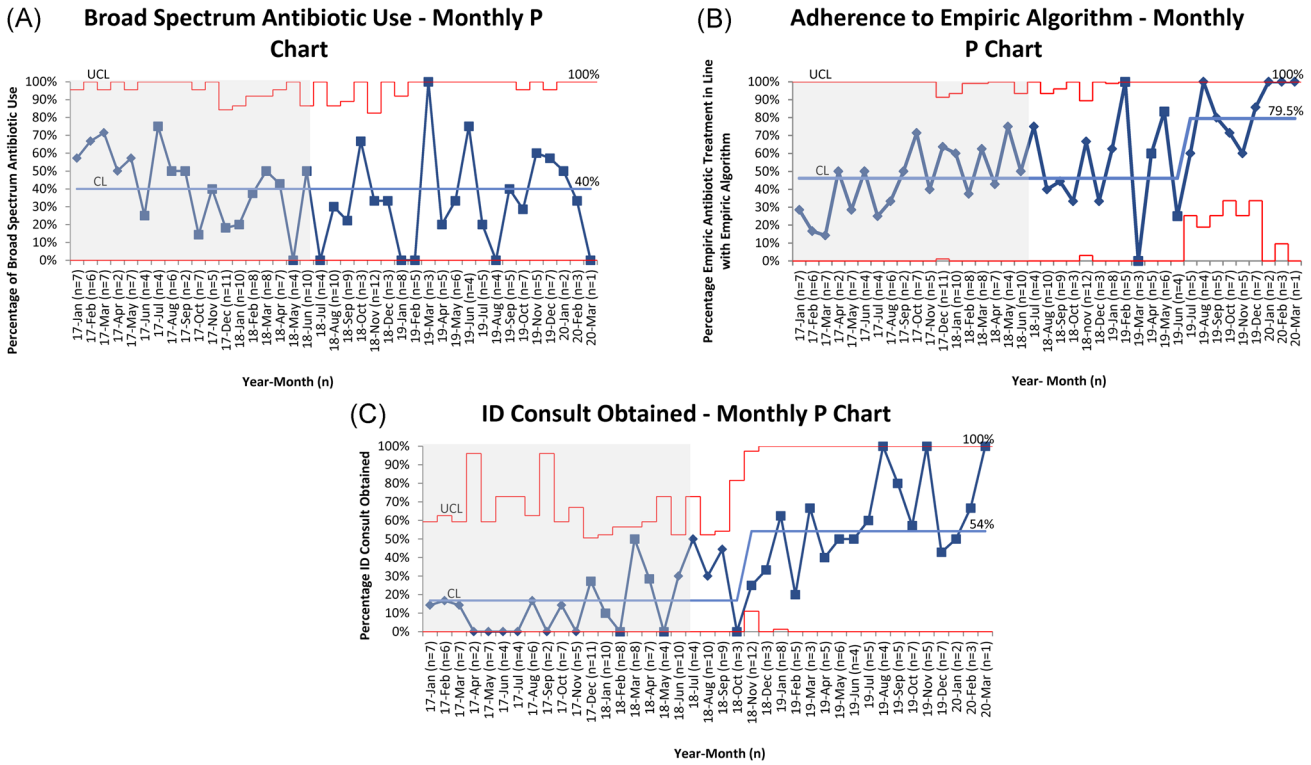

FIGURE 2 P-charts of primary and secondary outcome measures. (A) Broad-spectrum antibiotic use, P-chart for January 2017 to March 2020. (B) Percentage that Empiric Antibiotic Treatment was in line with the Empiric Antibiotic Algorithm, P-chart for January 2017 to March 2020. (C) Percentage that the ID Consult was obtained, P-chart for January 2017 to March 2020. Baseline period is shown in gray.
CL, centerline; UCL, upper control limit [Color figure can be viewed at wileyonlinelibrary.com]

3.5 | Pulmonary function

Pulmonary function results were assessed as percent recovery of baseline lung function at the end of treatment (Figure 3A) and increase in pulmonary function from pulmonary exacerbation to end of treatment (Figure 3B). Overall, 72% ($n = 131$ of 180) recovered at least 90% of their baseline ppFEV$_1$ immediately following PEx treatment and were similar in the baseline and intervention periods. More specifically, the mean (median) percent recovery of baseline ppFEV$_1$ at the end of treatment was 98% (98%) in the baseline group and 93% (95%) following the intervention. Additionally, the mean (median) increase in ppFEV$_1$ from pulmonary exacerbation to end of treatment was 13% (10%) in the baseline period and 10% (8%) following the intervention.

4 | DISCUSSION

With this quality improvement initiative, we demonstrated that the creation of an empiric antibiotic algorithm led to an increase in the use of empiric antibiotics per the algorithm, suggesting that care providers were consistently using the newly developed algorithm to assist their decision-making processes. While the frequency of broad-spectrum antibiotic use did not decrease, we did find that documentation and justification of broad-spectrum antibiotic use significantly increased following the intervention. Consultation with ID physicians also increased. All of these positive changes occurred without an increase in treatment failure. The biggest strength of this project is that these findings suggest antimicrobial stewardship quality improvement initiatives are relevant in the treatment of persons with CF. We found this initiative was extremely beneficial in fostering positive working relationships between pulmonologists, ID physicians, and pharmacists at our institution and resulted in the improved standardization of clinical care. While the role of antimicrobial stewardship in the provision of care to persons with CF is a challenging concept to many CF pulmonologists,[29] implementing antimicrobial stewardship in the context of care to persons with CF provides benefit in this complex patient population.

Antimicrobial stewardship programs are often headed by ID physicians and pharmacists, with the goal of optimizing several facets of antibiotic treatment including preventing bug/drug mismatch, facilitating transition from IV to oral antibiotics, shortening total duration of antibiotic therapy, and reducing the unnecessary use of broad-spectrum antimicrobials.[30] However, several aspects in the treatment of infections with persons with CF can complicate application of these tenets. These include the difficulties in obtaining and interpreting respiratory cultures, the occasional lack of association with antibiotic susceptibility results and clinical response, and the frequent polymicrobial nature of lung infection in persons with CF.[12,13,29] Thus, despite the framework being present few CF clinical

TABLE 2 Empiric antibiotic algorithm non-adherence and comparisons against remote history of bacterial infection

	January 2017 to June 2018 (*n* = 118)	July 2018 to March 2020 (*n* = 108)
Non-adherence, 6-month culture history[a]	**(*n* = 63)**	**(*n* = 41)**
Treating targeted organism(s)	17 (27%)	6 (15%)
Treating resistant organism(s)	22 (35%)	12 (29%)
Treating a remote organism(s)	12 (19%)	7 (17%)
Using appropriate but more narrow-spectrum therapy	2 (3%)	4 (10%)
Antibiotic allergy	0 (0%)	2 (5%)
Prior drug toxicity	0 (0%)	0 (0%)
Prior clinical failure	4 (6%)	8 (20%)
Other[b]	36 (57%)	15 (37%)
Non-adherence, remote culture history[a,c]	**(*n* = 95)**	**(*n* = 83)**
Treating targeted organism(s)	63 (66%)	62 (75%)
Treating resistant organism(s)	22 (23%)	12 (14%)
Treating a remote organism(s)	NA	NA
Using appropriate but more narrow-spectrum therapy	2 (2%)	4 (5%)
Antibiotic allergy	0 (0%)	2 (2%)
Prior drug toxicity	0 (0%)	0 (0%)
Prior clinical failure	4 (4%)	8 (10%)
Other[b]	39 (41%)	18 (22%)

[a]Sum can be greater than 100% as multiple options could be applicable.

[b]Other included any reason not listed above and/or no documentation of the provider's rationale. This was most often due to using a non-preferred beta-lactam in the absence of antibiotic resistance (e.g., meropenem + tobramycin for a susceptible *P. aeruginosa*) or a bug-drug mismatch (e.g., meropenem + tobramycin with a history of MRSA and *Stenotrophomonas*).

[c]Remote culture history is defined as occurring >6 months in the past.

TABLE 3 Secondary outcome measures, process measures, and balancing measures

	January 2017 to June 2018 (*n* = 118)	July 2018 to March 2020 (*n* = 108)
Secondary outcome measures		
Hospital days (mean, *SD*)	9.3 (6.4)	9.6 (9.3)
Total antibiotic days (mean, *SD*)	16.6 (5.9)	17.4 (9)
Empiric antibiotics changed (*n*, %)	47 (40%)	46 (43%)
Empiric antibiotic days (mean, *SD*)	13.9 (7.3)	12.4 (7.1)
Acute kidney injury (*n*, %)	3 (3%)	1 (1%)
Process measures		
Documentation of justification of broad-spectrum antibiotics (*n*, %)	27 of 48 (56%)	30 of 35 (86%)
Balancing measures		
Abx therapy greater >15 days (*n*, %)	53 (45%)	42 (39%)
Hospital readmission in 30 days (*n*, %)	24 (20%)	25 (23%)

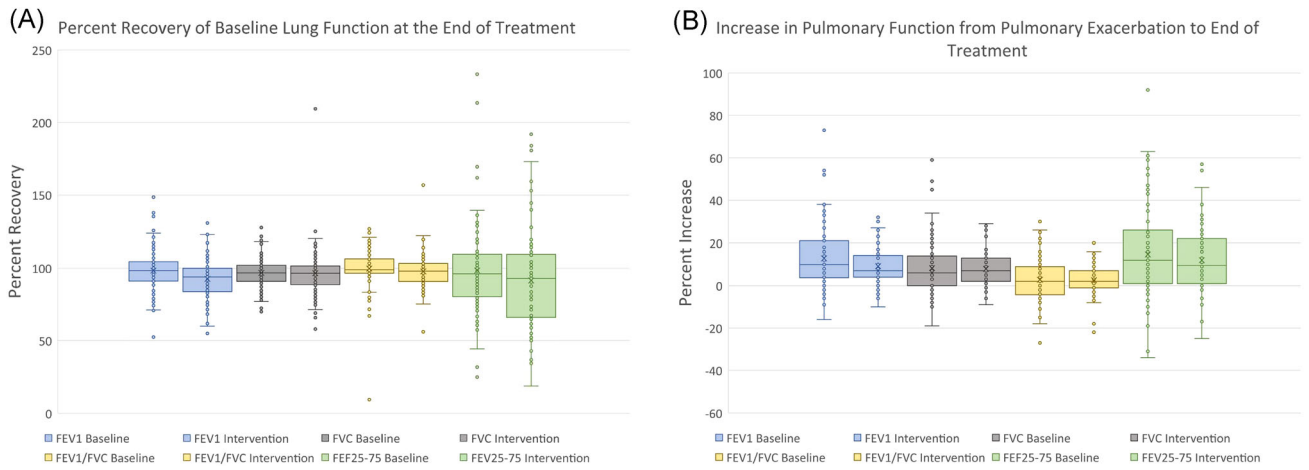

FIGURE 3 Improvement of lung function after pulmonary exacerbation. (A) Percent recovery of baseline lung function at the end of treatment. (B) Increase in pulmonary function from pulmonary exacerbation to end of treatment. FEF25–75, forced expiratory flow 25–75; FEV1, forced expiratory volume in one second; FVC, forced vital capacity [Color figure can be viewed at wileyonlinelibrary.com]

care teams engage with their antimicrobial stewardship programs for fear of restriction of antimicrobials or a lack of recognition of the benefits these relationships could provide for their patients.[29] First and foremost, this quality improvement initiative attests to the positive working relationships that can exist between CF pulmonologists, clinical pharmacists, ID physicians, and microbiologists. While not the focus of this quality improvement intervention, we have witnessed improved communication regarding the need for expanded antimicrobial susceptibility testing against newer antibiotic agents as well as when extended infusion of antibiotics may be beneficial for a given patient's treatment course. This may be related in part to the significant increase in ID consults that occurred after the intervention. Thus, development of an algorithm for empiric PEx treatment in CF has also led to improved coordination of care for persons with CF, which now encompasses an ID physician regularly attending both inpatient and outpatient weekly CF care rounds. In addition, the improved relationships amongst pediatric pulmonologists, ID physicians, and pharmacists have led to collaboration outside direct clinical care, including ID physicians and pharmacists being invited to present continuing medical education lectures on antibiotic treatment in CF and many original research manuscripts that have been published by our group.[17,26,31–33]

The primary aim of this intervention was to decrease the unnecessary use of broad-spectrum antimicrobials in persons with CF. We found that our intervention did not lead to a decrease in the selection of broad-spectrum antibiotics. However, we did find an increase in the documentation for the justification of broad-spectrum antibiotic therapy. These results indicate that engaging antibiotics stewardship experts/leaders do not necessarily lead to a reduction in broad-spectrum antibiotic use that might benefit a subset of persons with CF. We did not perform a cost–benefit analysis of this intervention, but future studies should also consider how such an intervention may or may not decrease health costs of PEx treatment (e.g., balancing antibiotic costs with the costs of additional ID consultations).

A study of 38 CF Foundation accredited pediatric centers across the United States showed there was substantial variability in CF PEx treatment and monitoring practices,[16] as did a study at our own center.[19] Following our intervention, we saw an improvement in the proportion of empiric antibiotic regimens that were consistent with our internally developed algorithm. This was especially true when focusing on the most recent 6-month history as providers were less apt to treat bacteria only grown remotely, likely due to presumed changes in chronic infectious pathogens over time. Importantly, adherence to the algorithm was not associated with an increase in treatment failure. We did not find that our intervention had an impact on the recovery of baseline lung function following treatment of PEx. However, a prior study has shown that about 25% of persons with CF treated with antibiotics for a PEx do not recover to baseline lung function (similar to our results) and suggest these reasons are multifactorial.[34] Further, as these persons with CF all received IV antibiotic therapy, there may be some bias toward increasing pulmonary severity detected in this project compared to the larger cohort of PEx treated with both IV and oral antibiotics. To support these assumptions, we also noticed a higher readmission rate (22%) than would be expected. Those who required readmission were more likely to have intermediate or advanced disease stage, a past history of MRSA infection, antibiotic use within 30 days before the hospitalization, the selection of narrow-spectrum antibiotics empirically followed by a change in antibiotics during the treatment period and an ID consult during the hospitalization. All of these characteristics suggest this population of persons with CF requiring treatment with IV antibiotics during the period of observation had more advanced disease and more difficult to treat infections. Finally, we should note that the majority (59%) of our study participants had antibiotic treatment courses that were considered in both the baseline and intervention groups, and that this was a longitudinal as opposed to a cross-sectional analysis. As CF is a progressive disease, it would not be surprising to see a decrease in pulmonary function and recovery over time in those persons experiencing multiple pulmonary exacerbations.[4]

There were several limitations to our intervention. The first was that while the empiric antibiotic algorithm was published in July 2018, there were no regularly scheduled educational updates as new providers joined our institution. Thus, pediatric residents and pulmonary fellows who are often responsible for ordering antibiotics did not have the benefit of direct education on the algorithm. This limitation was mitigated in part by a clinical pharmacist being part of the care team and increased consultation with ID physicians but may have affected the impact of our initiative. Another limitation in studying the impact of our intervention was the concurrent increase in the number of antibiotics requiring prior authorization for use. With both processes occurring during the same time frame, it is possible that there is confounding in our attribution of the increase in the documentation of justification for use of broad-spectrum antimicrobials to the empiric antibiotic algorithm that may have been due in part to the antibiotic prior authorization requirements. However, carbapenems were the only restricted beta-lactam antibiotics during the intervention. They contributed to 14% of beta-lactams given, and the increase in documentation following the intervention was 30%. Finally, it would be imprudent not to acknowledge the major impacts of highly effective CFTR modulators on the frequency of PEx and the expected changes of the microbial environment in the airway of persons with CF.[35–38] Future interventions will need to be able to adapt to changes in the needs of persons with CF over time, and antimicrobial stewardship programs will be an effective ally.

It should be noted that our empiric antibiotic algorithm was focused on inpatient hospitalizations, and thus the bacterial infections and interventions were *Pseudomonas*-centric as well as focused on more resistant organisms. Limited guidance was provided for other CF pathogens common in younger children such as *Haemophilus influenzae*, in part because this was not a common inpatient infection on review of our local experience.[19] We have recently updated our empiric antibiotic algorithm, in accordance with the principles above, and have included the revised guideline in the supplement (see Figure S2).

In conclusion, this quality improvement initiative led to increased adherence to the empiric antibiotic algorithm, increased documentation of the indication for broad-spectrum antibiotics, and increased consultation with ID physicians without an increase in treatment failure. To sustain these successes, our multidisciplinary team has recently revised and updated our algorithm with plans to create a complementary order set. As more children and young adults at our institution are started on highly effective CFTR modulators and we see a drop in the need for inpatient PEx treatment, development of an algorithm for outpatient treatment may become an unmet need. We would encourage other CF centers to explore their own trends in practice to determine whether a similar intervention may be both feasible and beneficial in the treatment of PEx in persons with CF.

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CONFLICT OF INTERESTS

The authors do not have any financial and personal relationships with other people or organizations that could inappropriately influence (bias) this study.

AUTHOR CONTRIBUTIONS

Charles Kennedy: Data curation (lead), formal analysis (supporting), writing – original draft (lead). Isabella Greenberg: Formal analysis (equal), writing – review and editing (equal). Geovanny F. Perez: Conceptualization (equal), methodology (equal), writing – review and editing (equal). Hollis Chaney: Conceptualization (equal), writing – review and editing (equal). Iman Sami: Conceptualization (equal), writing – review and editing (equal). Folasade Ogunlesi: Conceptualization (equal), writing – review and editing (equal). Anastassios C. Koumbourlis: Conceptualization (equal), writing – review and editing (equal). Benjamin Hammer: Conceptualization (equal), methodology (equal), writing – review and editing (equal). Rana F. Hamdy: Conceptualization (supporting), methodology (supporting), formal analysis (supporting), writing – review and editing (equal). Jonathan D. Cogen: Methodology (supporting), formal analysis (supporting), writing – review and editing (equal). Asha S. Payne: Methodology (equal), formal analysis (equal), writing – review and editing (equal). Andrea Hahn: Conceptualization (equal), methodology (equal), data curation (supporting), formal analysis (equal), writing – original draft (supporting), writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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