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Real-World Outcomes in Cystic Fibrosis Telemedicine Clinical Care in a Time of a Global Pandemic

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ABSTRACT

Background:
During the COVID-19 pandemic, the University of Virginia adult cystic fibrosis (CF) center transitioned from in-person clinical encounters to a model that included interdisciplinary telemedicine. The pandemic presented an unprecedented opportunity to assess the impact of the interdisciplinary telemedicine model on clinical CF outcomes.

Research Question:
What are the clinical outcomes of a care model that includes interdisciplinary telemedicine (IDC-TM) compared to in-person clinical care for persons with cystic fibrosis during the COVID-19 pandemic?

Study Design and Methods:
Adults with CF were included. Pre-pandemic year (PPY) was defined as March 17, 2019 through March 16, 2020 and pandemic year (PY) as March 17, 2020 through March 16, 2021. Subjects were enrolled starting in PY. Pre-pandemic data were gathered retrospectively. Telemedicine visits were defined as clinical encounters via secured video communication. Hybrid visits were in-person evaluations by physician, with in-clinic video communication by other team members. In-person visits were encounters with in-person providers only. All encounters included pre-visit screening. Outcomes were lung function, BMI, exacerbations, and antibiotic use. %FEV1, exacerbations, and antibiotic use were adjusted for the effect of elexacaftor/tezacaftor/ivacaftor (ETI).

Results:
124 subjects participated. 110 subjects were analyzed (mean age 35, range 18-69). 95% had access to telemedicine (n=105). Telemedicine visits accounted for 64% of encounters (n=260), hybrid visits with telemedicine support 28% (n=114), and in-person visits 7% (n=30). There was no difference in lung function or exacerbation rate during PY. BMI increased from 25 to 26 (t_{100} = -4.72, P < 0.001). Antibiotic use decreased from 316 episodes to 124 (z = 8.81, P < 0.0001).

Interpretation:
This CF care model which includes IDC-TM successfully monitored lung function and BMI, identified exacerbations, and followed guidelines-based care during the pandemic. A significant decrease in antibiotic use suggests social mitigation strategies were protective.

Clinical Trial Registration: NCT04402801

In the first four months of the COVID-19 pandemic, use of telemedicine in the US increased by 154% (1). The global pandemic presented an unprecedented opportunity to assess the impact of telemedicine on clinical outcomes in cystic fibrosis (CF). In recent years, CF survival has improved dramatically due to advances in therapeutics and widespread adoption of guideline-based interdisciplinary clinical care focused on early identification and treatment of CF pulmonary exacerbations (2). Telemedicine increases access to care for adults with CF living in regions remote to a CF specialty center, but routine use of telemedicine did not gain widespread traction until the COVID-19 pandemic (3). In March of 2020, the Adult CF team at the University of Virginia (UVA) rapidly transitioned from in-person clinical encounters to a CF care model that included interdisciplinary telemedicine (IDC-TM) using the Health Insurance Portability and Accountability Act (HIPAA)-compliant video communication (4). This prospective observational study set out to answer how a clinical care model that included IDC-TM compared to the classical CF clinical care model during the COVID-19 pandemic. Outcomes evaluated were lung function, rate of pulmonary exacerbation, maintenance of body mass index (BMI), and use of antibiotics, as well as qualitative observations on the potentially protective effects of social mitigation in CF patients during the COVID-19 pandemic on antibiotic use (5).

Study Design and Methods

Adult patients with CF were enrolled starting in March of 2020 (UVA Institutional Review Board for Health Sciences Research, Federal Wide Assurance 00006183, IRB #22327; NCT04402801). Subjects with CF age ≥18 were included (*Figure 1*). Incarcerated patients and patients unable to provide informed consent were excluded. Subjects provided informed consent to participate in a prospective observational cohort study, monitoring real-world clinical outcomes using a CF care model that includes IDC-TM. Subjects were invited by the UVA Adult CF Clinical Care Team as part of pre-visit planning (PVP) after the onset of the COVID-19 pandemic. The care model followed Cystic Fibrosis Foundation clinical care guidelines regarding frequency of clinical visits and spirometry once per quarter, with a comprehensive interdisciplinary evaluation at least annually (6). The pandemic year (PY) was defined as March 17, 2020 through March 16, 2021. The pre-pandemic year (PPY) was defined as March 17, 2019 through March 16, 2020. Primary outcome was stability of lung function; secondary outcomes were exacerbation rates, antibiotic use, and preservation of BMI. Data were collected by electronic medical record (EMR) communications and chart review. Spirometry was measured in-lab or by handheld home spirometers, previously demonstrated to be valid and reproducible for spirometry analysis (7). Data were analyzed using GraphPad Prism version 9.0.0 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com) and R version 4.1.0 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org). Power analysis was not applicable.

Demographic data. Demographic data including sex, age, ethnicity, mutation type, lung function, exacerbations per year, use of CFTR modulator therapy, microbiological data, status of CF-related diabetes (CFRD) and bone disease, and baseline BMI were obtained by chart review.

Clinical Encounters. Adult CF patients at UVA were contacted by secured health system email communication or by phone as part of routine PVP up to a week before scheduled appointments. With transition to the telemedicine intervention, PVP was adjusted to include screening questions to determine appropriateness for IDC-TM clinical care. Telemedicine eligibility was based on clinical stability, anticipated needs, and patient preferences, as well as access to required technology, including a Wi-Fi connection and a computer or smartphone with Internet, video, and audio access. Additional equipment that was encouraged, but not required, included home spirometry (HS), a scale for weight, pulse oximeter, and blood pressure cuff. “Telemedicine visits” were defined as any clinical encounter conducted entirely through secured video communication via the HIPAA-compliant platform WebEx® (Cisco Systems, San Jose, CA). “Hybrid visits” were visits in which the patient was seen in-person in the clinic by a subset of the team with additional in-clinic telemedicine support. During these visits additional team members communicate with the patient via secured webcam in the clinic room. Hybrid visits were recommended for patients who did not meet the prescreening criteria for telemedicine visits. “In-person visits” were clinical encounters in which

the patient was seen only by in-person team members, typically the CF physician and one other team member. “Telephone visits” were conducted completely by phone, where video communication was not possible (4).

Lung function. All patients who did not already own a home spirometer were provided one through the adult CF clinic at no cost to the patient. For telemedicine visits, the respiratory therapist (RT) provided education on HS by secured video communication. With each telemedicine encounter, the RT coached the patient through HS. Readings were sent by secured communication to the RT. The RT verified quality of HS and used the raw FEV1 to calculate Global Lung Initiative (GLI) percent predicted and difference compared to baseline. For hybrid- and in-person visits, spirometry was performed in the clinic using in-lab MedGraphics® CPFS/D™ USB spirometer (Medical Graphics Corp, St. Paul, MN). Lung function analysis was performed for all subjects who had at least one spirometry reading in both PY and PPY and adjusted for ETI use.

Exacerbation rates. The EMR was reviewed for all episodes of antimicrobial use. Exacerbation was defined as hospital admission and/or use of IV antimicrobials for treatment of CF. “All antibiotic use” additionally included all filled prescriptions for any 14-day course of oral antibiotics, excluding antibiotics intended for non-CF care. Exacerbation rates are reported in annualized exacerbations per patient.

BMI. BMI was calculated from aggregate data during PPY and PY. BMI was obtained from clinic weights and self-reported weights during telemedicine encounters using a scale at home. Patients who were pregnant at any time during the two-year period were excluded from BMI analyses.

Statistical Analysis

Descriptive statistics were produced for all clinical measures. %FEV1, exacerbations, antibiotic episodes, and BMI were collected as continuous variables. To analyze lung function, a series of linear mixed models were created that account for multiple measurements for each patient. One model was created to examine the effect of year alone, and a multivariate model was created to examine the effect of year after controlling for ETI use and other variables. Exacerbation rate was analyzed by developing a series of poisson mixed models. Again, one model investigated year and a multivariate model was built to understand the effect of year after adjusting for ETI therapy and other variables. Two final poisson mixed models were created to explain all antibiotic use; a univariate model for year and a multivariate model. For the multivariate models, full model statistics are reported along with estimated marginal means for any effect(s) of interest. Differences in BMI were analyzed using a paired two-tailed t-test. Subgroup analyses were performed on BMI cohorts using paired two-tailed t-tests that were then corrected for multiple testing using the Holm p-value correction. The p-value for significance was 0.05.

Results

Demographic data. (Table 1) 124 out of 143 patients were enrolled and participated in the telemedicine intervention. 110 subjects were included in final analysis; 14 were excluded due to lack of retrospective pre-pandemic data. None were lost to follow up. Patients who were ineligible for the study, unable to be reached during the enrollment window, declined to participate in the study, or joined the clinic later in the year, were given the option to utilize telemedicine care at their request; however, these patients were not included in data collection and outcomes analysis. The mean age at the start of PY was 35 (range 18-69), with 59 women (54%) and 51 men (46%). 95% of the enrolled patients were white and 5% Black. No other ethnicities were identified in this cohort. 90% had at least one del-F508 genetic mutation. 15% had advanced lung disease (FEV1<40%) at baseline. There were a total of 96 exacerbations during PPY (0.13/person/year) and 38 exacerbations during PY (0.05/person/year). CFTR modulators were taken by 93% of subjects during the study period (n=102). In PPY, 50% were prescribed tezacaftor/ivacaftor, 6% lumacaftor/ivacaftor, and 15% ivacaftor. During PPY, 88 subjects (80%) began ETI therapy. During PY, 2%

remained on tezacaftor/ivacaftor, 2% on lumacaftor/ivacaftor, 4% on ivacaftor, and an additional six patients began ETI (total 85%). Colonization with *P. aeruginosa* was identified in 60% PPY and 47% PY, methicillin sensitive *S. aureus* (MRSA) in 25% PPY and 22% PY, *S. maltophilia* in 18% PPY and 12% PY, *Burkholderia cepacia* complex in 4% PPY and 3% PY, Aspergillus *spp.* in 37% PPY and 13% PY, Achromobacter *spp.* in 9% PPY and 6% PY, and nontuberculous mycobacterium *spp.* in 21% PPY and 8% PY. 37% had confirmed CF-related diabetes and 33% had CF bone disease. In both the PPY and PY, 97% had BMI > 18.

Telemedicine participation and clinical encounters. *(Figure 2)* 95% of analyzed patients had access to a telemedicine-compatible device (n=105), while 5% had no telemedicine capability (n=5). The subjects with no telemedicine access were still eligible for other clinical encounter modes including hybrid visits with telemedicine support. A total of 407 encounters were conducted during the PY, between March 17, 2020 and March 16, 2021. Telemedicine encounters accounted for 64% of all clinical visits (n=260) while hybrid visits with telemedicine support accounted for 28% (n=114), and entirely in-person visits accounted for 7% (n=30) of all encounters. All fully in-person visits were urgent/sick appointments, or triggered as a follow up to previous telemedicine encounters. Phone visits accounted for under 1% of encounters (n=3), and all occurred between March and April of 2020.

Lung function. *(Figure 3)* 110 subjects were included in the analyses of lung function. Using a linear mixed model to explain lung function using just the year and a random effect for each patient, the mean %FEV1 in the pre-pandemic year was 69.27%, and increased by 4.28% during the pandemic year, $t_{480} = 8.71$, $P < 0.01$ (*Figure 3A*). During the study period, 85% of subjects (n=94) began taking ETI; 94% of these began therapy in the pre-pandemic year (n=88). Within the subgroup of subjects who began ETI in PPY, 68% had at least one spirometry value after initiation of therapy but before the start of the pandemic (n=60), allowing for determination of ETI effect on FEV1 independent of the pandemic. To this end, a linear mixed model was created with the 110 analyzed patients explaining %FEV1 using ETI use and controlling for the effects of time, sex, BMI, exacerbations, age group, year, baseline lung function cohort, the interaction between age group and year, and the interaction between baseline lung function cohort and year (Table 2). The effect of ETI on lung function after controlling for the effect of the pandemic and other variables was an increase in %FEV1 of 4.31%, $t_{474} = 5.16$, $P < 0.01$ (*Figure 3B*). Lung function adjusted for ETI use and other variables revealed no significant difference between PPY and PY, with a difference in %FEV1 of 1.30% in the PY, $t_{319} = 0.60$, $P = 0.55$ (*Figure 3C*).

Exacerbation rates and antibiotic use. *(Figure 4)* There were no patient deaths or lung transplants during the study period. Three exacerbations in the pandemic year were due to COVID-19. In the PPY, 14 exacerbations included treatment for confirmed or suspected influenza. There were no instances of confirmed or suspected influenza in PY. Based on a poisson mixed model explaining the number of exacerbations by year and a random effect of patient, exacerbations decreased by a factor of 2.5 from a total of 96 during PPY (0.13/person/year) to 38 during PY (0.05/person/year) ($z = -4.83$, $P < 0.01$). Using a model that adjusted for ETI use and other variables (Table 3), there was no significant difference in exacerbation rate in PPY and PY (0.065 vs 0.054/person/year, respectively ($z = 0.41$, $P = 0.68$). Exacerbations differed by sex, with females showing 2.2 times as many exacerbations (0.088/person/year, sum = 96) as males (0.040/person/year, sum = 38) ($z = 2.18$, $P = 0.03$, Table 3). Overall use of antibiotics decreased by a factor of 2.5, from 316 episodes in PPY (0.848/person/year) to 124 in PY (0.333/person/year) ($z = 8.81$, $P < 0.0001$). After adjusting for ETI use and other variables, this effect was preserved though less pronounced with 0.612/person/year in PPY to 0.366/person/year in PY ($z = 2.31$, $P = 0.02$, Table 4). During PY, 64% of all exacerbations were diagnosed during hybrid or in-person clinic encounters, while 36% were diagnosed during telemedicine clinic encounters.

Preservation of BMI. *(Figure 5).* After excluding patients who were pregnant during the study period (n=6) and patients who did not have BMI measurements in both the PPY and PY (n=3), 101 patients were included in the BMI analyses. BMI was not adjusted for ETI due to lack of post-ETI data prior to the start of

the pandemic. Overall, BMI increased during the PY, with mean BMI 25.2 in the PPY and 26.2 in the PY (t_{100} = -4.72, P < 0.001). Subgroup analysis by BMI cohort demonstrated that for patients under their BMI goal (BMI < 22 for women and < 23 for men) and for patients meeting their BMI goal (22–27 for women and 23-27 for men) a significant increase in BMI was observed during the pandemic period (t_{29} = -4.57, Adj. P < 0.001 and t_{41} = -3.03, Adj. P = 0.008, respectively). For patients with BMI > 27, no significant change was observed during PY (t_{28} = -1.37, Adj. P = 0.183).

Discussion

Rapid implementation of a CF clinical care model that included interdisciplinary telemedicine during the COVID-19 pandemic at the University of Virginia was associated with preservation of lung function and BMI, stability in the rate of pulmonary exacerbations, and decreased use of antibiotics. The introduction of elexacaftor/tezacaftor/ivacaftor (ETI) in October of 2019 improved lung function and exacerbation rates, but introduced a major confounder to clinical outcome analysis during the pandemic year. A significant improvement in lung function was initially observed in the pandemic year, which we attribute to swift deployment of ETI therapy in our patient population (8). After adjusting for modulator therapy, we identified no significant change in lung function or exacerbation rates during the pandemic. Nonetheless, it's important to recognize that ETI use likely contributed to overall clinical stability in this patient population during the pandemic year. Our clinical outcomes during the pandemic suggest that the UVA clinical care model that includes IDC-TM with PVP and home spirometry is comparable to the classical in-person CF care model employed pre-pandemic for monitoring lung function, BMI, and exacerbations during the COVID-19 pandemic. Moreover, this care model may offer significant advantages over the model employed pre-pandemic. One compelling finding was the use of *all* antibiotics declined significantly, even after adjusting for modulator use. While these findings suggest that social mitigation may play a protective role in CF, the use of ETI as a stabilizing therapy is also likely a factor. Combined, these observations suggest that, with appropriate pre-visit planning, adult CF clinical care with IDC-TM is an effective model for implementing guidelines-based CF care, and that social mitigation strategies may decrease antibiotic overexposure.

An important consideration in the success of this model is the use of pre-visit planning and triage. Pre-visit planning is not standardized, and practice varies by CF center. The UVA adult CF PVP process consists of communication with patients up to a week before scheduled clinical visits. Patients are contacted by phone or by secure health system messaging. Patients are encouraged to provide a patient-driven agenda, and asked about acute needs including changes in insurance, refill requests, and health questions to screen for potential exacerbations. With the transition to telemedicine, PVP was adjusted to include pre-screening questions to determine appropriateness for telemedicine as described above. We believe that appropriate pre-visit planning is a critical factor in the success of a care model that includes IDC-TM. In-person or hybrid visits triggered by PVP screening accounted for the diagnosis of nearly two thirds of all exacerbations. The remainder of diagnosed exacerbations were "missed" during PVP screening and identified during telemedicine clinic encounters with home spirometry, indicating that PVP alone is not sufficient for identifying all exacerbations.

In the first pandemic year, a total of three patients had COVID-19 (2%), significantly lower than the general US population estimated at 8% (9). Two were treated for exacerbation and recovered, while one experienced no pulmonary symptoms. Our patient population also saw a dramatic reduction in influenza. In contrast to the previous year in which 14 exacerbations were due to confirmed or suspected influenza, there were no cases of influenza in the pandemic year. This observation could be attributed to the protective role of social mitigation and widespread mask use during the pandemic year, and/or overestimation of influenza diagnosis and exposure in previous years.

There was a modest increase in BMI during the pandemic period. Subgroup analysis revealed that this effect was seen primarily in patients who were meeting the recommended BMI or below recommended BMI. We attribute this primarily to the introduction of ETI therapy in our patient population, although

quarantine-associated weight gain, which has been observed in the general population, may have also played a role (10). One limitation of this study was the use of home scales for self-reported weight measurements, which may not correlate with the scale used in clinic. BMI was not calculated for patients who were unwilling or unable to measure weight at home using a scale. BMI analysis was not adjusted for ETI use, due to lack of data for all patients pre- and post-ETI therapy. Patients above their BMI goal did not have a significant change in weight during the pandemic, suggesting that the overall increase in BMI may be attributed to ETI use, rather than lockdown-associated weight gain.

A significant strength of this study was the rapid implementation of telemedicine; no clinic days were canceled as a result of the COVID-19 pandemic due to transition to telemedicine, and adherence to guidelines-based recommendations for frequency of visits was maintained. Telemedicine utilization, either by telemedicine visits or in hybrid visits with in-clinic telemedicine support, accounted for 92% of all clinical encounters during the pandemic year.

Another strength is our relatively large patient population for a single center with high buy-in for telemedicine and home spirometry. While 86% of our patients consented to data collection for this study, additional patients requested and utilized telemedicine care. This included patients who were unable to be reached during the enrollment window, patients who joined the clinic later in the year, and patients who declined to participate in data collection. Over 90% of our patient population utilized some form of telemedicine care during the year, though as a single center study it is difficult to draw conclusions on the generalizability of these results. Nonetheless, in the pre-pandemic year, our center reported similar rates of exacerbation, lung function, and BMI compared to national data, suggesting external validity (11). One limitation of both in person and IDC-TM clinical models is that accuracy for adherence to pulmonary clearance therapies and other medications may be underreported, especially after the widespread implementation of ETI, and may influence outcomes.

One advantage of this model compared to previously published work is our interdisciplinary approach to home spirometry. Paynter *et al* recently published their investigation comparing twice-weekly HS to standard of care (12). This study highlighted the enormous potential of home spirometry, but also the pitfalls and limitations of its implementation. Subjects were provided in-person initial instruction on HS, but no maintenance instruction of spirometry technique over the course of the study, and encouraged to provide HS readings twice a week. Over the course of the investigation the authors observed that adherence to HS plummeted, and accuracy of HS readings deteriorated compared to in-lab results. This study underscores the importance of technique and proper coaching by a respiratory therapist, as well as acknowledgement of burnout on the part of the patient. One significant difference in our IDC-TM model was the use of one-on-one coaching by the RT to ensure accuracy of HS results, which were obtained under direct observation at the time of the clinical encounter.

To our knowledge, this is the first study to report on real-world clinical outcomes in cystic fibrosis using a clinical care model that incorporates pre-visit screening, interdisciplinary telemedicine, and quality-controlled home spirometry. One challenge in CF, as well as many other chronic systemic diseases, is the need for interdisciplinary care and frequent disease-specific monitoring. Future direction would include a multi-center randomized controlled outcomes-based trial comparing a care model that includes IDC-TM to the classical in-person care model. The Early Intervention in Cystic Fibrosis Exacerbation (eICE) study, a multi-center randomized controlled trial, previously compared the use of twice-weekly HS and self-reported symptom diaries to the usual care model (13). The authors concluded that regular, frequent monitoring of self-reported symptoms and HS increased detection of CF exacerbations; however, increased detection did not slow the decline in lung function over the 52 week period. Notably, eICE was completed prior to the introduction of ETI therapy, which has been shown to stabilize lung function and decrease exacerbations (14). An advantage to the care model described in our study is the near-seamless incorporation of guidelines-based care, specifically with regard to frequency of clinical encounters, spirometry, and

interdisciplinary evaluations. We anticipate that this model would have higher clinic retention and adherence in the long term compared to an eICE-style intervention.

Telemedicine broadly is associated with decreased travel costs, decreased time off from work or school, and high patient and provider satisfaction (15). With the widespread adoption of telehealth practices during the COVID-19 pandemic, and the many advantages it offers, we anticipate that telemedicine is here to stay (16). However, the advantages of telemedicine cannot come at the cost of quality care. This study is the first to demonstrate longitudinal real-world clinical outcomes in CF patients utilizing an adult CF clinical care model that includes IDC-TM, appropriate pre-visit screening, and properly-coached home spirometry as an alternative to the classical in-person clinic model.

Interpretation

The authors previously demonstrated that implementation of telemedicine during the COVID-19 pandemic reduced patient and staff interactions and by doing so preserved personal protective equipment (17). Here we demonstrate that real-world clinical outcomes of a clinical care model with IDC-TM are similar to the classical clinical care model, and in the time of a pandemic, this model may offer significant advantages to in-person care. We conclude that at this large single center, the adult CF clinical care model that includes IDC-TM, appropriate pre-visit screening, and properly-coached home spirometry is a feasible alternative to the classical in-person clinic model employed pre-pandemic for maintaining lung function and BMI, and identifying CF pulmonary exacerbations. Moreover, we observed a significant decrease in the overall use of antibiotics during the pandemic, suggesting that social mitigation plays a strong role in prevention of pulmonary exacerbations.

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Guarantor statement: Lindsay Somerville and Dana Albon accept official responsibility for the integrity of the manuscript, including ethics, data handling, reporting of results, and study conduct. All statements in this manuscript are true to the authors' knowledge.

Contributions

LALS: Primary author of original manuscript, co-investigator, performed primary analysis and interpretation of data, visualization, project administration including methodology and investigation, and final approval of manuscript. **RPL:** Project conceptualization, project administration including methodology, acquisition of data, writing and revisions of intellectual content. **MHC:** Project conceptualization, project administration including methodology, acquisition of data. **DJ:** Project conceptualization, project administration including methodology, acquisition of data, analysis and interpretation of data. **MKJ:** Statistical consultation, mixed model statistical analyses, figure and table generation, critical revision for intellectual content. **HMB:** Project conceptualization, project administration including methodology, acquisition of data, revisions for intellectual content. **RKM:** Project conceptualization, project administration including methodology, acquisition of data. **ERS:** Project conceptualization, project administration, acquisition of data, revisions for intellectual content. **KMW:** Demographic data acquisition. **LSG:** Project conceptualization, administration including methodology, revisions for intellectual content. **DPA:** Principal investigator, primary conceptualization, project administration including methodology, data acquisition and investigation, critical revision for intellectual content, final approval of manuscript.

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Take-Home Point:

Study Question:

How does a clinical care model that includes interdisciplinary telemedicine (IDC-TM) compare to in-person clinical care for persons with cystic fibrosis during the COVID-19 pandemic, measured by primary outcomes of lung function, pulmonary exacerbations, maintenance of body mass index (BMI), and use of antibiotics?

Results:

A clinical care model for cystic fibrosis that includes IDC-TM was found to have similar clinical outcomes compared to a fully in-person clinical care model in terms of maintaining lung function and BMI, and identifying CF pulmonary exacerbations during the COVID-19 global pandemic. This care model was also associated with decreased overall use of antibiotics.

Interpretation:

Our CF care model which includes IDC-TM successfully monitored lung function, identified exacerbations, and followed guidelines-based care during the global COVID-19 pandemic. A significant decrease in antibiotic use suggests social mitigation strategies were protective in adults with CF.

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FIGURE LEGENDS

Figure 1. Study design and enrollment flowchart. All 143 adult CF patients at the University of Virginia were considered for eligibility. Two were excluded due to inability to provide informed consent. One patient declined to participate. 16 were unable to be reached for consent. 124 subjects were enrolled and participated in the telemedicine intervention. 110 subjects were analyzed; 14 of the participants were excluded from final analysis due to lack of retrospective pre-pandemic data.

Figure 2. A) Clinic encounters during the pandemic year by quarter. A total of 407 clinical encounters were conducted between March 17, 2020 and March 16, 2021. B) Encounter types as a percentage of all encounters for the pandemic year. Telemedicine encounters made up the majority of visits with 64% (n=260). Hybrid visits which included in-clinic telemedicine support accounted for 28% (n=114), while 7% were in-person visits (n=30) and less than 1% were by phone (n=3). All phone visits took place between March 17 and June 30 of 2020.

Figure 3. Changes in lung function during the pandemic year. A) Without adjusting for ETI use and other variables, %FEV1 increased significantly from 69.3% pre-pandemic (PPY) to 73.5% during the pandemic year (PY) ($P < 0.01$). B) Determining the effect of triple combination CFTR modulator therapy on lung function adjusting for year and other variables. Lung function improved by 4.4% due to therapy ($P < 0.01$). C) Adjusting for ETI use and other variables revealed no change in lung function from PPY to PY (70.0 PPY vs 70.2 PY; $P = 0.55$).

Figure 4. Exacerbation rates. A) Exacerbation rate declined during PY from 0.133 exacerbations/ person/year to 0.053 exacerbations/person/year ($P < 0.01$). B) Exacerbation rates adjusted for ETI therapy and other variables demonstrated no significant difference in PPY vs PY (0.065 vs 0.054 exacerbations/person/year; $P = 0.68$). C) All antibiotic use, including both IV and oral antibiotics, adjusted for ETI therapy and other variables, decreased from 0.612 occurrences/person/year PPY to 0.366 occurrences/person/year in PY ($P = 0.02$).

Figure 5. Preservation of BMI during the pandemic year. An increase in BMI was observed during the pandemic period, with mean BMI of 25.2 PPY and 26.2 during PY (n=101; $P < 0.001$). Six subjects were excluded due to pregnancy and 1 due to missing data. BMI was not adjusted for ETI due to lack of pre- and post-ETI data. Lines show each subject's change. Subgroup analysis for BMI under goal (BMI < 22 for women or < 23 for men), and for BMI at goal (BMI 22-27 for women and 23-27 for men) demonstrated significant improvement during the pandemic year (Adj. $P < 0.001$ and Adj. $P = 0.008$, respectively). For BMI above goal, no significant change in BMI was observed in PY (Adj. $P = 0.183$).

Table 1. Patient characteristics.

	Pre-Pandemic (2019-2020)	Pandemic Year (2020-2021)
Gender		
Women	59 (54%)	-
Men	51 (46%)	-
Age		
18-24	27 (25%)	-
25-34	41 (37%)	-
35-44	19 (17%)	-
45-54	15 (14%)	-
55+	8 (7%)	-
Ethnicity		
White	105 (95%)	-
Black	5 (5%)	-
Hispanic	0	-
Genetics		
del F508 homozygous	59 (54%)	-
del F508 heterozygous	40 (36%)	-
Lung function (%FEV1)		
< 40%	17 (15%)	15 (14%)
40-69%	30 (27%)	29 (26%)
70-89%	39 (35%)	35 (32%)
>90%	24 (22%)	31 (28%)
Pulmonary exacerbations per year		
Total exacerbations	96	38
Annualized exacerbations per person	0.13	0.05
CFTR modulator use		
Elexacaftor/tezacaftor/ivacaftor	88 (80%)	94 (85%)
Tezacaftor/ivacaftor	55 (50%)	2 (2%)
Lumacaftor/ivacaftor	7 (6%)	2 (2%)
Ivacaftor	17 (15%)	4 (4%)
Microbiology of colonizing species		
P. aeruginosa	66 (60%)	52 (47%)
Methicillin-resistant S. aureus (MRSA)	28 (25%)	25 (22%)
S. maltophilia	19 (18%)	13 (12%)
B. cepacia complex	5 (4%)	4 (3%)
Aspergillus	40 (37%)	14 (13%)
Achromobacter	10 (9%)	7 (6%)
Nontuberculous mycobacterium	23 (21%)	9 (8%)
CF-related diabetes (CFRD)		
Yes	41 (37%)	45 (41%)
Negative screening during calendar year	38 (35%)	28 (25%)
Not screened during calendar year	31 (28%)	37 (34%)
CF bone disease		
Screened and normal	43 (39%)	50 (45%)
Osteopenia	33 (30%)	40 (36%)
Osteoporosis	3 (3%)	5 (5%)
Unknown	31 (28%)	15 (14%)
BMI		
≤ 17	3 (3%)	3 (3%)
18-23	51 (46%)	38 (35%)
≥ 24	56 (51%)	69 (62%)

Multivariate linear mixed model explaining lung function in adults with CF					
Term	Estimate	SE	df	t	*P*
(Intercept)	32.35	3.90	145.28	8.29	< 0.01
Quarter of year	0.15	0.27	418.88	0.56	0.57
Sex is male	-0.48	1.50	101.28	-0.32	0.75
BMI	0.00	0.13	167.69	0.03	0.98
Subject is taking ETI	4.31	0.84	474.48	5.16	< 0.01
Age 25-34	-3.56	1.95	100.78	-1.82	0.07
Age 35-44	-1.62	2.34	102.22	-0.70	0.49
Age 45-54	2.32	2.68	103.68	0.87	0.39
Age 55+	2.57	3.25	104.78	0.79	0.43
Year PY	1.30	2.15	319.33	0.60	0.55
%FEV1 40-69	24.67	2.30	103.63	10.71	< 0.01
%FEV1 70-89	49.68	2.32	106.84	21.40	< 0.01
%FEV1 >90	66.31	2.66	106.87	24.92	< 0.01
All antibiotic episodes	0.42	0.38	492.93	1.13	0.26
Exacerbations	-1.26	0.62	491.14	-2.04	0.04
Age 25-34:year PY	-0.96	1.53	228.47	-0.62	0.53
Age 35-44:year PY	0.12	1.76	233.08	0.07	0.95
Age 45-54:year PY	-2.62	2.07	225.44	-1.27	0.21
Age 55+:year PY	-1.77	2.39	225.30	-0.74	0.46
Year PY:%FEV1 40-69	0.61	1.77	226.98	0.34	0.73
Year PY:%FEV1 70-89	0.65	1.82	234.66	0.36	0.72
Year PY:%FEV1 >90	-1.33	2.09	235.90	-0.64	0.52

Table 2. Change in lung function explained by ETI use and controlling for other variables. A multivariate linear mixed model was created with the 110 analyzed patients explaining lung function using ETI use and controlling for the effects of time, sex, BMI, exacerbations, age group, year, lung function cohort, and the interaction between age group and year and between lung function cohort and year. A random slope over time was included for each participant. The effect of ETI on lung function after controlling for the effect of the pandemic and other variables was an increase in %FEV1 of 4.31%, $t_{474} = 5.16$, $P < 0.01$. Lung function adjusted for ETI use and other variables revealed no significant difference in lung function between PPY and PY, with a difference in %FEV1 of 1.30% in the PY, $t_{319} = 0.60$, $P = 0.55$.

Poisson mixed model explaining exacerbations in adults with CF				
Term	Estimate	SE	z	*P*
(Intercept)	0.22	0.91	0.24	0.81
Quarter of year	-0.17	0.11	-1.56	0.12
Sex is male	-0.78	0.36	-2.18	0.03
BMI	-0.02	0.03	-0.53	0.60
Subject is taking ETI	-0.43	0.33	-1.29	0.20
%FEV1 40-69	-0.42	0.51	-0.81	0.42
%FEV1 70-89	-0.69	0.52	-1.32	0.19
%FEV1 >90	-1.97	0.68	-2.91	< 0.01
Year PY	-1.12	0.77	-1.46	0.14
Age 25-34	-0.31	0.42	-0.73	0.46
Age 35-44	-1.16	0.57	-2.05	0.04
Age 45-54	-1.52	0.66	-2.30	0.02
Age 55+	-0.94	0.75	-1.25	0.21
Year PY:%FEV1 40-69	0.31	0.64	0.49	0.63
Year PY:%FEV1 70-89	0.66	0.63	1.04	0.30
Year PY:%FEV1 >90	1.49	0.79	1.88	0.06
Age 25-34:year PY	0.48	0.51	0.94	0.35
Age 35-44:year PY	-0.72	1.13	-0.63	0.53
Age 45-54:year PY	0.85	0.88	0.97	0.33
Age 55+:year PY	0.97	0.81	1.20	0.23

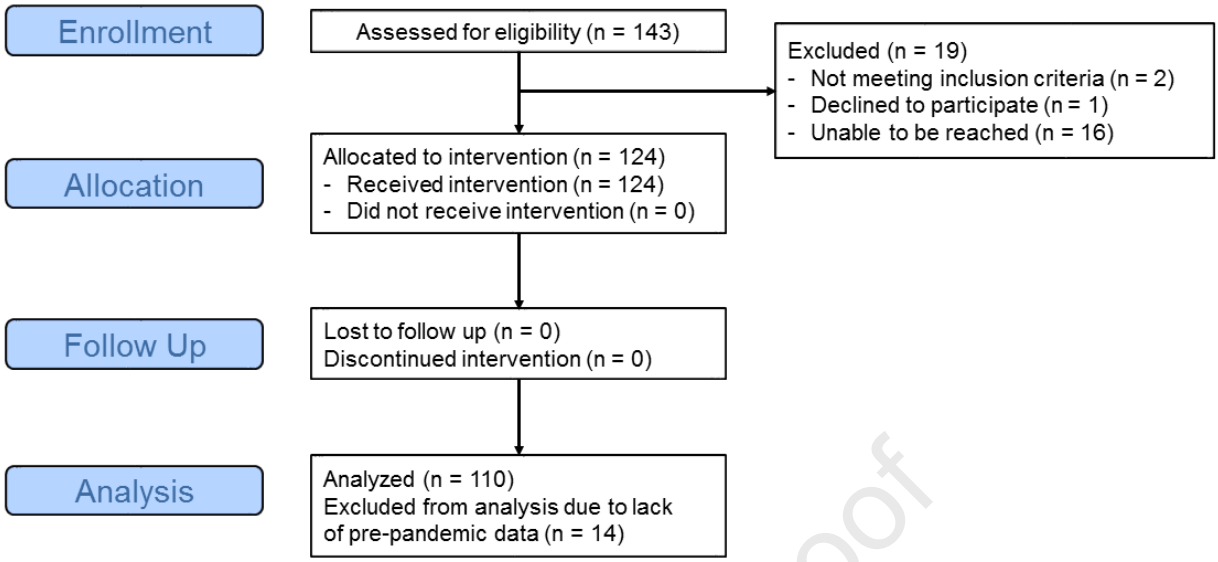
Effect of sex on exacerbation rate					Effect of year on exacerbation rate				
Sex	Rate	SE	z ratio	*P*	Year	Rate	SE	z ratio	*P*
F	0.088	0.03	2.18	0.03	PPY	0.065	0.02	0.41	0.68
M	0.040	0.02			PY	0.054	0.02		

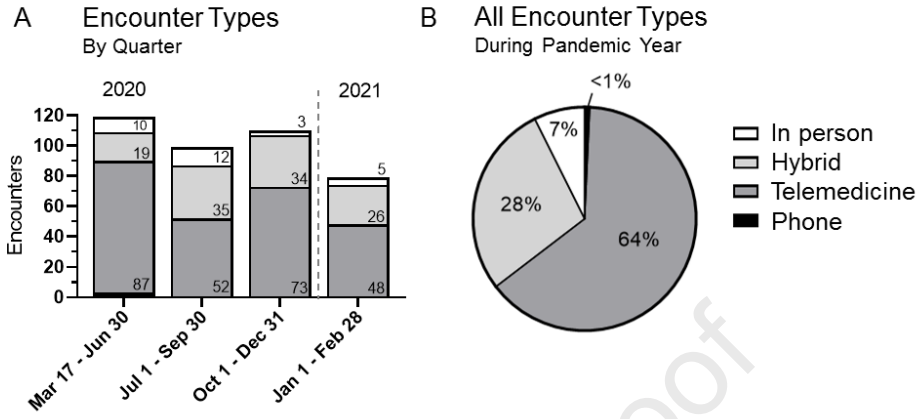
Table 3. Poisson mixed model explaining the number of exacerbations by year adjusted for ETI use, time, sex, BMI, year, lung function cohort, age group, and the interaction between year and lung function cohort and the interaction between age group and year. A random slope over time was included for each participant. There was no significant difference in exacerbation rate in PPY and PY (0.065 vs 0.054/person/year, respectively (z = 0.41, *P* = 0.68). Moderate exacerbations differed by sex, with females showing 2.2 times as many exacerbations (0.088/person/year, sum = 96) as males (0.040/person/year, sum = 38) (z = 2.18, *P* = 0.03).

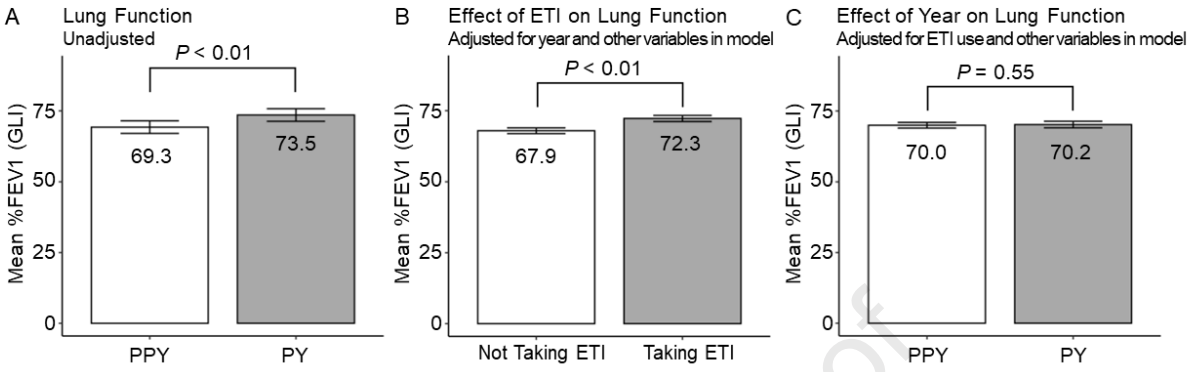
Poisson mixed model explaining antibiotic episodes per year in adults with CF				
Term	Estimate	SE	z	*P*
(Intercept)	0.21	0.45	0.48	0.63
Quarter of year	-0.10	0.05	-1.92	0.05
Sex is male	-0.39	0.16	-2.38	0.02
BMI	0.01	0.01	0.52	0.60
Subject is taking ETI	-0.09	0.17	-0.51	0.61
%FEV1 40-69	-0.29	0.25	-1.16	0.25
%FEV1 70-89	-0.39	0.25	-1.56	0.12
%FEV1 >90	-0.74	0.30	-2.48	0.01
Year PY	-0.82	0.40	-2.08	0.04
Age 25-34	0.07	0.21	0.33	0.74
Age 35-44	-0.26	0.26	-0.99	0.32
Age 45-54	-0.54	0.30	-1.78	0.08
Age 55+	-0.56	0.38	-1.47	0.14
Year PY:%FEV1 40-69	0.02	0.33	0.06	0.95
Year PY:%FEV1 70-89	0.20	0.33	0.62	0.54
Year PY:%FEV1 >90	0.32	0.40	0.81	0.42
Age 25-34:year PY	0.05	0.28	0.19	0.85
Age 35-44:year PY	-0.14	0.39	-0.36	0.72
Age 45-54:year PY	0.48	0.41	1.18	0.24
Age 55+:year PY	0.47	0.49	0.95	0.34

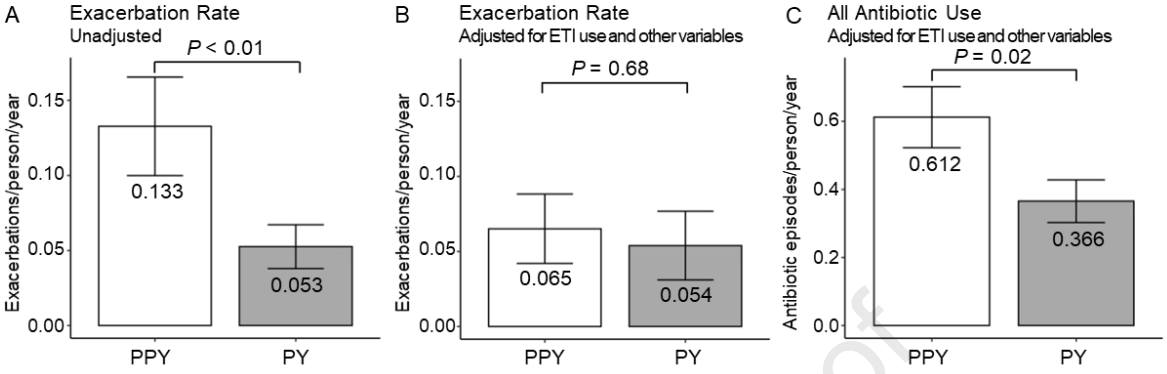
Effect of year on annual rate of antibiotic use per person				
Year	Rate	SE	z ratio	*P*
PPY	0.612	0.089	2.31	0.02
PY	0.366	0.062		

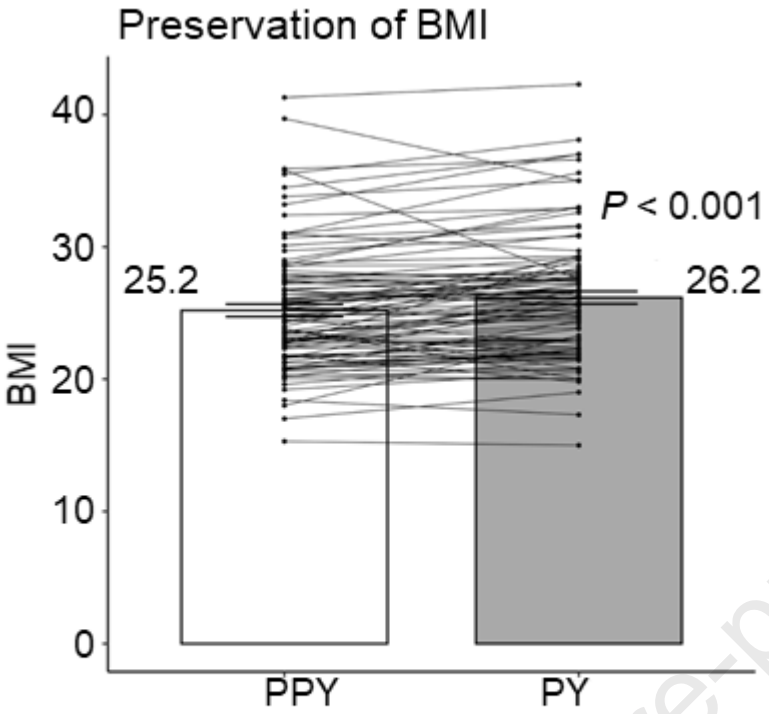
Table 4. Poisson mixed model explaining the number of antibiotic episodes per person per year adjusted for time, sex, BMI, and ETI use, year, lung function cohort, age group, and the interaction between lung function cohort and year, and the interaction between age group and year. A random slope over time was included for each participant. After adjusting for ETI use and other variables, use of antibiotics decreased in PY from 0.612/person/year in PPY to 0.366/person/year in PY (z = 2.31, *P* = 0.02).











BMI Cohort	Δ BMI PY-PPY	n	*P*	Adj. *P*
BMI < 22F / < 23M	1.3	30	< 0.001	< 0.001
BMI 22F / 23M – 27	0.9	42	0.004	0.008
BMI > 27	0.6	29	0.183	0.183

Abbreviations:

%FEV1: Percent predicted forced expiratory volume in one second

BMI: Body mass index

CF: Cystic fibrosis

CFRD: Cystic fibrosis-related diabetes

CFTR: Cystic fibrosis transmembrane conductance regulator

COVID-19: Coronavirus disease of 2019

EMR: Electronic medical record

ETI: elexacaftor/tezacaftor/ivacaftor+ivacaftor

HIPAA: Health Insurance Portability and Accountability Act

HS: Home spirometry

IDC-TM: Interdisciplinary telemedicine

PPY: Pre-pandemic year

PVP: Pre-visit planning

PY: Pandemic year

RT: Respiratory therapist