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Association of site of treatment with clinical outcomes following intravenous antimicrobial treatment of a pulmonary exacerbation

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Abstract

Background: In the STOP2 (Standardized Treatment of Pulmonary Exacerbations-2) study, intravenous (IV) antimicrobial treatment duration for adults with cystic fibrosis (CF) experiencing pulmonary exacerbations (PEx) was determined based on initial treatment response. The impact of home vs hospital care remains an important clinical question in CF. Our hypothesis was that STOP2 participants treated at home would have less improvement in lung function compared to those treated in the hospital.

Methods: Treating clinicians determined PEx treatment location, which was a stratification factor for STOP2 randomization. Lung function, weight, and symptom recovery were evaluated by treatment location. Propensity scores and inverse probability treatment weighting were used to test for differences in clinical response by treatment location.

Results: In all, 33% of STOP2 participants received IV antimicrobials in the hospital only, 46% both in the hospital and at home, and 21% at home only. Mean (95% CI) ppFEV$_1$ improvement was significantly ($p < 0.05$) lower for those treated at home only, 5.0 (3.5, 6.5), compared with at

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home and in the hospital, 7.0 (5.9, 8.1), and in the hospital only, 8.0 (6.7, 9.4). Mean weight ($p < 0.001$) and symptom ($p < 0.05$) changes were significantly smaller for those treated at home only compared to those treated in the hospital only.

Conclusions: Compared to PEx treatment at home only, treatment in the hospital was associated with greater mean lung function, respiratory symptom, and weight improvements. The limitations of home IV therapy should be addressed in order to optimize outcomes for adults with CF treated at home.

Keywords

cystic fibrosis; exacerbations; antimicrobials; clinical trials

Introduction

Cystic fibrosis (CF) lung disease is manifested by impaired mucociliary clearance, persistent microbial infection, and an exaggerated inflammatory response (1). Episodes of clinical worsening with increased cough and sputum production, acute loss of lung function, and weight loss, among other signs and symptoms, termed pulmonary exacerbations (PEx), are a common complication (2). PEx are associated with accelerated disease progression (3, 4) and reduced survival (5–7). Beyond general agreement that increased airway clearance and treatment of lung infection with antimicrobials are important components of CF PEx management, there has been a lack of consensus with respect to best PEx treatment practices, including treatment location (8). Some studies have suggested that treatment in the hospital is associated with superior lung function recovery compared with treatment at home (9–12), while others have suggested there is no difference in lung function response based on treatment location (13–15). Retrospective analyses have been limited by inability to fully adjust for potential indication bias (16) and differences in other treatment parameters (e.g., antimicrobial durations) (17). A recent large retrospective registry study that adjusted for indication bias using propensity scoring and instrumental variables concluded that PEx outcomes, defined as return of percent predicted forced expiratory volume in 1 second ($ppFEV_1$) to greater than or equal to 90% of baseline post-treatment, were better for people with CF treated in the hospital than for those treated at home (16).

The Standardized Treatment of Pulmonary Exacerbations (STOP) program was initiated by the CF Foundation to develop interventional trials for the purpose of identifying best practices for PEx management. STOP2 (NCT02781610) was a large, randomized study comparing durations of intravenous (IV) antimicrobial treatment that concluded that, for adults with CF with early treatment improvement, 10 days of IV antimicrobials is not inferior to 14 days, and for those with less improvement after one week, 21 days is not superior to 14 days (18). STOP2 did not dictate where treatment had to occur; decisions about home or hospital treatment were made by clinicians and participants. However, randomization was stratified by treatment location, which balanced the allocation of participants treated at home and in the hospital across treatment duration arms, allowing assessment of site of treatment on clinical responses without confounding by treatment duration. Our hypothesis was that STOP2 participants treated at home would have less mean improvement in lung function compared to those treated in the hospital.

Methods

The STOP2 study design and results have been reported in detail elsewhere (18, 19). The study (NCT02781610), approved by participating Institutional Review Boards, enrolled adults with CF diagnosed with a PEx for which IV antimicrobials were prescribed. Antimicrobial PEx treatments were selected by investigators based on a prespecified algorithm relying on respiratory culture results from the preceding two years. Corticosteroids could be used at the discretion of the treating clinician, with a request that this decision was made prior to randomization. Participants continued chronic therapies and airway clearance methods were enhanced as per usual practice.

The site of treatment was determined by treating clinicians, not by the study protocol. Participants could be treated entirely in the hospital or at home, or transition between the hospital and home during treatment. Screening occurred at Visit 1, within (–3, 1) days of IV antimicrobial treatment initiation, at which time spirometry ($ppFEV_1$) and respiratory symptoms (Chronic Respiratory Infection Symptom Score; CRISS (20)) were captured (19). At Visit 2, occurring 7 to 10 days after Visit 1, spirometry and respiratory symptoms were collected again and participants were categorized as either early robust responders (ERR) or not (NERR), based upon $ppFEV_1$ and CRISS changes from Visit 1 (19). ERR participants were randomized to receive either 10 (±1) or 14 (±1) total days of IV antimicrobial treatment (inclusive of treatment occurring before Visit 2); NERR subjects were randomized to receive either 14 (±1) or 21 (±3) total days of IV antimicrobial treatment. Randomizations were stratified by treatment location (location of IV treatment by Visit 2 (exclusively home versus any hospital nights)), $ppFEV_1$ at treatment start (<50 versus ≥50), history of IV antimicrobial treatments in the prior year (0–1 versus ≥2), and systemic corticosteroid by Visit 2. Two weeks after the scheduled end of IV antimicrobial treatment (Visit 3), spirometry and respiratory symptoms were again collected. Socioeconomic status (SES) was based on occupational prestige scores for participants or their caregiver and categorized into 4 levels: no-tier (for participants who either were not working or declined to answer), low-, middle- and high- tiers based on occupational prestige scores for self or caregiver (21). Distance to site was based on participant report of their average travel time to their CF Center.

Statistical Analyses

For the current analyses, participants were categorized as receiving IV antimicrobial treatment exclusively in the hospital, exclusively at home, or a combination of the two. Distribution of hospital days and home days were summarized separately for ERR and NERR and by treatment duration. The primary STOP2 endpoint was absolute $ppFEV_1$ change from the start of IV antimicrobials (Visit 1) to 14 days following scheduled treatment completion (Visit 3) (18). Secondary and safety endpoints included differences in CRISS and weight changes over the same period, need for antimicrobial re-treatment after IV completion, time to next PEx requiring IV antimicrobials acquired via the US CF Foundation Patient Registry (CFFPR) (22), and adverse events (AE). AEs were defined as new or worsening of signs or symptoms, including clinically significant abnormal clinical laboratory values, that occurred after randomization (Visit 2) until Visit 3. In the current

analysis, the same outcomes were compared separately among ERR and NERR groups by treatment location category. Given that the STOP2 primary and secondary efficacy outcomes for ERR and NERR groups did not differ by treatment duration (18), no adjustments were included for treatment duration within ERR or NERR groups.

To address selection bias, propensity scores using inverse probability treatment weighting (IPTW) were applied when testing for differences in clinical response by treatment location category (hospital only, both home and hospital, home only) (23). Propensity scores were derived from a multinomial logistic model adjusting for predictors thought to be associated with both site of treatment and outcomes, including age and $ppFEV_1$ at Visit 1, sex, race, ethnicity, number of PEx in year prior, SES, body mass index (BMI) ≤18 kg/m^2, allergic bronchopulmonary aspergillus (ABPA), and insulin-dependent cystic fibrosis related diabetes (CFRD). The fitted IPTW models are modified generalized linear models (GLMs) with weights proportional to the inverse of the predicted probabilities (propensity scores) from the multinomial model. Outcomes were also assessed using standard GLM models without propensity scores to examine the effect of adjusting for indication bias with IPTW. Both IPTW and GLM models were adjusted for the same covariates as for the STOP2 primary endpoint i.e., site of IV treatment, $ppFEV_1$ < 50% at Visit 1, corticosteroid use and the number of PEx in the last year (0–1 vs 2+).

Among those participants treated both in the hospital and at home, associations between days in the hospital and change in $ppFEV_1$ were examined graphically, with pair-wise t-tests, and by linear regression. Time to re-treatment with antimicrobials was evaluated based on propensity weighted Cox proportional hazards models adjusting for age, sex and randomization strata and by Kaplan-Meier graphs. Statistical significance was defined as a two-sided p-value of ≤ 0.05. All analyses were performed with R version 4.0.2 and higher (R Foundation for Statistical Computing, Vienna, Austria).

Results

Treatment locations

In all, 982 participants were randomized at Visit 2 and made up the Intent-to-treat (ITT) population (Figure 1), of whom 328 (33%) received IV antimicrobials in the hospital only, 449 (46%) both in the hospital and at home, and 205 (21%) at home only. Participants treated in the hospital only were more likely to be categorized as ERR than were those treated entirely at home (41% vs. 18%, p <0.001). In the combined ERR groups, 48% received IV antimicrobials in the hospital only, 38% at home and in the hospital, and 13% at home only. In the combined NERR groups, 28% received IV antimicrobials in the hospital only, 49% at home and in the hospital, and 24% at home only.

Participant characteristics

Several features distinguished participants treated only in the hospital from other treatment location groups; on average, they tended to be younger, in a lower SES tier, with the longest driving distance to their center, and with lower mean BMI and $ppFEV_1$ (Table 1). They also had a higher proportion of male and non-white participants, and were less likely to

be on highly effective modulator therapy (HEMT) and more likely to be in the 10-day ERR treatment arm. The average $ppFEV_1$ in the 6 months prior to Visit 1 (derived from the CFFPR) was numerically lower for participants treated only in the hospital, though not statistically significant. Declines in $ppFEV_1$ from the 6-month pre-PEx average to Visit 1 did not differ by treatment location (Table 1). A minority of participants were treated with oral antimicrobials, inhaled antimicrobials, or oral corticosteroids while receiving IV antimicrobials (Table E1). Numerically more participants receiving their treatment both in the hospital and at home began home treatment after randomization, but there were few differences based on location at Visit 2 (Table E2). Those who were discharged to home after Visit 2 were more likely to have higher SES, a lower mean BMI, and to live a greater distance from the treatment center.

Treatment durations

By design, overall treatment duration was shorter for participants in the ERR group compared to the NERR group, but the average ERR treatment duration in the hospital was numerically longer (Table 2). For both ERR and NERR groups, mean times spent in the hospital were greater for those participants randomized to the longer treatment durations, i.e., 14 days for ERR and 21 days for NERR. There was a difference in mean duration in hospital for participants assigned to receive 14 days of treatment in the ERR and NERR groups, with mean duration in hospital significantly longer in the 14-day ERR group: 8.9 days (95% CI 8.0, 9.8), compared with 6.9 days (6.3, 7.5) in the 14-day NERR group.

Among participants that received IV antimicrobials both at home and in the hospital, the average hospital treatment durations were similar for ERR and NERR participants (Table 2). Overall, 219 (49%) of participants treated at home and in the hospital went home at or after Visit 2 (Randomization). This proportion was greater in the 14-day ERR treatment arm (58%) than in the 10-day ERR treatment arm (41%), but was similar between the 21-day (50%) and 14-day NERR treatment arms (47%).

Treatment outcomes

Mean $ppFEV_1$ change from Visit 1 to Visit 3, adjusted for randomization strata in IPTW models, was statistically significantly lower for participants receiving IV antimicrobials only at home only compared to others. Those treated for some portion in the hospital had a greater mean response of $ppFEV_1$ of 2.0% (95% CI 0.1, 3.8) and those treated only in the hospital had a greater mean $ppFEV_1$ response of 3.0% (95% CI 1.0, 5.0) compared to those treated at home only (Figure 2). Mean $ppFEV_1$ response for those treated only in the hospital was nominally greater than for those treated at hospital and home which was not statistically significant (Figure 2). Similarly, mean increase in weight and decrease in CRISS were greater for the groups who received all or some treatment in the hospital compared to those treated at home alone, although the differences were only statistically significantly different when comparing all treatment in the hospital to those treated at home alone (Figure 2). Similar patterns were seen comparing treatment location within the ERR and NERR groups. The same analysis using GLM models yielded consistent results, albeit with slightly larger differences between location groups (Table E3). Location of treatment

was not associated with elevated risk for re-treatment with antimicrobials based on Cox proportional hazards model results (Figure E3 and Table E4).

Participants receiving care in both the hospital and home were studied in greater detail to determine if a specific duration in the hospital was associated with a greater clinical benefit. No statistically significant differences in mean ppFEV$_1$ change from Visit 1 to Visit 3 were observed in either the ERR or NERR populations as a function of days spent in the hospital either by t-test (Figure E1) or by linear regression (Figure E2).

There were no differences in the proportion of participants reporting an AE from randomization to end of follow-up according to treatment location; overall 11% of participants reported at least one AE (Table 3). The AE tended to be mild to moderate in severity, but there were numerically more AE recorded as severe in participants treated for some or all time in the hospital. There were few serious AE (SAE) overall, especially in the group treated at home only. Two participants treated in the hospital only had SAEs (PEx), both deemed probably associated with IV antimicrobial treatment. One participant treated at home only had an SAE (acute kidney injury), which was deemed definitely related to IV antimicrobial treatment.

Discussion

IV antimicrobial treatment location is a key decision in the management of CF pulmonary exacerbations (8). The ability to deliver antimicrobials through IV catheters that may remain in place for extended periods (e.g., peripherally inserted central catheters (PICC) or indwelling ports) has made home therapy a common occurrence for people with CF. Indeed, two-thirds of the participants in the STOP2 trial received at least some of their IV antimicrobials in the home setting. Whether this is a best practice, however, has been the subject of some debate. Although the STOP2 protocol did not randomize subjects to be treated at home or in the hospital, this treatment decision was included in the randomization allocation to assure balance for site of treatment among ERR and NERR treatment duration groups. Therefore, the STOP2 trial offers greater insight into the question of whether treatment is better at home or in the hospital.

Overall, mean lung function improvement was greater for participants treated at least partially in the hospital, and mean improvements in respiratory symptoms and weight were greater for participants treated entirely in the hospital, as compared to those treated entirely at home. The greater improvements in lung function and respiratory symptoms for participants treated entirely in the hospital were even seen by Visit 2, as participants treated in the hospital only were more likely to be categorized as ERR than were those treated entirely at home. These outcomes did not differ by duration of IV antimicrobials, an important confounding factor of previous reports on site of treatment. Other limitations to previous comparisons of site of IV treatment have been that they have largely been small, single-center, underpowered retrospective analyses, with no accounting for indication bias. STOP2 was a large multicenter study, with a substantial number of participants, overcoming some of these obstacles, yet there remains the question of indication bias.

The decision of where to treat is often made conjointly by the clinician and the patient. Although many perceive hospitalization as an indication of exacerbation severity, hospitalization is also likely influenced by social factors, including absence of sufficient home support, health insurance allowances, and previous treatment experience. We were not able to know specific reasons for treatment in the hospital as opposed to treatment at home at the individual level, yet we did find key differences between these groups. STOP2 participants treated in the hospital did have more severe disease (i.e., lower mean BMI and $ppFEV_1$) but also less access to outpatient care (e.g., lower socioeconomic status, longer distance to travel) compared to those treated at home. Racial and ethnic minorities had a higher proportion of being treated in the hospital (Black and Hispanics). When we controlled for these factors, we still found improvement in outcomes for hospitalized participants. Males were more likely to be treated in the hospital; whether this is because females were more likely to be treated at home so they could maintain their typically larger role as primary caregivers is unknown. However, if treatment outcomes are truly superior in the hospital, then this raises the possibility that a preference for home treatment could contribute to the lower overall health outcomes for women with CF (24–26).

Our findings are consistent with other studies of this question. A single prospective study randomized participants to home versus hospital IV antimicrobials (13). Participants treated in the hospital had a non-significant greater improvement in $ppFEV_1$ compared to participants treated at home. Notably, the study excluded a large proportion of the potentially eligible participants who were felt to not be suitable for home IV antimicrobials. Furthermore, those who did receive home IV antimicrobials received multiple supportive visits during their treatment, which may not be routine practice, or even be available, in all areas. A more recent large retrospective registry study demonstrated greater improvements in $ppFEV_1$ and recovery of previous baseline $ppFEV_1$ values at centers that provided a greater proportion of IV antimicrobials in the hospital compared to centers more likely to have patients treated at home (16). The results were consistent using multiple techniques to adjust for indication bias and across multiple outcome measures.

Our study has several limitations. As noted earlier, treatment location was not randomized but was accounted for in the stratification of participants for randomization and regression analyses. Nonetheless, residual confounding is possible. However, if indication bias were present, one would predict sicker individuals would be more likely to be hospitalized while those with better home support and adherence to treatments would be more likely to be treated at home, which would introduce bias towards hospitalization not being superior to home IV treatment. The rationale for treatment location was not collected during the study, so we can only speculate why participants were or were not treated at home. The majority of participants who were treated initially in the hospital and completed therapy at home were discharged before Visit 2, i.e., before treatment duration was assigned, so it is unlikely that anticipated treatment duration assignment contributed to treatment location decisions. However, we cannot exclude residual indication bias as a reason that we do not see a positive correlation between days in the hospital and outcomes among those treated at both locations. Exclusion criteria for this study included pediatric patients, those admitted to an intensive care unit, and patients with frequent IV-treated PEx, so these results may not be applicable to them. Differing treatment practices and outcomes at non-study sites or sites outside the

US may also limit generalizability for those groups. The STOP2 study was completed before the widespread availability of elexacaftor-tezacaftor- ivacaftor (ETI), which has greatly reduced the number of IV-treated PEx (27). A prior study of a highly effective CFTR modulator (ivacaftor) did not demonstrate improved return to baseline $ppFEV_1$ compared to subjects on placebo following PEx treatment, suggesting CFTR modulators may not influence exacerbation treatment response (28). However, it is not known how treatment location would affect PEx outcomes in people with CF taking ETI.

In conclusion, among adults with CF treated with IV antimicrobials for a PEx in STOP2, there was benefit to treatment in the hospital with greater mean improvements in lung function, respiratory symptoms, and weight, compared to treatment entirely at home. These benefits occurred despite STOP2 participants treated in the hospital having more severe disease and potentially less access to care than participants treated at home. The improved outcomes for patients treated in the hospital may owe to a more aggressive model of care and monitoring they received, so whether home IV treatment can be improved (e.g., with home respiratory therapy support) to reduce this disparity is unknown. The limitations of home IV antimicrobial therapy should be addressed in order to optimize outcomes for adults with CF being treated at home.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The impact of home vs hospital care is an important clinical question in the treatment of pulmonary exacerbations (PEx)
- We assessed treatment responses for adults with CF treated for PEx with intravenous antibiotics at home, in the hospital, or both
- Compared to PEx treatment at home only, treatment in the hospital was associated with greater mean lung function, respiratory symptom, and weight improvements.

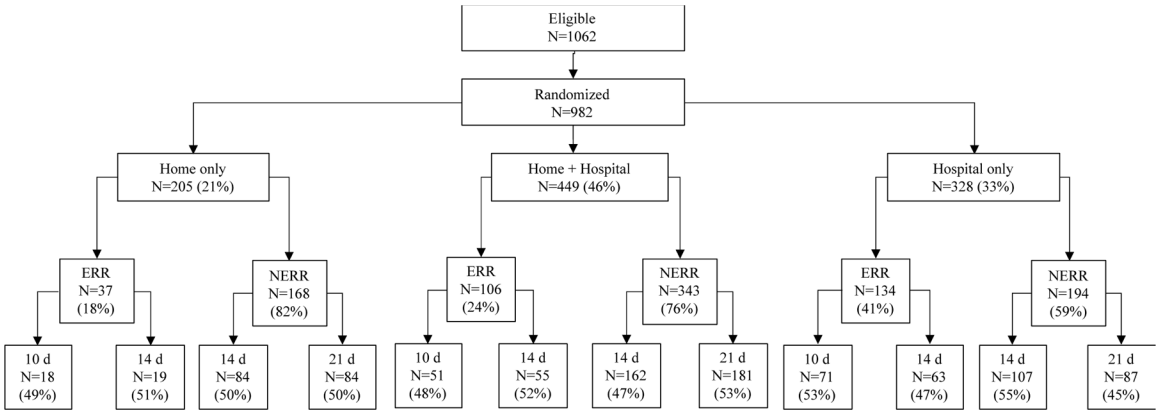

Figure 1.
Consort diagram

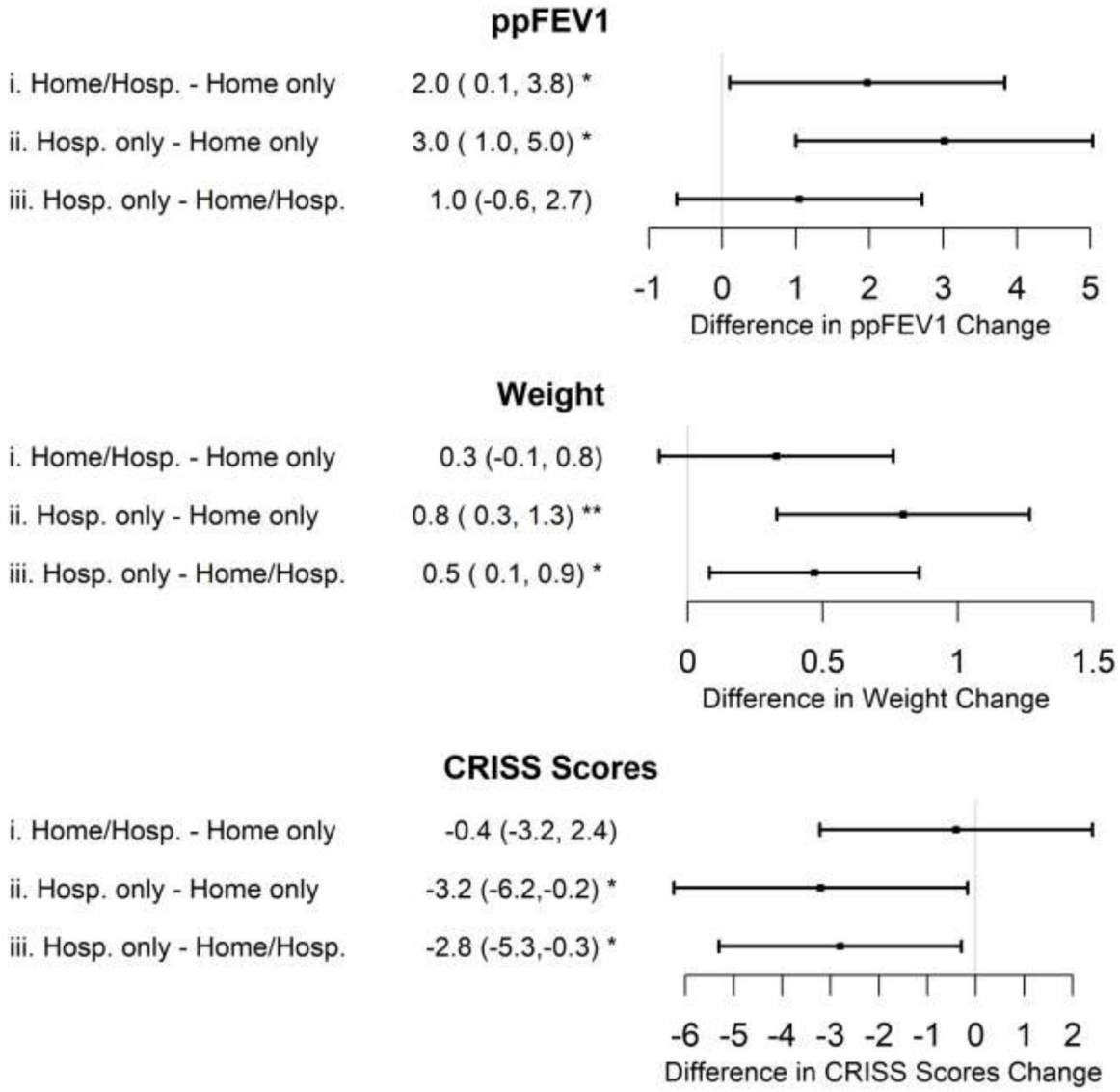

Figure 2.

Point estimates and 95% Confidence Intervals for changes from Visit 1 to Visit 3 for $ppFEV_1$, CRISS, and weight (kg) according to treatment location, estimated using IPTW models.

** indicates p-values ≤0.001, * indicates p-values ≤0.05; For each outcome, p-values are adjusted for family-wise comparison using Tukey's method.

Table 1.

Characteristics at enrollment of participants by location of IV antimicrobial treatment

	Home Only (N=205) n (%)	Home + Hospital (N=449) n (%)	Hospital Only (N=328) n (%)	Total (N=982) n (%)	p-value *[1]*
Female sex	115 (56.1%)	246 (54.8%)	135 (41.2%)	496 (50.5%)	< 0.001
Race					0.056
White	195 (95.1%)	423 (94.2%)	295 (89.9%)	913 (93.0%)	
Black	3 (1.5%)	13 (2.9%)	19 (5.8%)	35 (3.6%)	
Other/Mixed	7 (3.4%)	13 (2.9%)	14 (4.3%)	34 (3.5%)	
Hispanic ethnicity	8 (3.9%)	23 (5.1%)	33 (10.1%)	64 (6.5%)	0.005
CFTR genotype					0.37
Homozygous F508del	98 (47.8%)	214 (47.7%)	169 (51.5%)	481 (49.0%)	
Heterozygous F508del	75 (36.6%)	182 (40.5%)	113 (34.5%)	370 (37.7%)	
Other/Unknown	32 (15.6%)	53 (11.8%)	46 (14.0%)	131 (13.3%)	
BMI ≤18 kg/m^2	16 (7.8%)	38 (8.5%)	57 (17.4%)	111 (11.3%)	< 0.001
ppFEV$_1$ ≥50%	95 (46.3%)	220 (49.0%)	126 (38.4%)	441 (44.9%)	0.012
≥2 PEx in prior year	118 (57.6%)	255 (56.8%)	199 (60.7%)	572 (58.2%)	0.54
Chronic oral antimicrobials	106 (51.7%)	252 (56.1%)	159 (48.5%)	517 (52.6%)	0.10
HEMT	19 (9.3%)	34 (7.6%)	13 (4.0%)	66 (6.7%)	0.037
Insulin dependent CFRD	59 (28.8%)	126 (28.1%)	95 (29.0%)	280 (28.5%)	0.96
Non-insulin dependent CFRD	17 (8.3%)	45 (10.0%)	33 (10.1%)	95 (9.7%)	0.75
ABPA	22 (10.7%)	41 (9.1%)	26 (7.9%)	89 (9.1%)	0.55
NTM treated in last 2 years	6 (2.9%)	29 (6.5%)	15 (4.6%)	50 (5.1%)	0.14
Pneumothorax in last 2 years	3 (1.5%)	11 (2.4%)	4 (1.2%)	18 (1.8%)	0.41
Treatment Duration					< 0.001
10 days	18 (8.8%)	51 (11.4%)	71 (21.6%)	140 (14.3%)	
14 days	103 (50.2%)	217 (48.3%)	170 (51.8%)	490 (49.9%)	
21 days	84 (41.0%)	181 (40.3%)	87 (26.5%)	352 (35.8%)	
SES					< 0.001
No-tier	71 (34.6%)	181 (40.3%)	162 (49.4%)	414 (42.2%)	
Low-tier	31 (15.1%)	77 (17.1%)	74 (22.6%)	182 (18.5%)	
Mid-tier	24 (11.7%)	52 (11.6%)	33 (10.1%)	109 (11.1%)	
High-tier	79 (38.5%)	139 (31.0%)	59 (18.0%)	277 (28.2%)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age, years	32.6 (10.8)	30.5 (9.4)	28.5 (9.1)	30.3 (9.7)	< 0.001
BMI, kg/m ^{2}	22.2 (3.7)	22.4 (4.1)	21.5 (4.0)	22.1 (4.0)	0.007
Visit 1 ppFEV$_1$	51.0 (19.0)	51.2 (20.5)	47.3 (20.8)	49.8 (20.3)	0.021
Average ppFEV$_1$ 6 months prior to Visit 1 *[3]*	55.7 (19.4)	55.2 (20.2)	52.3 (20.4)	54.3 (20.1)	0.099
Change from average ppFEV$_1$ 6 months prior to Visit 1	−4.1 (8.3)	−4.0 (8.9)	−4.3 (9.7)	−4.1 (9.1)	0.88
Distance to site, hours *[2]*	1.0 (1.0)	1.3 (1.3)	1.5 (1.5)	1.3 (1.3)	< 0.001

HEMT=highly effective modulator use (ivacaftor, elexacaftor/tezacaftor/ivacaftor), CFRD = cystic fibrosis related diabetes; ABPA=allergic bronchopulmonary aspergillosis; NTM=non-tuberculosis mycobacterium

[1]For categorical values, p-values are derived from chi-squared test with Yates' continuity correction and for continuous variables p-values are from the ANOVA test.

[2]5 participants indicated distance to site >12 hours. These were constrained to 12 hours.

[3]6 Canadian participants were missing CFFPR data and an additional 47 (4.8%) participants did not have a ppFEV$_1$ measure in the 6 months prior to Visit 1. 134 (13.8%) participants had only 1 ppFEV$_1$ measure whereas 795 (81.5%) had >1 ppFEV$_1$ measures in the 6 months prior.

Table 2.

Duration of IV antimicrobials by treatment arm.

All ITT Participants Days of Hospitalization	**ERR All (N=277)**	**ERR 10 days (N=140)**	**ERR 14 days (N=137)**	**NERR All (N=705)**	**NERR 14 days (N=353)**	**NERR 21 days (N=352)**	**Total (N=982)**
Mean (SD)	8.0 (4.6)	7.1 (3.8)	8.9 (5.2)	7.3 (6.5)	6.9 (5.7)	7.7 (7.2)	7.5 (6.0)
Median (Min, Max)	9 (0, 21)	9 (0, 15)	9 (0, 21)	6 (0, 28)	6 (0, 28)	6 (0, 23)	7 (0, 28)
Home + Hospital Participants Days of Hospitalization	**ERR All (N=106) (N=51)**	**ERR 10 days**	**ERR 14 days (N=55)**	**NERR All (N=343)**	**NERR 14 days (N=162)**	**NERR 21 days (N=181)**	**Total (N=449)**
Mean (SD)	6.2 (2.7)	5.5 (2.1)	6.9 (3.0)	6.2 (3.6)	5.7 (2.8)	6.7 (4.1)	6.2 (3.4)
Median (Min, Max)	6 (2, 21)	6 (2, 9)	7 (2, 21)	6 (1, 22)	5 (1, 16)	6 (1, 22)	6 (1, 22)

Table 3.

Adverse events from randomization to end of follow-up.

Randomized IV duration	Home Only (N=205)	Home + Hospital (N=449)	Hospital Only (N=328)	Total (N=982)
Adverse events (AEs)				
Total number AEs	25	75	50	150
Maximum severity of adverse event:				
Mild	8 (32%)	13 (17%)	12 (24%)	33 (22%)
Moderate	16 (64%)	31 (41%)	19 (38%)	66 (44%)
Severe	1 (4%)	27 (36%)	17 (34%)	45 (30%)
Life-Threatening	0 (0%)	4 (5%)	2 (4%)	6 (4%)
Participants with any adverse event	19 (9%)	51 (11%)	40 (12%)	110 (11%)
Person-months follow-up	155	352	218	725
AE rate (AEs/ person-month)	0.16	0.21	0.23	0.21
Serious adverse events (SAEs)				
Total number of SAEs	5	29	18	52
Relatedness of SAE				
Unrelated	4 (80%)	28 (97%)	12 (67%)	44 (85%)
Possibly	0 (0%)	1 (3%)	4 (22%)	5 (10%)
Probably	0 (0%)	0 (0%)	2 (11%)	2 (4%)
Definitely	1 (20%)	0 (0%)	0 (0%)	1 (2%)
Participants with any serious adverse event	3 (1%)	23 (5%)	17 (5%)	43 (4%)
SAE rate (SAEs/person-month)	0.03	0.08	0.08	0.07