Evaluation of Rescue Oral Glucocorticoid Therapy during Inpatient Cystic Fibrosis Exacerbation

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Abstract

Acute pulmonary exacerbation (APE) in CF is characterized by increased pulmonary symptoms attributed to an increase in inflammation. Antimicrobials, airway clearance and nutritional support remain the mainstay of therapy. However, when patients fail to improve, corticosteroids have been reported as an adjunct therapy. We retrospectively examined the use of rescue steroids in a children's hospital during CF APE following at least one week of inpatient therapy without expected improvement from 2013 - 2017. 106 encounters, of 53 unique patients: aged 6-20 years; who had FEV1 percent predicted (FEV1pp) data at baseline, admission, midpoint, and discharge; and had admission duration of at least 12 days were studied. Encounters treated with steroids had less improvement at midpoint percent change from admission in FEV1pp (4.9, $\pm$11.3) than admissions not given steroids change in FEV1pp=20.1, $\pm$24.6; p-value<0.001. Failure to improve as expected was documented 98% of the time as the rationale for steroid use. At discharge, there was no difference in mean FEV1pp (p=0.76). Propensity matching was also evaluated and revealed no difference in admission, midpoint, or discharge FEV1pp between groups. Equally, no difference in FEV1pp at follow-up visit or in time until next APE was detected between groups. Moreover, delay in steroid therapy by waiting until the end of the second week increased length of stay. Secondary analysis for associations including gender, genotype, fungal colonization, or inhaled antimicrobials were non-significant. Our data suggest rescue use of corticosteroids during APE does not predictably impact important outcome measures in CF APE.

INTRODUCTION

In Cystic Fibrosis (CF) lung disease, inflammation due to bacterial colonization and neutrophil recruitment increases during an Acute Pulmonary Exacerbation (APE) [1]. Typical treatment of moderate to severe APE supported by the evidence based CF pulmonary guidelines include intravenous (IV) antibiotics in the hospital setting, maintenance of chronic therapies for lung health, and more frequent administration of airway clearance therapy [2]. Despite these treatments, as many as 25% of patients fail to recover to their baseline FEV1 after treatment [3].

Corticosteroid therapy and its potent anti-inflammatory property has long been postulated to be of benefit in CF either by preventing decline in baseline FEV1 percent predicted (FEV1pp) or reversing decline associated with APE. CF pulmonary guidelines for maintenance of lung health report that there is insufficient evidence to recommend routine use of oral corticosteroids in children with CF due to "net-negative" effects [4].

In clinical practice, steroid use remains variable. Across 38 CF centers treating hospitalized pediatric patients with CF, steroid treatment use ranged from 3-61% during APE [5]. In the STOP trial, a prospective observational study that assessed APE treatment practices at 11 CF centers, 21% of the 220 enrolled patients were given corticosteroids as adjunct therapy [6]. Our pediatric CF center providers have an informal practice of five to seven day "rescue" steroid treatment when standard treatment fails to demonstrate expected improvement in FEV1pp following at least one week of guideline driven hospital based therapy. We hypothesized that use of oral corticosteroids during failed inpatient APE management would increase FEV1pp at discharge and at

hospital follow-up visit. We also wanted to understand when and why providers engage in this approach. To evaluate our hypotheses, we conducted a retrospective study examining a cohort of CF patients and recovery to their baseline FEV1pp after hospital admission for APE, FEV1pp at follow up visit, and time to next APE compared to routine treatment. We also employed a propensity score matching scheme to more fairly estimate treatment effect by controlling specific covariates.

METHODS

Study Sample

As part of this retrospective cohort study, we identified encounters in which patients with CF were hospitalized from 6/1/2013 through 8/31/2017 at Doernbecher Children's Hospital. Of the 822 CF patient admissions during our study period, corticosteroids were ordered in 188 encounters and 122 of those met the following inclusion criteria: patient age of 6-20 years; patient able to perform spirometry; and, admission duration of at least 12 days (Figure 1). We additionally excluded encounters if the following were true: missing FEV1pp data at baseline, admission, midpoint or discharge, steroids were ordered by care teams other than pulmonary, such as for otolaryngology procedures; steroids were ordered upon admission; patient history of adrenal insufficiency or chronic oral steroid use; patient diagnosis of CF related diabetes; FEV1pp less than 40% at baseline; patient with CPAP/BiPAP requirement; and, patient history of ABPA or lung transplant. Prior to data abstraction, we selected non-steroid treated, comparison encounters that were similar in date, age, and gender to the steroid encounters; these comparison encounters were selected blindly from CF encounters that would have otherwise met our inclusion/exclusion criteria. Our final study sample consisted of 106 encounters, with 53 unique patients; 63 encounters included corticosteroid use and 43 were matched non-steroid encounters. This study was approved by the Oregon Health and Science University Institutional Review Board (IRB#16866).

Variable Definitions

Outcomes. 1) FEV1 percent predicated (FEV1pp) (measured at admission, midpoint, discharge, hospital follow up). At admission values are typically in the clinic when decision to admit was made, midpoint was between 5-7 days after hospitalization, discharge reflects the day of discharge or 1-2 days prior, hospital follow-up was typically 4-6 weeks following discharge. We also evaluated restoring patients to their baseline FEV1pp after hospital admission for APE (discharge/baseline FEV1pp), and time to next APE compared to routine treatment. The baseline FEV1pp was the best value in the 12 months. A secondary outcome was length of hospital stay.

Steroids. Reason for steroid prescription was recorded; reasons documented included: poor improvement in FEV1pp, IgE elevation (but not ABPA diagnosis), previous positive response to steroids (FEV1pp).

Covariates. Demographic and additional clinical data collected included gender (male/female), genotype (dF508/dF508, dF508/other, other/other), length of stay, IgE values, antimicrobial treatment regimen, sputum culture data and best baseline spirometry.

Statistical Analysis

In brief, we present encounter characteristics for our overall sample and a propensity score matched sample (PS-matched sample). We generated a PS-matched sample to account for potential confounding, specifically confounding by indication, and selection bias. When modeling the association between steroid administration and our outcomes, we used only the PS-matched sample of encounters.

Descriptive statistics were used to summarize characteristics of our overall sample of encounters and our PS-matched sample; frequencies and percentages were calculated for categorical variables, while means and standard deviations were calculated for continuous variables. Encounters in which patients received a corticosteroid were compared with encounters in which patients did not receive a corticosteroid by using t-tests or Somers' D for continuous variables and chi-square tests for categorical variables. As a patient may be

represented more than once in our study sample, leading to a potential correlation of encounters within a patient, we adjusted these tests for clustered errors as suggested by Donner & Klar [7] and Newsom[8].

We estimated average length of stay in our overall sample for a patient who received a steroid and the average day in which that steroid was administered using an intercept only regression with cluster-robust standard errors. We then regressed day of administration on length of stay to determine the correlation between these clinical course measures. A cluster-robust variance estimator was used to account for the possible repeated encounters within a patient.

In order to assess the association between steroid use and our outcomes, we built a series of regression models, which included an unadjusted (Model 1) and a fully-adjusted model (Model 2). Restoration of patients to their baseline FEV1pp after hospitalization and FEV1pp at follow-up were modeled using linear regression. Time to next APE was modeled using a Cox's proportional hazard (PH) regression. In each model, we included only our PS-matched cohort (see section below for details). Additionally, we accounted for the correlation of encounters within patients who were hospitalized more than once using cluster-robust variance estimators. We utilized a change-in-estimate variable selection strategy [9] to create our fully-adjusted models (Model 2), in which a covariate or combination of covariates were retained in the model if they changed the regression coefficient for steroid by approximately 20% or more. Model assumptions and fit were assessed; steroid administration violated the proportional hazards assumption, which we addressed by splitting our follow-up period at the median event time, creating two Cox PH models [10]. We censored patients still at risk after the median event time in the first Cox PH model, and included only patients still at risk beyond the median event time in the second Cox PH model.

Propensity Score Methods

As corticosteroid use was not randomly assigned to each encounter, we created a propensity score model [11] for steroid prescription in order to account for potential confounding and selection bias; we used the propensity score estimated from this model to create our PS-matched sample. In this study, the propensity score was the conditional probability that a patient would receive a steroid during their hospitalization, given a set of covariates. For each of our encounters, we estimated the propensity for steroid prescription using a non-parsimonious multivariable logistic regression model (C statistic= 0.8779). We used the following variables in our propensity score model: sex, genotype, inhaled steroids, IgE value, asthma, reactive airway disease or impaired glucose tolerance diagnosis, best baseline spirometry, admission FEV_1, change from baseline to admission FEV_1, change from admission to midpoint FEV_1, change in antibiotics treatment during hospitalization, positive fungal sputum culture, history of nontuberculous mycobacteria, and bacteria present in sputum cultures.

As some patients were represented more than once in our study sample, we initially modeled the propensity score using a random-effects logistic regression model. Likelihood ratio tests indicated that the random-effects model did not outperform the traditional logistic regression model. As well, the estimated ICC from the random-effect model indicated that the odds of steroid administration was only slightly correlated within the individual patient. As few propensity score methodologies and applied works exist using clustered data[12], and greater than half of our patient pool was represented by one encounter (54%; only 26% of patients had >=3 encounters), we chose to use a traditional logistic regression when estimating our propensity score and a simple matching algorithm when matching encounters.

We matched encounters 1:1 using a greedy algorithm on the logit of the propensity score and a caliper width of 0.2 the standard deviation of the logit of the propensity score. This resulted in a PS-matched sample of 25 non-steroid encounters and 25 steroid encounters, representing 19 and 17 patients in each group, respectively. We evaluated the balance in the distribution of encounter characteristics between the two groups using t-tests or Somers' D for continuous variables and chi-square tests for categorical variables; we adjusted these tests for clustered errors as described in the previous section. When modeling the association between our outcomes and steroid administration, we used this PS-matched sample to compare our outcomes among encounters with equivalent likelihood of corticosteroid prescription. All analyses were conducted in Stata/SE, version

15 (StataCorp, College Station, TX).

RESULTS

The total study sample was 106 encounters. In 63 (59%) of these encounters, corticosteroid were prescribed; Table 1 summarizes encounter characteristics according to steroid administration. Fifty-three patients were represented by the 106 encounters, 11 patients (21%) were never given a steroid over all their hospitalizations and 27 patients (51%) were always administered a steroid, while the remainder (28%) had hospitalizations with and without steroids given. Twenty-nine (55%) of our study sample was hospitalized once, 19% was hospitalized twice, and 17% experiences [?]3 hospitalizations.

Our analyses revealed that >98% of documented reasons for steroid use was for poor improvement in clinical response. In our overall sample, encounters in which patients were given steroids had less improvement at midpoint (average percent change from admission in FEV1pp=4.9, SD=11.3) than encounters in which patients were not given steroids (average percent change in FEV1pp=20.1, SD=24.6; p-value<0.001; Table 1).

Because of the potential for confounding by indication, we generated a propensity score matched (PS-matched) sample, which controlled for the non-equivalent likelihood of steroid use in the overall sample. The PS-matched sample included 25 matched encounters, representing 36 patients total (Table 2, Figure 2). In the PS-matched sample, there was no longer a significant difference between groups for the change in FEV1pp at midpoint (p-value=0.661). FEV1pp did not differ between groups at baseline, at admission, or at discharge in either the overall sample or the PS-matched sample.

Length of Stay

Length of stay (LOS) data was compared for the overall sample. The estimated average LOS for a patient who received a steroid was 17.68 days (standard error [SE]=0.47) and the estimated average day in which that steroid was administered was 10.8 (SE=0.34). The day of steroid administration and LOS were moderately correlated (r=0.465). Figure 3 displays this association. The estimated average length of stay for a patient who did not receive a steroid was 14.44 days (SE=0.37).

Steroid Dosing

The mean dose was 50.86 mg (SD=11.85) and the mean dose per weight was 1.27 mg/kg (SD=0.49) (Table 1). The duration of treatment was 6.78 (SD=6.24). The large SD was attributed to four patients who were treated for 42, 37, 25, 16 days respectively. The provider team utilizes doses of 2 mg/kg per day with an upper limit of 60 mg per day of oral prednisone in clinical practice.

Restoring patients to their baseline FEV1pp

Our fully-adjusted PS matching model (Model 2) suggests no difference in final FEV1 improvement at discharge between the treated and untreated groups. Steroid use was not associated with restoration of the CF patient to their baseline FEV1pp (fully-adjusted β=-0.025, 95% CI: -0.071, 0.020; Table 3). Patients who received steroid therapy restored to an estimated 90.7% (standard error=2.1) of their baseline FEV1pp, while patients who did not receive a steroid restored to an estimated 93.3% (SE=1.2) of their baseline FEV1pp; the difference in restoration of baseline FEV1pp was 2.5% lower for encounters in which CF patients were given a steroid (p-value=0.271). This was not statically significant.

FEV1pp at Follow-up

For patients given a steroid during hospitalization, follow-up FEV1pp was 4.152 percentage points higher when compared to patients who were not given a steroid (fully-adjusted β=4.152, 95% CI: -1.203, 9.506, p-value=0.129; Table 3). Follow-up FEV1pp was an estimated 79.8 percentage points (SE=1.79) for encounters in which patients were given a steroid and was an estimated 75.7 percentage points (SE=2.08) for encounters in which patients were not given a steroid. This was not statically significant.

Time to Next APE

In the PS-matched sample, all 48 of the encounters with follow-up data required new antimicrobial treatment and the median event time was 82 days. Figure 3 displays Kaplan-Meier plots for each group and we can see that steroid administration had a time-varying effect on next APE. To overcome this violation of the proportional hazard assumption, we created a Cox model censoring patients still at risk after 82 days, and another model including only patients still at risk beyond 82 days. The effect of steroid administration reduced the risk of APE for the first model (fully-adjusted HR=0.534, 95% CI: 0.208, 1.372, p-value=0.193; Table 3), while steroid use appeared to increase risk in the second model (HR=1.716, 95% CI: 0.431, 6.838, p-value=0.444). However, the results were not significant.

Discussion

This overall sample result in this study would appear to suggest that steroids positively alter FEV1pp trajectory when there is initial failure to progress during APE when we examine all eligible encounters (Table 1). This assumes that all CF admissions were 12-14 days in length and that persons not showing improved FEV1pp after 5-7 days of treatment do not return to baseline lung function after two weeks of conventional treatment. Those assumptions are incorrect and highlight the limits of retrospective cohort studies. To address this limitation, we then used propensity score matching within our data set. This allows the construction of a non-steroid treated control group against the steroid treated group by matching characteristics such as gender, lung function at baseline, or CFTR mutation (Model 1, Table 2). This PS-matching approach has been called a "retrospective randomization" by some authors as it seeks to reduce assignment bias and mimic randomization[13]. Thus in Models 1 and 2, we found no significance difference in FEV1pp at baseline or discharge. Moreover, extended analysis including FEV1pp at follow-up visit and time to next exacerbation were not significantly different.

Although our data showed a non-significant trend in time to next exacerbation requiring antimicrobial therapy, this is likely due to size of sample. The median time to next antibiotics is 99 (IQR: 51, 123.5) in the steroid group versus 70.5 (IQR: 37-152). The Kaplan-Meier graph (Figure 3) shows that for the first 80 days, the no-steroid group is more likely to need antimicrobial treatment, however beyond 80 days, the steroid group is more likely. The factors such as low number of patients (n=34) in the PS-matched sample, as well as the retrospective nature of the study and non-standardized follow up appointments could contribute to the non-significance.

When FEV1pp or clinical health fails to improve as expected during APE treatment, providers and patients alike look for alterations in the treatment plan to improve lung function to baseline and overall well-being. At our center, approaches might include changing the antimicrobial regimen, increasing the total days of IV therapy, increasing airway clearance therapy frequency from 4 to 5 session per day, or adding corticosteroids. These options are presented to the patient and family. Our center generally utilizes a "rescue" dose of oral prednisone 2 mg/kg/day up to 60 mg given for 5-7 days. Considerations for steroid therapy include: positive response on previous use, suspected asthma, and physical exam finding including wheezing. Although not reviewed in the study, management of hyperglycemia can be a concern even in short term rescue use. Currently, there is no published guidance or recommendation concerning steroid use during CF exacerbations.

There has been previous interest in oral steroid therapy in CF. Long-term (12 week) prednisolone therapy in 24 clinically stable children with CF demonstrated decreased concentration of inflammatory markers including IL-1α, sIL-2R, and IgG [14]. This study protocol dosed prednisolone at 2 mg/kg/day for the first week, then tapered to 1 mg/kg every other day for the following 10 weeks. FEV1 benefit was associated with the steroid group at day 14, however significance was not maintained at week 12. While there is some data that alternate-day steroid use for three weeks to four years improves pulmonary function [14-16], adverse events such as poor glucose tolerance, insufficient linear growth, and *Pseudomonas aeruginosa* colonization are noted after long-term administration of steroids in CF.

Short-term use of systemic high dose steroids appears to have even less evidence for use. CF pulmonary exacerbation treatment guidelines report that there is insufficient evidence for use of oral corticosteroids during APEs [2]. Three studies show that short term therapy for three to ten days show modest efficacy in

improving pulmonary function. In a pilot placebo-controlled study of oral prednisone therapy (2 mg/kg, max 60 mg) administration for the first five days of hospitalization in patients with APE, FEV1pp was consistently higher in the steroid-treated group, however the FEV1 difference did not reach statistical significance in this small study of 24 patients [17]. A case report of four young patients under age six with no clinical improvement after IV antimicrobial therapy for APE showed dramatic improvement in respiratory distress and oxygen requirements after IV methylprednisolone burst (1 g/1.73 m^2 per day for 3 days) [18]. A study of 20 infants with APE demonstrated a statistically significant increase in forced expiratory flows after treatment with hydrocortisone in addition to standard therapy, with no significant increase in placebo treated group [19]. Additionally, several of the infants given placebo in this study, and none of the steroid-treated infants, had a recurrence in respiratory symptoms between discharge and outpatient follow up. Overall, studies remain poorly powered and larger clinical trials would be needed to better elucidate the role of steroids used during treatment of pulmonary exacerbations.

An alternate approach when failure to improve is noted during APE is to increase the number of treatment days. However, in our experience most families and their children are opposed to longer hospital stays. Antimicrobial therapy in CF exacerbation ranges from 10-21 days with most individuals treated between 10 and 14 days. [20]Studies examining length of IV therapy suggest diminishing returns after 14 days of therapy [21]. Treatment durations of 10 versus 14 versus 21 days of conventional therapy has also been recently been studied by the CF Foundation and is also uncertain benefit (NCT02781610) [Goss]. The longer length of stay noted in our overall study cohort was primarily due to initiating steroid after poor response to 10- 14 days of therapy. As our conventional therapy duration is 10-14 days, the providers' intent was to reassess lung function prior to steroid therapy. This often resulted in at least five more days of hospital care and additional spirometry at the end of the steroid treatment while continuing other treatments including antimicrobial therapy. Despite anecdotal reports of improvement, our Models 1 and 2 suggest no benefit overall to acute rescue steroids. Waiting until day 12-14 to start steroid treatment may only add unnecessary hospital days.

To our knowledge, there are no trials showing the effectiveness of switching antimicrobial therapy when using respiratory culture-based guided therapy when patients fail to progress. As summarized by Chmiel et al current thinking of CF airway pathogens is based on the recovery of a known cohort on surveillance cultures [22]. Extended culturing techniques have demonstrated previously undocumented species in the CF microbiome including anaerobic species, however, these techniques are not in use in routine care. While diverse in youth, the CF microbiome diversity narrows as the patient ages[23], suggesting the ability to tightly narrow antimicrobial coverage. Importantly, considering agents against MRSA or*Pseudomonas aeruginosa* when not treated might be an alternate when confronted with failure to progress.

There is conflicting evidence that corticosteroid use is a risk factor for nontuberculous mycobacteria (NTM) colonization. Review of the literature notes that isolation of *Aspergillus spp* or Allergic Bronchopulmonary Aspergillosis (ABPA) diagnosis more common in NTM positive patients. Corticosteroid therapy is the mainstay of ABPA treatment [24]. In a study of 139 patients with CF in Israel, six developed NTM lung disease [25]. Five of the six patients had prolonged steroid treatments, four of which were treatment for an ABPA diagnosis prior to NTM acquisition. Of the 133 patients without NTM, only one had ABPA and prolonged steroids ($p<0.001$), therefore suggesting steroids as a risk factor for NTM. Conversely, a nested-cohort study found there was less steroid exposure days patients with NTM disease meeting ATS criteria than those who were NTM negative ($p<0.05$) [26]. This study included 159 patients. Sixty were NTM positive, 22 of which had NTM disease meeting ATS criteria. A multicenter study in Israel reviewed 186 patients, 42 of which had NTM isolation [27]. A multivariate analysis found an increased odds of *Aspergillus spp*in the NTM positive cohort (odds ratio 5.14, 95% CI 1.87–14.11). In a retrospective database review in the US, NTM was noted in 166 individuals of the 1216 [28]. *Aspergillus fumigatus* was more frequently found in NTM positive patients 13.9% vs. 7.2%, respectively, $p<0.01$. It appears that the Aspergillus colonization, not the steroids themselves may be the association with NTM positivity. Of the studies concerning for steroids, they include prolonged use, thus short "rescue" dosing regimens of steroids may not warrant alarm for development of NTM infection.

Our analysis is limited by sample size and retrospective nature, these data suggest a prospective trial with clear criteria for starting "rescue" treatment should be undertaken. There continues to be interest in the use of steroids in CF APE and a clear understanding of their use is warranted. A current randomized, double blind, placebo controlled trial of prednisone for patients failing to recover their FEV1 baseline at 7 days into IV antibiotic treatment for APE underway (NCT03070522) [Waters].

1. Bhatt JM. 2013. Treatment of pulmonary exacerbations in cystic fibrosis. Eur Respir Rev. 22(129):205-216.

2. Flume PA, Mogayzel PJ, Jr., Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, Marshall BC. 2009. Cystic fibrosis pulmonary guidelines: Treatment of pulmonary exacerbations. American journal of respiratory and critical care medicine. 180(9):802-808.

3. Sanders DB, Hoffman LR, Emerson J, Gibson RL, Rosenfeld M, Redding GJ, Goss CH. 2010. Return of fev1 after pulmonary exacerbation in children with cystic fibrosis. Pediatric pulmonology. 45(2):127-134.

4. Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ, Jr., Willey-Courand DB, Bujan J, Finder J, Lester M, Quittell L et al. 2007. Cystic fibrosis pulmonary guidelines: Chronic medications for maintenance of lung health. American journal of respiratory and critical care medicine. 176(10):957-969.

5. Cogen JD, Oron AP, Gibson RL, Hoffman LR, Kronman MP, Ong T, Rosenfeld M. 2017. Characterization of inpatient cystic fibrosis pulmonary exacerbations. Pediatrics. 139(2).

6. West NE, Beckett VV, Jain R, Sanders DB, Nick JA, Heltshe SL, Dasenbrook EC, VanDevanter DR, Solomon GM, Goss CH et al. 2017. Standardized treatment of pulmonary exacerbations (stop) study: Physician treatment practices and outcomes for individuals with cystic fibrosis with pulmonary exacerbations. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 16(5):600-606.

7. Flynn TN. 2001. Design and analysis of cluster randomization trials in health research.: Allan donner and neil klar. London: Arnold, 2000, pp.178, £35.00. Isbn: 0-340-69153-0. International Journal of Epidemiology. 30(2):407-408.

8. Newson R. 2006. Confidence intervals for rank statistics: Somers' d and extensions. The Stata Journal. 6(3):309-334.

9. MacDonald KD, Vesco KK, Funk KL, Donovan J, Nguyen T, Chen Z, Lapidus JA, Stevens VJ, McEvoy CT. 2016. Maternal body mass index before pregnancy is associated with increased bronchodilator dispensing in early childhood: A cross-sectional study. Pediatric pulmonology. 51(8):803-811.

10. Bellera CA, MacGrogan G, Debled M, de Lara CT, Brouste V, Mathoulin-Pélissier S. 2010. Variables with time-varying effects and the cox model: Some statistical concepts illustrated with a prognostic factor study in breast cancer. BMC Med Res Methodol. 10:20-20.

11. Adelson JL, McCoach DB, Rogers HJ, Adelson JA, Sauer TM. 2017. Developing and applying the propensity score to make causal inferences: Variable selection and stratification. Front Psychol. 8:1413.

12. Arpino B, Cannas M. 2016. Propensity score matching with clustered data. An application to the estimation of the impact of caesarean section on the apgar score. Stat Med. 35(12):2074-2091.

13. Jupiter DC. 2017. Propensity score matching: Retrospective randomization? J Foot Ankle Surg. 56(2):417-420.

14. Greally P, Hussain MJ, Vergani D, Price JF. 1994. Interleukin-1 alpha, soluble interleukin-2 receptor, and IgG concentrations in cystic fibrosis treated with prednisolone. Archives of disease in childhood. 71(1):35-39.

15. Auerbach HS, Williams M, Kirkpatrick JA, Colten HR. 1985. Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis. Lancet (London, England). 2(8457):686-688.

16. Eigen H, Rosenstein BJ, FitzSimmons S, Schidlow DV. 1995. A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. Cystic fibrosis foundation prednisone trial group. The Journal of pediatrics. 126(4):515-523.

17. Dovey M, Aitken ML, Emerson J, McNamara S, Waltz DA, Gibson RL. 2007. Oral corticosteroid therapy in cystic fibrosis patients hospitalized for pulmonary exacerbation: A pilot study. Chest. 132(4):1212-1218.

18. Ghdifan S, Couderc L, Michelet I, Leguillon C, Masseline B, Marguet C. 2010. Bolus methylprednisolone efficacy for uncontrolled exacerbation of cystic fibrosis in children. Pediatrics. 125(5):e1259-1264.

19. Tepper RS, Eigen H, Stevens J, Angelicchio C, Kisling J, Ambrosius W, Heilman D. 1997. Lower respiratory illness in infants and young children with cystic fibrosis: Evaluation of treatment with intravenous hydrocortisone. Pediatric pulmonology. 24(1):48-51.

20. Plummer A, Wildman M, Gleeson T. 2016. Duration of intravenous antibiotic therapy in people with cystic fibrosis. Cochrane Database Syst Rev. 9:CD006682.

21. Collaco JM, Green DM, Cutting GR, Naughton KM, Mogayzel PJ, Jr. 2010. Location and duration of treatment of cystic fibrosis respiratory exacerbations do not affect outcomes. American journal of respiratory and critical care medicine. 182(9):1137-1143.

22. Chmiel JF, Aksamit TR, Chotirmall SH, Dasenbrook EC, Elborn JS, LiPuma JJ, Ranganathan SC, Waters VJ, Ratjen FA. 2014. Antibiotic management of lung infections in cystic fibrosis. I. The microbiome, methicillin-resistant staphylococcus aureus, gram-negative bacteria, and multiple infections. Ann Am Thorac Soc. 11(7):1120-1129.

23. Stokell JR, Gharaibeh RZ, Hamp TJ, Zapata MJ, Fodor AA, Steck TR. 2015. Analysis of changes in diversity and abundance of the microbial community in a cystic fibrosis patient over a multiyear period. Journal of Clinical Microbiology. 53(1):237-247.

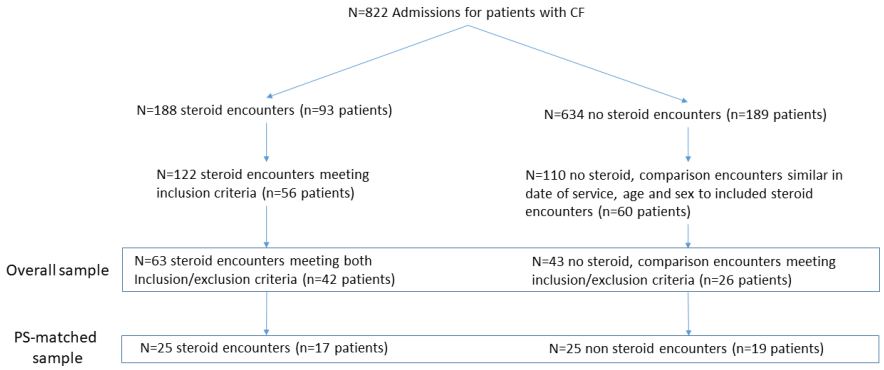
24. Janahi IA, Rehman A, Al-Naimi AR. 2017. Allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Ann Thorac Med. 12(2):74-82.

25. Mussaffi H, Rivlin J, Shalit I, Ephros M, Blau H. 2005. Nontuberculous mycobacteria in cystic fibrosis associated with allergic bronchopulmonary aspergillosis and steroid therapy. Eur Respir J. 25(2):324-328.

26. Olivier KN, Weber DJ, Lee JH, Handler A, Tudor G, Molina PL, Tomashefski J, Knowles MR. 2003. Nontuberculous mycobacteria. Ii: Nested-cohort study of impact on cystic fibrosis lung disease. American journal of respiratory and critical care medicine. 167(6):835-840.

27. Levy I, Grisaru-Soen G, Lerner-Geva L, Kerem E, Blau H, Bentur L, Aviram M, Rivlin J, Picard E, Lavy A et al. 2008. Multicenter cross-sectional study of nontuberculous mycobacterial infections among cystic fibrosis patients, israel. Emerg Infect Dis. 14(3):378-384.

28. Esther CR, Jr., Esserman DA, Gilligan P, Kerr A, Noone PG. 2010. Chronic mycobacterium abscessus infection and lung function decline in cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 9(2):117-123.



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