Inhaled Tobramycin Effectively Reduces FEV₁ Decline in Cystic Fibrosis

An Instrumental Variables Analysis

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Abstract

Rationale: The efficacy of inhaled tobramycin on chronic *Pseudomonas aeruginosa* infections in patients with cystic fibrosis (CF) has been established in clinical trials. However, little is known about its clinical effectiveness on lung function outside randomized controlled trial settings; conventional analysis of existing registry data has heretofore been confounded by treatment selection bias.

Objective: To determine effectiveness of inhaled tobramycin on FEV₁ decline in patients with chronic *P. aeruginosa* infections using observational data from the Cystic Fibrosis Foundation Patient Registry.

Methods: Patient-level tobramycin use was measured at first chronic *P. aeruginosa* infection (n = 13,686 patients; age, 6–21 yr). Decline in FEV₁ 2 years after infection was estimated for patients treated with tobramycin and compared with untreated patients. Multiple linear regressions with confounder adjustment and propensity scores were used to estimate mean FEV₁ decline for each group. Because care is organized by centers, we used center-specific

prescription rates as an instrument to reduce treatment-by-condition bias.

Measurements and Main Results: Using center-level prescribing rates, instrumental variables analysis showed less FEV₁ decline for patients who received tobramycin when first eligible compared with those who did not receive tobramycin (difference, 2.55% predicted; 95% confidence interval, 0.16–4.94; P = 0.0366).

Conclusions: Inhaled tobramycin is effective in reducing lung function decline among patients 6 to 21 years of age with CF. Because CF care is organized by center, using center-specific prescription rates as an instrumental variable is a feasible approach to using the Cystic Fibrosis Foundation Patient Registry to determine treatment effectiveness. More generally, this approach can correct for treatment-by-condition bias arising from observational studies.

Keywords: cystic fibrosis; pulmonary function; tobramycin effectiveness; epidemiology; treatment selection bias

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Respiratory failure is the primary cause of death in cystic fibrosis (CF), a lung disease characterized by chronic airway infection, inflammation, and progressive loss of lung function. Because *Pseudomonas aeruginosa* is the most common chronic pulmonary infection in patients with CF (1)

and is associated with increased airway inflammation, a higher frequency of pulmonary exacerbations, faster pulmonary function decline, and higher mortality (2–4), evidence for the effectiveness of treatments for chronic *P. aeruginosa* infection is needed.

Inhaled tobramycin has been established as an efficacious, well-accepted therapy for treating chronic *P. aeruginosa* infection in CF through several randomized clinical efficacy trials and expert evidence review (5–8). Chronic use of inhaled tobramycin received the highest grading in

the CF Pulmonary Guidelines (5) and has been recommended by the Cystic Fibrosis Foundation (CFF) for patients 6 years of age and older with chronic *P. aeruginosa* infection. Despite evidence for efficacy and these recommendations, only 65.9% of patients meeting recommendations were prescribed inhaled tobramycin in 2011 (1). Although quality deficits are associated with a range of variables (9), evidence for effectiveness (as opposed to efficacy) of tobramycin in clinical practice might spur efforts to close this gap.

In the absence of long-term randomized trials of effectiveness, observational studies are the most likely source of evidence for effectiveness. However, randomized controlled trials and observational studies can have conflicting results, usually arising from treatment selection bias that occurs because, in observational studies, treatment is related to severity of illness. Thus, in observational studies, one is likely to demonstrate that sicker patients receive more treatment and experience worse outcomes (because they are sicker). Indeed, a previous observational study using the Cystic Fibrosis Foundation Patient Registry (CFFPR) found that treatment with tobramycin was associated with an increased risk of death (10). Although the authors note that treatment is most likely protective, they also mention that conclusions are likely affected by the presence of uncontrolled confounding. Although a more recent assessment of the CFFPR showed that tobramycin use was associated with a lower risk of death (11), such inconsistency highlights the need for specialized analytic approaches in observational studies to control for this treatment selection bias.

One approach that has been previously used to address unmeasured confounding is instrumental variables analysis, which seeks to identify a variable—an “instrument”—that is related to the outcome only through the treatment (12, 13). In this sense, randomization is an excellent instrument in that it is, by design, related to outcome only through treatment allocation. Propensity scores and regression are other methods to account for treatment selection bias (14), but they account only for measured confounders (e.g., measured comorbidities and severity of illness). Instrumental variables analysis has the advantage of additionally accounting for unmeasured confounding (12, 13, 15, 16) (e.g., patient-,

family-, or care-level variables that may affect outcomes but that do not exist in the database).

Identifying an appropriate instrument is challenging and requires strong statistical and content-based assumptions (17). One promising avenue is the use of preference-based instruments, such as provider practice patterns (18–20). A given patient treated at a CF center with high rates of prescribing inhaled tobramycin is, *ceteris paribus*, more likely to receive this treatment than if they had gone to a CF center with low rates of prescribing. Because CF care is organized by center and because variation in treatment patterns, including prescribing inhaled tobramycin, has been shown to exist across centers (1), we use CF center-specific prescribing patterns as a proxy for randomization to account for unmeasured treatment-by-condition bias. For patients whose treatment status is affected by center-specific prescribing, an instrumental variable may be useful to predict treatment effectiveness. This marginal effect, although less generalizable than a standard average treatment effect, provides meaningful information in observational settings where confounding-by-indication is a major concern and cannot be addressed with standard approaches. Preliminary study results have been previously reported in an abstract (21).

Methods

Population

Data were obtained from the CFFPR, which has been tracking outcomes data for more than 40 years, and contains information from all accredited CF centers in the United States. Eligible patients included those aged 6 to 21 years who were chronically infected with *P. aeruginosa*. Age restrictions were chosen to limit the cohort to valid pulmonary function tests (above 6 yr of age), to capture first occurrences of chronic *P. aeruginosa* infection (below 21 yr of age), and to focus on periods of increased risk for rapid lung function decline (22). Data acquired after organ transplantation were not included. Because inhaled tobramycin was consistently documented annually by 1998, we considered data from January 1, 1998 to December 31, 2009. A modified version of Leeds criteria (23) was used to identify *P. aeruginosa* infection as follows:

Patients who cultured positive more than 50% of the time in a given year were classified as having chronic *P. aeruginosa* infection. The first year of chronic *P. aeruginosa* infection was considered the baseline year. Patients with *Burkholderia cepacia* complex at baseline were considered ineligible for tobramycin based on established criteria from clinical trials (6, 24, 25). Patients who never cultured positive for *P. aeruginosa* or had only intermittent *P. aeruginosa* infection were excluded.

Study Design and Measurements

The design was a retrospective cohort study comparing mean decline in FEV₁ for eligible patients treated and not treated with tobramycin. Patient-level tobramycin use was defined as receiving inhaled tobramycin within 6 months of eligibility based on CFF care guidelines. Our primary outcome was mean change in FEV₁% predicted. Baseline FEV₁ was defined as the closest FEV₁ measurement recorded within 6 months after meeting modified Leeds criteria. Patients who did not have a recorded FEV₁ measurement within 6 months after meeting the criteria for chronic *P. aeruginosa* infection were excluded. Follow-up FEV₁ was defined as the closest recorded FEV₁ within 1.5 to 2.5 years of the baseline FEV₁. Short-term effectiveness of inhaled tobramycin was studied to facilitate use of instrumental variables, which still pose several challenges in longitudinal settings with multiple data points and time-varying exposures (17). Decline in FEV₁ was calculated as the difference between follow-up and baseline FEV₁ for each patient. A negative value implies that FEV₁ declined over the 2-year period; a positive value indicates that FEV₁ increased over the 2-year period.

Statistical Analyses

We summarized baseline patient characteristics using means, standard deviations, medians, and interquartiles for continuous measures and percentages for categorical measures. We compared characteristics of patients treated and not treated with inhaled tobramycin using Wilcoxon Mann-Whitney tests for continuous measures and χ^2 tests for categorical measures. Potential confounders, identified from previous literature (26–28), included sex, baseline measurements for age, FEV₁, weight-for-

age percentile, insurance coverage, CF-related diabetes (with or without fasting hyperglycemia), dornase alfa use, pancreatic insufficiency (defined as taking pancreatic enzymes), and number of hospitalizations in the preceding year. Relationships between FEV₁ decline and potential covariates were assessed using scatterplot smoothing (29).

Instrumental Variables Analysis. To account for observed and unobserved confounding, we used two-stage instrumental variables regression (16). We used a preference-based instrument; center-level prescribing rates for inhaled tobramycin were measured as the percentage of time patients at the center were recorded as receiving inhaled tobramycin when first eligible. Each patient's designated center was his or her primary center during onset of chronic infection with *P. aeruginosa*. The instrumental variables approach requires that the instrument be correlated with outcome only through its effect on treatment. In the first-stage analysis, we obtained the predicted probability of receiving tobramycin adjusted for the instrument and observed confounders. To determine if this choice of instrument is related to whether a patient receives treatment with tobramycin, we used the first-stage F-statistic. In the second-stage analysis, linear regression was used to estimate mean change in FEV₁ for the treated and untreated groups. Sensitivity analyses were performed to examine instrumental variable assumptions, particularly heterogeneity of treatment effect potentially caused by confounding from another medication or center-specific quality of care. The quality of care markers were obtained from the CFF Annual Report (1) and calculated for each center; these included proportion of subjects who received the annual influenza vaccine and the proportion of subjects who had at least four visits in a given year. Subgroup analyses were used to examine the impact of another medication on treatment effectiveness. Relationships between CF center-level prescribing rates and quality of care markers were examined using standard measures of association. To further examine generalizability, we performed secondary analysis of patients with *B. cepacia* who would otherwise have been included in the study.

Conventional Regression Analyses. To demonstrate the effect of analytic approach,

we also performed two common types of regression models to compare patients receiving tobramycin with those not receiving tobramycin once eligible. First, we considered a multiple linear regression model with standard adjustment. Groups were compared using the difference in least-squares means. Second, to account for observed confounding, we used propensity score analysis. Propensity scores were calculated using logistic regression to predict the probability of receiving tobramycin at baseline. Based on the corresponding inverse probabilities (inverse propensity score for treated patients and inverse of one minus the propensity score for untreated patients), we used weighted linear regression to compare least-squares means of the treated and untreated groups (30). Potential confounders were included as covariates in each analytic approach.

Standard analyses were implemented in SAS 9.2 (SAS Institute, Cary, NC). Two-stage instrumental variable regressions were conducted using STATA 10.0 (StataCorp,

College Station, TX). The study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center.

Results

Study Cohort Characteristics

From 1998 to 2009, there were 36,134 patients with data in the CFFPR (Figure 1). During this period, 14,900 patients did not meet inclusion criteria based on age, positive culture for *B. cepacia*, or a lack of culture results for *P. aeruginosa*, leaving 21,234 eligible patients. There were 13,686 patients with chronic *P. aeruginosa* infection; the remaining patients had only intermittent *P. aeruginosa* infection ($n = 2,101$) or had no cultures positive for *P. aeruginosa* ($n = 5,447$). After excluding patients with no FEV₁ available at baseline, our analysis cohort had 12,706 patients from 246 care centers. The median number of eligible patients at each CF center was 37.0 (interquartile range, 17.0–67.0).

Figure 1. Diagram of study population in the Cystic Fibrosis Foundation Patient Registry with number of patients excluded from study and analysis. CFFPR = Cystic Fibrosis Foundation Patient Registry; Pa = *Pseudomonas aeruginosa*.

The mean age at first chronic infection with *P. aeruginosa* was 12.8 years (SD, 4.6 yr). There were 6,255 patients (49.2%) who did not receive inhaled tobramycin when first eligible. Patients who received tobramycin at the onset of chronic *P. aeruginosa* infection had increased illness severity at baseline compared with patients who did not receive it (Table 1). Treated patients had significantly lower FEV₁ and weight-for-age percentile compared with untreated patients, but both groups were similar in age, prevalence of pancreatic insufficiency, and insurance status. The treated group had a higher prevalence of CF-related diabetes at baseline, more female patients, and more hospitalizations in the prior year compared with the untreated group. The treated group also had a higher frequency of dornase alfa use than the untreated group (79.3 vs. 49.4%; $P < 0.0001$). There were 244 patients with *B. cepacia* who were otherwise eligible for study entry; 59% were treated with tobramycin.

Instrumental Variables Analysis

The first stage of instrumental variables regression was used to obtain predicted patient-level inhaled tobramycin use at baseline (Table 2). This model included measured confounders in Table 1 and the instrument, center-level prescribing rate for inhaled tobramycin. The first-stage F-statistic was significant ($F = 796.02$; $P < 0.0001$), indicating that center-level prescribing use is a strong instrument for treatment selection. This multivariable

model, which adjusted for observed patient characteristics and center-level prescribing, suggested that being male and having state/federal or no insurance, lower weight-for-age percentile, and hospitalizations in the prior year were associated with decreased inhaled tobramycin use, whereas taking dornase alfa at baseline was associated with increased use. Sensitivity analyses of instrumental variable assumptions showed that lower recorded tobramycin use was weakly correlated with standard markers of care for influenza vaccine and annual visits across CF centers (Spearman correlation coefficient, 0.15 [$P = 0.02$] and -0.04 [$P = 0.50$], respectively).

The second-stage instrumental variables regression estimated the association between predicted patient-level inhaled tobramycin use (obtained in the first stage) and change in lung function (Table 2). This model indicated that inhaled tobramycin use at baseline was associated with less FEV₁ decline compared with no use (-1.40 vs. -3.95 ; $P = 0.0366$). Compared with the untreated group, the average loss of lung function was smaller for the treated group (difference, 2.55% predicted; 95% confidence interval [CI], 0.16–4.94).

Conclusions were similar in subgroup analyses of concomitant dornase alfa use. The first-stage F-statistic in each of the two subgroups, patients with reported use of dornase alfa and patients with no reported use of dornase alfa, indicated that the strength of the instrument was preserved ($F = 739.36$ and $F = 163.83$, respectively;

both $P < 0.0001$). Patients treated with dornase alfa and tobramycin had less lung function decline than those treated with dornase alfa alone (difference, 3.90% predicted; 95% CI, 0.67–7.13; $P = 0.0181$). Comparisons in the smaller subgroup of patients who did not use dornase alfa were similar but not statistically significant. The difference in the treated and untreated groups was 2.16% predicted (95% CI, -1.31 to 5.63 ; $P = 0.22$).

Secondary instrumental variables analysis, which included patients with *B. cepacia*, had a significant first-stage F-statistic for instrument ($F = 171.72$; $P < 0.0001$) but was not associated with tobramycin use in the first-stage regression ($P = 0.81$). Second-stage estimates for treated and untreated subjects were 3.97 and 2.38% predicted, respectively; the group difference was 1.59% predicted (95% CI, -1.06 to 4.24 ; $P = 0.24$). Results were similar to the primary analysis of untreated subjects but not treated subjects.

Standard Regression Models

The results of naive multiple linear regression and propensity score weighted regression are in Table 3. Both models suggest that receiving tobramycin at baseline is associated with greater FEV₁ decline. In the naive analysis, the treated group had significantly greater decline in lung function compared with the untreated group (-5.13 vs. -3.39% predicted; $P < 0.0001$), implying that over the 2-year period after baseline, the treated group lost 1.74% predicted more lung function than

Table 1. Baseline characteristics of study cohort

Characteristics	Treated with Tobramycin	Not Treated with Tobramycin	P Value*
Age, mean $\pm$ SD (n), yr	12.82 $\pm$ 4.68 (6,451)	12.78 $\pm$ 4.59 (6,255)	0.84
Male sex, % (n)	47.2 (3,046)	53.5 (3,346)	<0.0001
FEV ₁ % predicted, mean $\pm$ SD (n)	74.46 $\pm$ 25.33 (6,451)	83.69 $\pm$ 22.68 (6,255)	<0.0001
Weight-for-age percentile, mean $\pm$ SD (n)	30.05 $\pm$ 26.08 (6,446)	33.92 $\pm$ 26.88 (6,252)	<0.0001
CF-related diabetes, % (n)	2.3 (150)	1.5 (96)	0.0012
Pancreatic insufficiency, % (n)	95.3 (6,145)	94.8 (5,932)	0.27
No or state/federal insurance, % (n)	32.3 (2,082)	30.5 (1,910)	0.0348
Prior hospitalizations [†] % (n)			
None	57.2 (3,360)	75.7 (4,448)	<0.0001
1	23.9 (1,401)	16.0 (940)	
2	9.3 (546)	4.6 (273)	
3 or more	9.6 (566)	3.7 (219)	
Dornase alfa	79.3 (5,116)	49.4 (3,087)	<0.0001

Definition of abbreviation: CF = cystic fibrosis.

*P values from Wilcoxon Mann-Whitney or χ^2 test.

[†]Number of hospitalizations in the year before baseline.

Table 2. Using instrumental variables to predict lung function decline

Variables	Stage 1*		Stage 2†	
	Coefficient (SE),	P Value	Coefficient (SE),	P Value
Patient tobramycin use				
Treated			2.55 (1.22)	0.0366
Not treated			0	
Age	−0.013 (0.003)	0.0002	−0.86 (0.04)	<0.0001
Baseline FEV ₁	−0.010 (0.001)	<0.0001	−0.27 (0.01)	<0.0001
Sex				
Female	0.112 (0.027)	<0.0001	−1.23 (0.30)	<0.0001
Male	0		0	
Weight-for-age percentile	−0.000 (0.001)	0.74	0.06 (0.01)	<0.0001
CF-related diabetes				
Yes	0.112 (1.27)	0.38	1.93 (1.44)	0.18
No	0		0	
Pancreatic insufficiency				
Yes	0.064 (0.074)	0.39	0.52 (0.83)	0.54
No	0		0	
Insurance				
None or state/federal	−0.128 (0.030)	<0.0001	−1.58 (0.34)	<0.0001
Other	0		0	
Baseline hospitalizations				
None	−0.598 (0.064)	<0.0001	5.44 (0.69)	<0.0001
1	−0.251 (0.068)		2.89 (0.74)	
2	−0.148 (0.080)		0.48 (0.87)	
3 or more	0		0	
Dornase alfa use				
Yes	0.224 (0.036)	<0.0001	0.28 (0.40)	0.48
No	0		0	

Definition of abbreviation: CF = cystic fibrosis.

*Stage 1 predicts patient tobramycin use. For each categorical variable in the first-stage model, the coefficient is the difference in patient tobramycin use between the indicated category and the reference category (labeled as coefficient = 0). For each continuous variable, it is the change in patient tobramycin use when the variable is increased by 1 unit. A negative value implies decreased patient tobramycin use.

†Stage 2 predicts change in lung function. Predicted treatment obtained in Stage 1 serves as propensity score in Stage 2. For each categorical variable in the second-stage model, the coefficient is the difference in FEV₁ decline between the indicated group and the reference group (labeled as coefficient = 0). For each continuous variable, it is the change in FEV₁ when the variable is increased by 1 unit. A negative value implies greater FEV₁ decline.

the untreated group (95% CI, 1.12–2.35). Propensity score analysis results were similar to naive regression results, except the change in FEV₁ was slightly smaller for the treated and untreated groups (−4.47% predicted and −2.91% predicted, respectively). Nevertheless, similar to the naive analysis, the propensity score analysis suggested that the treated group lost an excess 1.71% predicted in lung function over the 2-year period (95% CI, 1.12–2.31; $P < 0.0001$). Most associations for measured confounders were similar to instrumental variables regression results.

Discussion

This study, the first to assess the effectiveness of inhaled tobramycin use on decline in lung function for patients meeting

CFF guidelines, showed that inhaled tobramycin use reduced the decline in lung function for patients with CF in a 6- to 21-year-old cohort. Thus, this study adds substantially to the clinical literature by extending research on the short-term clinical efficacy of inhaled tobramycin to suggest that increasing adherence to established prescribing guidelines of inhaled tobramycin use is effective at slowing FEV₁ decline. Furthermore, this is the first analysis of CFFPR data that attempts to account for measured and unmeasured confounding caused by treatment selection bias. Given that CF care is organized through CF care centers, center-level, preference-based instrumental variables is a promising approach to interrogating the CFFPR and, potentially, other such patient registries.

Comparing the treated and untreated cohorts demonstrates the potential usefulness of an instrumental variables approach: the treated cohort was significantly sicker than the untreated cohort, clearly demonstrating that treatment selection bias would exist in retrospective analyses. The use of propensity scores, which are commonly used to balance group differences based on measured confounders, was unable to combat the treatment selection bias present in this study. Indeed, the instrumental variables analysis was consistent with findings from randomized controlled trials and was substantively different from traditional multiple linear regression and propensity score analysis approaches, highlighting the known limitations of conventional regression analyses applied to observational data (31).

The confounding-by-indication bias apparent in our study was most recently reported in a study by Sawicki and colleagues (11). Besides reduced mortality, inhaled tobramycin use was associated with younger, female patients with increased numbers of comorbidities and infections and with more frequent use of other treatments and acute care resources. Although both studies examine tobramycin use reported in the CFFPR and encounter similar biases, there are important distinctions that warrant different analytic approaches to adjust for sources of confounding. There is a well-established link between FEV₁ and CF mortality, but the influence of individual predictors on outcomes can vary and may depend on initial age of the cohort (26, 32). Mortality studies typically involve older CF cohorts compared with lung function studies, where FEV₁ decline occurs primarily during adolescence and young adulthood (28, 33). Concomitant dornase alfa use was associated with less lung function decline during follow-up in subgroup analysis. For patients who used concomitant dornase alfa, the tobramycin effect on lessening lung function decline persisted. Although the results did not meet statistical significance, we found that tobramycin use also lessened lung function decline in patients who did not use dornase alfa. In each analysis, center-specific prescribing rate remained a strong instrument based on statistical testing. These findings show consistency in the relationship between inhaled tobramycin use and lung function changes, highlighting the importance of accounting

Table 3. Using standard approaches to predict lung function decline

Variables	Type of Model*			
	Multiple Linear Regression [†]		Propensity Score Regression [‡]	
	Coefficient (SE)	P Value	Coefficient (SE)	P Value
Patient tobramycin use				
Treated	−1.74 (0.31)	<0.0001	−1.71 (0.30)	<0.0001
Not treated	0		0	
Age	−0.87 (0.04)	<0.0001	−0.86 (0.04)	<0.0001
Baseline FEV ₁	−0.27 (0.01)	<0.0001	−0.27 (0.01)	<0.0001
Sex				
Female	−1.16 (0.30)	<0.0001	−1.15 (0.31)	0.0002
Male	0		0	
Weight-for-age percentile	0.06 (0.01)	<0.0001	0.05 (0.01)	<0.0001
CF-related diabetes				
Yes	2.06 (1.44)	0.15	2.19 (1.36)	0.11
No	0		0	
Pancreatic insufficiency				
Yes	0.52 (0.83)	0.54	0.44 (0.83)	0.60
No	0		0	
Insurance				
None or state/federal	−1.66 (0.34)	<0.0001	−1.66 (0.34)	<0.0001
Other	0		0	
Baseline hospitalizations				
None	5.05 (0.70)	<0.0001	4.63 (0.69)	<0.0001
1	2.74 (0.74)		2.26 (0.74)	
2	0.40 (0.87)		0.37 (0.87)	
3 or more	0		0	
Dornase alfa use				
Yes	−0.46 (0.39)	0.25	−0.38 (0.40)	0.34
No	0		0	

Definition of abbreviation: CF = cystic fibrosis.

*Each model is adjusted for measured confounders by including each listed variable as a covariate. For each categorical variable, the coefficient is the difference in FEV₁ decline between the indicated category and the reference category (labeled as coefficient = 0). For each continuous variable, it is the change in FEV₁ decline when the variable is increased by 1 unit. A negative value implies greater FEV₁ decline.

[†]Multivariable analysis with standard adjustment for confounding by including characteristics as covariates.

[‡]Multivariable analysis weighted using propensity scores.

for treatment selection bias beyond observable covariates, even in more complex analyses.

There are several limitations. To appropriately select subjects meeting CFF guidelines for tobramycin use, inclusion criteria were based on modified Leeds criteria, a more stringent measure for chronic *P. aeruginosa* infection, and established clinical trials. Some measurements, such as inhaled tobramycin use, are recorded on an annual level (and later by clinical encounter) for the analysis time frame; therefore, specific information on inhaled tobramycin cycles, which would be necessary to establish a dose-response causal relationship, cannot be recovered. Most importantly, without adherence monitoring, the patient's use of medications cannot be precisely measured. Secondary

analysis suggested that patients with *B. cepacia* who were treated with tobramycin were less responsive than patients who were otherwise eligible and received treatment. Our study findings demonstrate resistance to therapies and rapid disease progression, which cannot be easily addressed through analytic approaches due to the low prevalence of this infection.

The instrumental variables regression relies heavily on the validity of the instrument, in this case center-level prescribing patterns. Although calculations may be influenced by variation in data entry patterns, few patients (6.3%) were excluded due to incomplete culture information or unrecorded lung function data during the study period. These exclusions were not concentrated at particular centers. First-stage analyses show that center-level

prescribing rate was predictive of treatment after adjustment for observed confounding, statistically demonstrating that this is a strong instrument for treatment selection. Bivariate analyses of center-specific tobramycin use and delivery of standard care measures showed no statistically significant correlation with meeting the recommended four annual visits. Although a statistically significant correlation existed between tobramycin use and receipt of influenza vaccine, this is anticipated given that correlations were assessed for a large sample size (i.e., more than 240 CF centers). Actual coefficients indicate that CF centers that provide less tobramycin do not necessarily less frequently deliver other clinical care measures. The approach also requires that the instrument is not directly associated with the outcome (i.e., that center-level prescribing rates are associated with the outcome only through burden of illness). Although this assumption is not directly testable and patients are not randomly assigned to CF centers, it is reasonable to assume that patients select primary centers without knowledge of center-specific prescribing patterns. This is a common, well-described assumption for preference-based instruments (19, 20, 34, 35). CFF center-specific measures, now publicly reported, show few subjects (5.8%) transferred to different centers before or during the study period. Transition rates were similar before and after public release of this information in 2006 (5.7 and 6.8%, respectively). It has been demonstrated that hospital- or center-level instruments for treatment selection produce more consistent estimates of treatment effectiveness than patient-level instruments or traditional multivariable adjustment for confounding (36). CF centers with larger numbers of eligible patients have more opportunities for individual providers to prescribe tobramycin, which may lead to more variation among physician practices. Physician information is undocumented in the CFFPR, but annual reporting has focused on center-specific outcomes with the assumption that physicians within a center collectively participate in quality improvement initiatives (8, 37, 38). Methodological advancements in instrumental variables approaches are needed to examine longer-term treatment effectiveness, time-varying exposures, and more flexible model fitting. Treatment effect estimates from standard statistical

approaches showed no benefit to tobramycin use for patients with CF in this observational study. Both methods are limited by a lack of adjustment for unmeasured treatment-by-condition bias (13). Instrumental variables analysis estimates marginal treatment effect. The likelihood of being prescribed tobramycin depends on unmeasured characteristics at the patient, family, or care level (30). Under certain assumptions, this marginal treatment effect may be interpreted as an average causal effect across patients with

CF in the population or in a subpopulation of treated and untreated individuals (16). In this study, treatment effect estimates correspond to patients with CF who would have received tobramycin at centers with higher rates of prescribing but would not have received tobramycin at centers with lower rates of prescribing. In the absence of long-term clinical trials or well-designed studies to assess population effectiveness of tobramycin, this study demonstrates that inhaled tobramycin use among younger patients

with CF contributed to reduced decline in lung function in actual clinical practice, after using an instrumental variables approach to minimize treatment selection bias. ■

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