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Probability of Treatment Following Acute Drop in Lung Function in Children with Cystic Fibrosis is related to baseline pulmonary function

Wayne J. Morgan, MD¹, Jeffrey S. Wagener, MD², Ashley Yegin, MD³, David J. Pasta, MS⁴, Stefanie J. Millar, MS⁴, Michael W. Konstan, MD⁵, and on behalf of the Scientific Advisory Group, investigators, and coordinators of the Epidemiologic Study of Cystic Fibrosis*

¹Department of Pediatrics, University of Arizona, Tucson, AZ

²Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO

³Genentech, Inc., South San Francisco, CA

⁴ICON Late Phase & Outcomes Research, San Francisco, CA

⁵Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH

Abstract

Objective—To hypothesize whether the association between high forced expiratory volume in 1 second (FEV₁) and increased rate of decline in FEV₁ in children with cystic fibrosis could be due to less frequent intervention after acute drops (sudden decline events) in FEV₁.

Study design—Patients with CF aged 6–17 years enrolled in ESCF were assessed for a sudden decline event, defined as a 10% relative drop in FEV₁ % predicted from an average of 3 consecutive stable baseline spirometries. The likelihood of therapeutic intervention within 14 days before and 56 days after this event was then related to their baseline FEV₁ % predicted age-specific decile using a logistic regression adjusting for age group (6–12y, 13–17y) and presence of *Pseudomonas aeruginosa* on respiratory culture.

Results—10,888 patients had at least one sudden decline event in FEV₁. Patients in the highest FEV₁ decile were significantly less likely than those in the lowest decile to receive intravenous antibiotics (odds ratio [OR], 0.14; 95% confidence interval [CI], 0.11–0.18; *P* < .001) or be hospitalized (OR, 0.18; 95% CI, 0.14–0.23; *P* < .001) following decline.

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Correspondence and reprint requests to: Wayne J. Morgan, MD, CM Phone: (520) 626-6754 Department of Pediatrics Fax: (520) 626-9465 University of Arizona wmorgan@arc.arizona.edu Tucson, AZ 85724.

*A list of the Scientific Advisory Group members, investigators, and coordinators of the Epidemiologic Study of Cystic Fibrosis is available at www.jpeds.com (Appendix).

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Conclusions—Children and adolescents with high baseline lung function are less likely to receive a therapeutic intervention following an acute drop in FEV₁, which may explain their greater rate of FEV₁ decline.

Keywords

cystic fibrosis; child; adolescent; lung; epidemiology; respiratory function tests; spirometry; forced expiratory volume; hospitalization; antibacterial agents

Cystic fibrosis (CF) lung disease is characterized by airway obstruction, chronic infection, and inflammation leading to progressive damage with irreversible obstructive airway disease.¹ The forced expiratory volume in 1 second (FEV₁) has been studied in patients with CF to better understand the progression of CF lung disease.²⁻⁶ Many factors have been associated with the rate of FEV₁ decline, including high lung function.^{2,7,8} More recently, we used data from the Epidemiologic Study of Cystic Fibrosis (ESCF) to show that baseline FEV₁ values of at least 100% of predicted were associated with a subsequent relative increase in the rate of decline ranging from 12% in adolescents to 46% in children ages 6 to 8 years when compared with the overall rate of decline.⁹ We reasoned that this increased risk of decline for those with the highest FEV₁ values could have been due to a lack of a therapeutic response following a clinically relevant drop in lung function in these children. In other words, we suspected that a disparity in health care may exist in children with high FEV₁ values due to a bias to be less therapeutically aggressive in these apparently healthy children.

We have previously shown that pulmonary exacerbations are associated with progressive lung function decline.⁹ This has been confirmed and there is evidence that patients frequently fail to return to baseline following an exacerbation.^{10,11} One factor that predicted a failure to recover lung function after treatment with intravenous (IV) antibiotics was a delay in treatment.¹¹ This suggests that the increased rate of decline we have observed in children with high lung function could be due to delayed or deferred response to an acute progression of their disease. We hypothesized that following a meaningful relative decline in FEV₁, children with high lung function at baseline would be less likely to be treated with either hospitalization or IV antibiotics.

METHODS

ESCF is a large multicenter, longitudinal, prospective observational study of the clinical course of patients with CF in the United States and Canada from 1994 through 2005.¹² Data collected on each patient included clinical demographics, signs and symptoms of lung disease, information on growth and nutrition, results of spirometry, results of respiratory tract cultures, use of routine therapies, and information on pulmonary exacerbations and their treatment. Informed consent was obtained based on decisions by local human subjects review boards.

To be included in the current analysis, patients had to be enrolled in ESCF and have at least four FEV₁ values meeting certain criteria. Patients had to have a baseline FEV₁ % predicted established by a moving average of three spirometries obtained when the patient was

clinically stable and that spanned 30-365 days. At least one recorded clinical encounter must have occurred in this period. If within 1 year from the last stable spirometry there was a relative decline in FEV₁ % predicted of at least 10% from baseline, this was considered a sudden decline event (Figure 1). To be included, patients with a sudden decline event were required to have a respiratory tract culture recorded in the year prior and not have been hospitalized between the last stable spirometry and the sudden decline event. For each patient, only the first qualifying sudden decline event was analyzed.

Clinical interventions were then assessed around the time of the sudden decline event. Hospitalization was defined as an intervention if it occurred on the day of, or up to 56 days following, the sudden decline event. Antibiotic interventions were assessed between 14 days before and 56 days following the sudden decline event. This window was chosen to give time for therapeutic interventions to be started, but prior to the next routine clinic visit. Any IV antibiotic therapy during this period was considered a clinical intervention. Other antibiotic therapies were considered new interventions provided they had not been reported at the last encounter during the baseline period. When the last stable spirometry occurred within 14 days prior to decline, therapies started in this time frame were also considered new interventions. These interventions were categorized as either inhaled antibiotics, oral quinolone antibiotics, or other oral antibiotics.

Due to the progressive decline in lung function with age in patients with CF, we reasoned that baseline severity of lung disease would be better characterized relative to children with CF of the same age rather than by comparison with the general CF population. We therefore developed reference values by calculating deciles of FEV₁ % predicted for each integer year of age from 6 to 17 years using all spirometry data recorded in ESCF. We used these deciles to evaluate treatment response by lung disease severity. Values for FEV₁ % predicted were calculated from Wang¹³ for males through age 17 years and for females through age 15 years and from the equations of Hankinson¹⁴ for patients above these ages.

For each intervention, patient counts and percentages were produced for each FEV₁ decile and age group (children aged 6-12 years and adolescents aged 13-17 years). Differences across deciles but within age groups were assessed by the Mantel-Haenszel χ^2 statistic. We evaluated the relationship between baseline FEV₁ age-specific decile and the likelihood of therapeutic intervention using a logistic regression adjusting for the presence of *Pseudomonas aeruginosa* on respiratory culture, weight-for-age percentile category, and age category. Because of the importance of symptoms for defining a CF-related pulmonary exacerbation,¹⁵⁻¹⁷ we repeated the analysis for only those patients who had daily cough, daily sputum production, and crackles on physical examination at the visit closest to the decline event. Furthermore, the analysis was repeated for only those patients with positive *Pseudomonas aeruginosa* on respiratory culture. Odds ratios (ORs) and associated 95% confidence intervals (CIs) are reported, as is the *P* value for the linear trend of OR by FEV₁ decile.

Statistical analyses were performed using SAS 9.1 (SAS Institute, Inc., Cary, NC). *P* values <.05 were considered significant. No adjustments were made for multiple comparisons.

RESULTS

Of all children and adolescents enrolled in ESCF between 1994 and 2005, 16,524 had sufficient FEV₁ data. Of these, 11,276 (68%) patients had three stable baseline FEV₁ values, were 6-17 years of age at the first of these values, and demonstrated at least one sudden decline event. We excluded 388 patients because either (1) during the moving average period, they had no respiratory cultures or no encounters, or (2) they were hospitalized before or during all their sudden decline events. This left 10,888 patients for this analysis.

Baseline demographic data and clinical status by age group at the time of the decline event are presented in Table I (available at www.jpeds.com). As expected, the adolescents demonstrated lower FEV₁ % predicted and weight-for-age percentile values than the children and had higher prevalence of *Pseudomonas aeruginosa* infection and of respiratory signs and symptoms. The median span of the baseline spirometries was approximately 6 months in both age groups. In both age groups, the median time from the last baseline spirometry to the sudden decline event was 91 days (range, 1-364).

Although the threshold for sudden decline was a 10% relative drop, the actual drops in FEV₁ were much larger, with the mean decline being a relative drop of $19.7\% \pm 9.8$ (median, 16.5) in the children and $19.8\% \pm 9.9$ (median, 16.4) in the adolescents. Among the children with a sudden decline event, over 85% had an absolute drop of at least 10 points in FEV₁ % predicted, and over 25% had a drop of at least 20 points. For the adolescents, who have a lower average starting value, nearly 73% had an absolute drop of at least 10 points and over 18% at least 20 points. Yet, no new intervention was reported in a substantial proportion of these patients. Even among those with absolute drops of at least 20 points, nearly one-third of the children and one-fourth of the adolescents were neither hospitalized nor treated with a new course of antibiotic therapy (data not shown).

Therapeutic Intervention by Baseline Lung Function Decile

Hospitalizations were recorded following sudden decline for 18.3% of children and 26.1% of adolescents with any IV antibiotic therapy reported for 22.7% and 30.9%, respectively (Table I). The likelihood of IV antibiotic therapy and hospitalization were both significantly lower in patients with higher lung function in both age groups (linear trend $P < .001$; Figure 2). Although over half of the children and adolescents in the lowest decile received IV antibiotic therapy, less than 20% of patients in the top four deciles received such therapy.

The likelihood of new inhaled antibiotics was also lower in patients with higher lung function (linear trend $P < .001$ for both age groups). Similar findings were observed for new quinolone antibiotics for children. However, the linear trend was weaker for children receiving other new oral antibiotics and for adolescents receiving new quinolone antibiotics or other new oral antibiotics ($P > .05$) (data not shown).

Figure 3 relates antibiotic interventions to FEV₁ decile. Although approximately 80% of patients in the lowest decile received some acute intervention, only 49% of children and 58% of adolescents in the highest decile were treated.

The multivariate logistic regression (Table II) demonstrated that after adjusting for age category, respiratory culture status, and weight for age (< 25th percentile vs > 25th percentile), high lung function at baseline still predicted a low rate of therapeutic intervention with antibiotics following a sudden decline in FEV₁. As compared with patients in the lowest FEV₁ decile at baseline, those in the highest decile were significantly less likely to be hospitalized (OR, 0.20; 95% CI, 0.16-0.26; $P < .001$) or receive IV antibiotics (OR, 0.15; 95% CI, 0.12-0.20; $P < .001$). Adolescents and patients with a positive culture for *Pseudomonas aeruginosa* were more likely to be hospitalized, receive IV antibiotics, or receive new antibiotic therapy. Those with low weight for age were also more likely to be hospitalized or receive IV antibiotics (Table II).

Importantly, the inverse relationship between baseline lung function and likelihood of treatment persisted even when limited to patients who had daily cough, daily sputum, and crackles on lung examination at the time of decline. At the visit nearest the sudden decline event, 13.8% of children ($n = 7544$) and 24.5% of adolescents ($n = 3126$) had all three of these signs and symptoms. Even in the presence of cough, sputum, and crackles, patients in the highest decile were less likely to receive IV antibiotics (OR, 0.47; 95% CI, 0.27-0.80) or be hospitalized (OR, 0.62; 95% CI, 0.36-1.08) (data not shown). Similarly, when the analysis was limited to those individuals who were positive for *Pseudomonas aeruginosa*, patients in the highest decile were still less likely to receive IV antibiotics (OR 0.17; 95% CI, 0.13-0.22) compared with those in the lowest FEV₁ decile. However, although there was a trend for a lower rate of hospitalization, it was no longer significant (OR 0.23; 95% CI, 0.17-1.31).

DISCUSSION

This study demonstrates that the likelihood of therapeutic intervention after a substantial and clinically meaningful decline in lung function is inversely related to the level of baseline lung function. Overall, the rate of IV antibiotic therapy or hospitalization for treating patients with CF was surprisingly low when using a threshold of a 10% relative drop in FEV₁ % predicted. In fact, these patients experienced large absolute declines in lung function in less than a single year. The mean absolute drop in FEV₁ % predicted in children and adolescents was 17.1 (standard deviation [SD], 8.9; median, 14.5) and 14.9 (SD, 8.3; median, 12.8) points, respectively. These are strikingly greater than the average annual decline in FEV₁ % predicted of 1.66 points for children and 2.34 points for adolescents reported by Konstan et al in 2007.⁹

Despite this marked loss in lung function, only 12% of children and 19% of adolescents in the highest FEV₁ decile at baseline received IV antibiotics. Furthermore, only 52% of these patients with high lung function received any new antibiotic intervention. After adjusting for age group and *Pseudomonas aeruginosa* infection, patients in the highest FEV₁ decile were about one-sixth as likely to be hospitalized and slightly less likely to receive IV antibiotics when compared with patients in the lowest decile. Although it may be understandable that sicker patients are treated more aggressively, in a disease such as CF where progressive loss of lung function is the rule, failure to respond with hospitalization or new antibiotic therapy for those with potentially more controllable disease is disheartening.

Pulmonary exacerbations in CF are commonly characterized by worsening signs and symptoms including reduced exercise tolerance and increased cough and sputum,¹⁶ and also by loss in lung function and increased physical findings such as crackles on chest examination.¹⁷ Even when we limited our analysis to patients with daily cough, daily sputum, and crackles, the negative impact of high lung function on the likelihood of clinical intervention was still apparent.

The fact that more rapid lung function decline occurs in patients with CF with higher lung function seems counterintuitive, as these patients appear clinically healthier. In contrast to another chronic inflammatory lung disease, chronic obstructive pulmonary disease (COPD), the rate of FEV₁ decline in CF seems to be proportional to the remaining lung function. In COPD, lung function decline is not linear, but seems to accelerate (not decelerate) with age and disability.^{18,19} The pattern of decline in lung function seen in patients with CF may be inherent to the biology of the disease. However, our findings suggest that caregivers may be less aggressive in treating patients who appear to be healthy.

As with any epidemiologic study we were only able to evaluate the information provided by study sites. Underreporting of therapies, particularly oral antibiotics, would result in underestimating the true frequency of intervention. Most likely, any underreporting would apply to all patients and furthermore is unlikely to explain the large differences between the highest and lowest deciles for major interventions such as hospitalization and IV antibiotic therapy. However, underreporting of oral antibiotics could preferentially affect the highest deciles. Also, we did not assess changes in nonantibiotic therapies. Another potential limitation is that these data were collected from 1994 to 2005 and it is possible that practice patterns have improved since 2005 with the recent focus on early intervention. Our analysis was limited to consideration of a single event and therefore we did not assess the long-term impact of multiple events. To evaluate the long-term effect on rate of lung function decline of a series of treatment decisions associated with exacerbations would require a different analytic approach.

In conclusion, children and adolescents with high baseline lung function are less likely to be hospitalized or receive IV antibiotic therapy following a substantial and clinically meaningful decline in FEV₁ than those with low lung function. This disparity in care may help explain the greater risk of FEV₁ decline seen in children with high lung function and should challenge all providers to be more vigilant in the care of apparently healthy children with cystic fibrosis.

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Appendix

Epidemiologic Study of Cystic Fibrosis Investigators included: Alabama: Dana Brasfield, Raymond Lyrene, Lawrence Sindel; Alaska: Dion Roberts; Arkansas: John Carroll, Robert Warren, Louay Nassri, Paula Anderson; Arizona: Mark Brown, Amy Silverthorn, Peggy Radford, Gerald Gong, Gregory Legris; California: Gerald Greene, Reddivalam Sudhakar, Arnold Platzker, Bruce Nickerson, Karen Hardy, Ivan Harwood, Gregory Shay, Bryon Quick, Allan Lieberthal, Richard Moss, Chris Landon, Yvonne Fanous, Jay Lieberman, Eugene Spiritus, Bradley Chipps, Ruth McDonald, Mark Pian, Gerd Cropp, Nancy Lewis, Dennis Nielson, Bertrand Shapiro; Colorado: Jeff Wagener, Frank Accurso, Milene Saavedra; Connecticut: Karen Daigle, Jacob Hen, Regina Palazzo; Delaware: Kathryn Dodds, Raj Pad-man, John Goodill; District of Columbia: Glenna Winnie, Lea Davies; Florida: Tony Kriseman, Jorge Sallent, Joseph Chiaro, Martin Kubiet, Sue Goldfinger, Morton Schwartzman, Carlosenrique Diaz, Kevin Maupin, Eduardo Riff, David Geller, Floyd Livingston, Kunjana Mavunda, Jose Birriel Jr, Luis Faverio, David Rosenberg, David Schaeffer, James Sherman, Mary Wagner, Michael Light, Bruce Schnapf; Georgia: Gary Montgomery, Kevin Kirchner, Mark Weatherly, Daniel Caplan, Margaret Guill, Valera Hudson; Illinois: Javeed Akhter, Donald Davison, Steven Boas, Susanna McColley, Youngran Chung, Rennee Latner, Gabriel Aljadeff, Youngran Chan, Jerome Kraut, Arvey Stone, John Lloyd Still, Girish Sharma, Lanie Eagleton, Patricia Hopkins, Umesh Chatrath, Lucille Lester, Young-Jee Kim; Indiana: Veena Anthony, Howard Eigan, Michelle Howenstine, Pushpom James, Edward Gergesha, James Harris, Robert Plant; Iowa: Veljko Zivkovich, Angela Collins, Edward Nassif, Richard Ahrens; Kansas: Daniel Doornbos, Joseph Kanarek, Richard Leff, Pamela Shaw, Elanor Demoss, Maria Riva, Leonard Sullivan; Kentucky: Michael Anstead, Jamshed Kanga, Nemr Eid, Ron Morton; Louisiana: Bettina Hilman, Kim Jones, Scott Davis; Maine: Ralph Harder, Tom Lever, Anne Marie Cairns, Edgar Caldwell, Jonathan Zuckerman; Maryland: Peter Mogayzel, Beryl Rosenstein, John McQuestion, Donna Perry, Samuel Rosenberg; Massachusetts: Robert Gerstle, Andrew Colin, Mary Ellen Wohl, Allan Lapey, William Yee, Brian O'Sullivan, Robert Zwerdling; Michigan: Ibrahim Abdulhamid, Adrian O'Hagan, John Schuen, Lawrence Kurlandsky, Richard Honicky, Douglas Homnick, John Marks, Bohdan Pichurko, Norma Maxvold, Samya Nasr, Richard Simon, Wan Tsai, Dana Kissner; Minnesota: John Mc Namara, Nancy Henry, Stephen Marker, Michael Pryor, Warren Regelman, Lynn Walker; Mississippi: Jim Woodward, Louis Mizell, Suzanne Miller; Missouri: Daniel Rosenbluth, Philip Black, Michael McCubbin, Alan Cohen, Thomas Ferkol, George Mallory, Anthony Rejent, Bruce Rubin, Gavin Graff, Peter Konig; Nebraska: John Colombo, Peter Murphy; New Hampshire: William Boyle, Worth Parker; New Jersey: Chandler Patton, Robert Zanni, Arthur Atlas, Nelson Turcios, Lourdes Laraya-Cuasay, Dorothy Bisberg, Helen Aguila; New Mexico: Sarah Allen, David James, Elizabeth Perkett, Marsha Thompson; Nevada: Sonia Budhecha, Ruben Diaz; New York: Jonathan Rosen, Robert Kaslovsky, Ronald Percciacante, Drucy Borowitz, Joseph Cronin, Colin McMahon, Lynne Quittell, Robert Giusti, Rubin Cohen, Joan DeCelie-Germana, Jack Gorvoy, Kalpan Patel, Meyer Kattan, Allen Dozor, Emily DiMango, Maria Berdella, Ran Anbar, Debra Ianuzzi, James Sexton, Catherine Tayag-Kier, John McBride, Clement Ren, Karen Voter, Mary Dimaio; North Carolina: John Georgitis, Joseph Marc Majure, Maria Martinez, Clarke McIntosh, Margaret Leigh, Michael Schechter,

Hugh Black; North Dakota: James Hughes, Anand Kantak; Ohio: Robert Wilmott, Gregory Omlor, Robert Stone, Karen McCoy, James Acton, Carl Doershuk, Michael Konstan, Robert Fink, Michael Steffan, Pierre Vauthy, Patricia Joseph; Oklahoma: Santiago Reyes, John Kramer, James Royall; Oregon: Jay Eisenberg, Michael Wall; Pennsylvania: Stanley Fiel, Thomas Scanlin, Shroti Phadke, Glenna Winnie, Joel Weinberg, William Sexauer, Stephen Wolf, Douglas Holsclaw, Debra Klein, Stuart Warren, Robert Kinsey, Carlos Perez, Muttiah Ganeshanathan, James Shinnick, Howard Panitch, Laurie Varlotta, Cynthia Robinson; Puerto Rico: Jose Rodriguez Santana; Rhode Island: Mary Ann Passero; South Carolina: Jane Gwinn, Robert Baker, Michael Bowman, Patrick Flume, Daniel Brown, Roxanne Marville; South Dakota: James Wallace, Rodney Parry; Tennessee: Don Ellenburg, John Rogers, Ricky Mohon, Joel Ledbetter, Aram Hanissian, Robert Schoumacher, Preston Campbell, Christopher Harris, Bonnie Slovis, Dennis Stokes; Texas: Kathryn Hale, Marcia Katz, Dan Seilheimer, Marianne Sockrider, Allan Frank, James Daniel, James Cunningham, Iley Browning, John Bray, Amanda Dove, Fernando Mandujano, Larry Tremper, Martha Morse, Donna Willey-Courand, Steven Copenhaver, John Pohl, Bennie McWilliams, Marie Martine-Logvinoff, Marsh Wallace, Robert Klein, Rodolfo Amaro, Leslie Couch, Michael Brown, Claude Prestidge, Stephen Inscore, Andrew Lipton; Utah: Barbara Chatfield, Theodore Liou, Bruce Marshall; Virginia: Karl Karlson, Ignacio Ropoll, Thomas Rubio, Joel Schmidt, David Thomas, John Osborn, Deborah Froh, Benjamin Gaston, Greg Elliott; Vermont: Thomas Lahiri, Donald Swartz, Laurie Whittaker; Washington: Ronald Gibson, Bonnie Ramsey, Michael McCarthy, Lawrence Larson, David Ricker, Mark Robbins, Moira Aitken, Julia Emerson;

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Scientific Advisory Group members include: Wayne Morgan (chair), Michael Konstan (co-chair), Ted Liou, Susanna McColley, Ann McMullen, Alexandra Quittner, Warren Regelman, Clement Ren, Margaret Rosenfeld, Greg Sawicki, Michael Schechter, Donald VanDevanter, Jeffrey Wagener, Marlyn Woo.

Abbreviations used

CF	cystic fibrosis
COPD	chronic obstructive pulmonary disease
ESCF	Epidemiologic Study of Cystic Fibrosis
FEV₁	forced expiratory volume in 1 second
IV	intravenous

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Figure 1.

Analytical schema showing the baseline FEV₁ averaged from three values obtained at a time of clinical stability (open circles) followed by a decline in FEV₁ below the threshold of a 10% relative decline (filled square). Therapeutic interventions included new antibiotic therapy (evaluated from 14 days before until 56 days following the decline) and hospitalization (evaluated only for 56 days following the decline).

Figure 2.

Therapeutic intervention by baseline lung function decile by age group. $P < .001$ for linear trend by severity deciles for both age groups and for both intravenous antibiotic therapy (A) and hospitalization (B).

Figure 3.

Frequency distribution of new antibiotic interventions (evaluated from 14 days before until 56 days following the decline) and hospitalizations (evaluated only for 56 days following the decline), by baseline lung function decile by age group.

Table I**Demographic and Clinical Characteristics by Age Group^{*}**

Characteristic	Ages 6-12 (N = 7695)	Ages 13-17 (N = 3193)
Age, mean $\pm$ SD	8.8 $\pm$ 2.1	15.3 $\pm$ 1.4
Female, n (%)	3847 (50.0)	1492 (46.7)
F508 Homozygous [†] n (%)	3030 (55.2)	1050 (54.0)
Weight for age (percentile), mean $\pm$ SD	30.6 $\pm$ 26.3	28.5 $\pm$ 26.7
FEV ₁ % predicted at moving average, mean $\pm$ SD	88.6 $\pm$ 19.9	77.4 $\pm$ 22.5
FEV ₁ % predicted at decline, mean $\pm$ SD	71.5 $\pm$ 19.3	62.5 $\pm$ 20.8
FEV ₁ % predicted % change, mean $\pm$ SD	-19.7 $\pm$ 9.8	-19.8 $\pm$ 9.9
<i>Pseudomonas</i> positive, n (%)	4375 (56.9)	2399 (75.1)
Pulmonary signs and symptoms positive [‡] n (%)		
Daily cough	4583 (60.1)	2262 (71.5)
Daily sputum production	2652 (35.0)	1701 (54.2)
Clubbing	4300 (56.2)	2074 (65.2)
Crackles	1937 (25.3)	1124 (35.3)
Wheeze	687 (9.0)	312 (9.8)
Hospitalized within 56 days of decline, n (%)	1406 (18.3)	834 (26.1)
Therapies received within -14 and +56 days of decline, n (%)		
IV antibiotics	1745 (22.7)	986 (30.9)
New inhaled antibiotics	1684 (21.9)	812 (25.4)
New quinolone antibiotic	1616 (21.0)	1037 (32.5)
New oral non-quinolone antibiotics	1951 (25.4)	701 (22.0)

^{*} *P* values for age group comparisons were obtained from *t* test or χ^2 test statistic, as appropriate. All *P* < .001 with the exception of female (*P* = .002), F508 homozygous (*P* = .35), FEV₁ (% pred.) % change (*P* = .61), and wheeze (*P* = .15).

[†] Includes patients with nonmissing data at baseline. 2206 patients aged 6-12 years and 1,248 patients aged 13-17 years were missing data for F508 homozygous.

[‡] Symptom data are unavailable for 24 to 122 patients 6-12 years of age and 11 to 55 patients 13-17 years of age, depending on the symptom.

Table II

Adjusted Logistic Regression Predicting Treatment Associated with Sudden Decline

Adjustment	N	Hospitalizations		IV Antibiotics		Any Treatment*	
		n (%) Treated	OR (CI)	n (%) Treated	OR (CI)	n (%) Treated	OR (CI)
<i>Pseudomonas</i> negative (ref. group)	4114	567 (13.8)	--	669 (16.3)	--	2099 (51.0)	--
<i>Pseudomonas</i> positive	6774	1673 (24.7)	1.54 (1.38-1.72)	2062 (30.4)	1.68 (1.51-1.86)	4607 (68.0)	1.76 (1.62-1.91)
Weight-for-age percentile 25 (ref. group)	5202	835 (16.1)	--	1030 (19.8)	--	3039 (58.4)	--
Weight-for-age percentile <25	5686	1405 (24.7)	1.22 (1.10-1.35)	1701 (29.9)	1.17 (1.06-1.29)	3667 (64.5)	1.04 (0.95-1.13)
Age 6-12 years (ref. group)	7695	1406 (18.3)	--	1745 (22.7)	--	4579 (59.5)	--
Age 13-17 years	3193	834 (26.1)	1.55 (1.40-1.72)	986 (30.9)	1.49 (1.35-1.65)	2127 (66.6)	1.26 (1.15-1.37)
1st FEV ₁ decile (ref. group)	492	212 (43.1)	--	280 (56.9)	--	396 (80.5)	--
2nd FEV ₁ decile	757	299 (39.5)	0.89 (0.70-1.12)	366 (48.4)	0.73 (0.58-0.91)	576 (76.1)	0.78 (0.59-1.04)
3rd FEV ₁ decile	868	261 (30.1)	0.60 (0.48-0.76)	332 (38.3)	0.50 (0.40-0.62)	598 (68.9)	0.57 (0.44-0.74)
4th FEV ₁ decile	1048	250 (23.9)	0.46 (0.36-0.58)	312 (29.8)	0.35 (0.28-0.44)	688 (65.7)	0.51 (0.40-0.66)
5th FEV ₁ decile	1162	264 (22.7)	0.43 (0.34-0.55)	310 (26.7)	0.31 (0.24-0.38)	768 (66.1)	0.53 (0.41-0.68)
6th FEV ₁ decile	1239	242 (19.5)	0.37 (0.30-0.47)	292 (23.6)	0.27 (0.22-0.34)	755 (60.9)	0.44 (0.34-0.56)
7th FEV ₁ decile	1335	226 (16.9)	0.31 (0.25-0.39)	261 (19.6)	0.21 (0.17-0.27)	785 (58.8)	0.40 (0.31-0.51)
8th FEV ₁ decile	1354	191 (14.1)	0.26 (0.20-0.33)	222 (16.4)	0.18 (0.14-0.22)	759 (56.1)	0.36 (0.28-0.47)
9th FEV ₁ decile	1384	156 (11.3)	0.20 (0.16-0.26)	176 (12.7)	0.13 (0.10-0.17)	732 (52.9)	0.33 (0.25-0.42)
10th FEV ₁ decile	1249	139 (11.1)	0.20 (0.16-0.26)	180 (14.4)	0.15 (0.12-0.20)	649 (52.0)	0.31 (0.24-0.40)
Decile trend (<i>P</i> value)	--	--	<.001	--	<.001	--	<.001

* "Any treatment" is defined as any new antibiotic therapy, evaluated from 14 days before until 56 days following the decline, or hospitalization, evaluated only for 56 days following the decline.