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Oral, Inhaled, and Intravenous Antibiotic Choice for Treating Pulmonary Exacerbations in Cystic Fibrosis

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SUMMARY

Rationale—Patients with cystic fibrosis experience frequent pulmonary exacerbations (PEs). Clinicians manage these episodes of worsening signs and symptoms in a variety of ways.

Objectives—To characterize the antibiotic management and associated change in lung function following PEs.

Methods—We used 2003-5 data from the Epidemiologic Study of Cystic Fibrosis to examine antibiotic treatment and the immediate and long term lung function change associated with clinician reported PEs.

Results—45,374 PEs were reported in 13,194 unique patients. Most PEs (73%) were treated with oral antibiotics, while 39% were treated IV and 24% were treated with inhaled antibiotics. The likelihood of non-IV vs. IV antibiotic treatment was associated with the patient's age, stage of lung disease, and magnitude of lung function drop prior to the PEx. Following treatment, the average improvement in the FEV₁ was 3.4±12.2 % predicted with a greater (5.1±12.7 % predicted) improvement following IV antibiotic treatment than with non-IV treatment (2.0±11.6 % predicted). When the best FEV₁ from the year before was compared with 180 days following the PEx there was an average fall of 3.8±10.5 % predicted with little difference observed between

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Disclosure of Conflict of Interest

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antibiotic treatment routes. Patients with only one exacerbation during the 3-year study had a similar loss of lung function to patients with no reported exacerbations.

Conclusion—Clinicians treat the majority of PExs with oral antibiotics, particularly in younger, healthier patients. Pulmonary function improves with antibiotic therapy, however PExs are associated with lung function deterioration over time.

Keywords

cystic fibrosis; pulmonary exacerbation; antibiotics; epidemiology

INTRODUCTION

Lung disease in patients with cystic fibrosis (CF) is characterized by episodic increases in respiratory symptoms such as cough and sputum production, systemic symptoms such as fatigue and weight loss, and a fall in pulmonary function. Although no consensus definition exists for these episodes, they are collectively referred to as pulmonary exacerbations (PExs).⁽¹⁻⁴⁾ Pulmonary exacerbations are associated with reduced health-related quality of life,⁽⁵⁻⁷⁾ accelerated pulmonary function decline,^(8, 9) and decreased survival.⁽¹⁰⁻¹³⁾ Treatment of PExs usually involves antibiotics with frequent airway clearance and varies between individual clinicians and clinical care centers.⁽¹⁴⁾ Standardized recommendations for PEx management have been limited by a lack of objective evidence for optimal therapy.^(15, 16)

Pulmonary exacerbations are defined in a variety of ways.⁽¹⁷⁾ Clinical trials frequently have used the clinician's decision to treat with intravenous (IV) antibiotics as the definition for a PEx.⁽¹⁸⁻²³⁾ Studies with IV antibiotics used to treat PExs generally show the patient's pulmonary function returning to baseline in 7-10 days.^(24, 25) However a sub-population of patients fails to completely respond and many patients experience multiple exacerbations over the following year.^(24, 26-28) Furthermore, studies of IV treatment fail to recognize that clinician-defined PExs may be treated only with oral or inhaled antibiotics. Although clinical and microbiologic improvement has been demonstrated following IV treatment for a PEx, little is known of the outcomes from oral or inhaled treated exacerbations.

The Epidemiologic Study of Cystic Fibrosis (ESCF) is a multicenter, prospective, encounter based, longitudinal study of therapy and the natural history of CF.⁽²⁹⁾ Beginning in 2003 an electronic data collection form related to PExs was initiated in ESCF by which clinicians could report treatment with antibiotics including IV, inhaled or oral. We analyzed these ESCF data to evaluate clinical use of antibiotics for treating PExs, measure pulmonary function change associated with treatment, and determine the association of PExs and PFT change over time.

METHODS

All 18,140 patients enrolled in the ESCF between 2003 and 2005 were eligible for this analysis. A PEx was defined prospectively as any new or increased respiratory symptoms or any clinical worsening in pulmonary status for which the clinician decided to initiate new

antibiotic therapy. All therapies were determined by the clinician and all antibiotics used to treat the PEx were recorded. The onset of the PEx was defined as the date at the start of new antibiotic therapy. Age at exacerbation was defined as the patient's age at the onset of the exacerbation and all reported PExs separated by at least 14 days were included in the analysis. Our initial analysis focused on the antibiotic treatment of an exacerbation. We then looked at a sub-group of exacerbations where pulmonary function test (PFT) results were available to better understand the impact of a PEx. The forced expiratory volume in 1 second (FEV₁) was normalized to percent predicted values according to the method of Wang et al.(30) for female patients <16 years old and male patients <18 years old, and Hankinson et al.(31) for older patients. Two analyses of FEV₁ were performed. To evaluate the short-term impact of an exacerbation, the FEV₁ value closest to the PEx onset (within the 30 days prior) was compared with the FEV₁ value closest to the end of antibiotic treatment (within the 90 days following onset). Long-term pulmonary function impact was evaluated by comparing the highest FEV₁ within one year prior to the PEx and the highest FEV₁ within 180 days following the PEx onset.

A separate analysis was undertaken to better define the pulmonary impact of a single exacerbation on an individual patient. For this analysis, patients with only one PEx during the 3 year study period were compared with patients who had no recorded exacerbations. Only patients with pulmonary function results were included since the aim was to study the impact of an exacerbation on pulmonary function. Similar criteria for pulmonary function testing were used, including both short-term and long-term impact.

All analyses were conducted using SAS 9.1 (SAS Institute, Inc., Cary NC). Due to the large number of exacerbations in the dataset, statistical significance was defined as $p < 0.001$ unless otherwise noted.

RESULTS

During 2003-2005 45,374 exacerbations were reported involving 13,194 unique patients (25.3% had one, 20.0% had two, 15.8% had three, 11.4% had four, and 27.5% had >4 exacerbations over three years). The mean patient age at the time of an exacerbation was 16.3 ± 11.0 years, with 15.8% of reported PExs occurring in patients <6 years old, 25.1% in 6-12 year olds, 20.0% in 13-17 year olds, 20.2% in 18-24 year olds, and 18.8% in patients 25 years old or older (Table 1). The average number of PExs reported per patient year varied by age group (Figure 1), but was highest in the youngest patients (< 6 years of age with 1.35 PExs per patient year) and lowest in older adults (1.17 PExs per patient year).

Antibiotics were used to treat 44,512 PExs (see supplemental table), with oral antibiotics used in 73.2%, inhaled antibiotics used in 23.9%, and IV antibiotics used in 38.7 %, with frequent overlap of more than one route of administration (Figure 2). Forty-four percent of exacerbations were treated with oral antibiotics alone and 15% were treated with inhaled \pm oral antibiotics. For exacerbations treated with IV antibiotics, tobramycin was used 69.6% of the time. When tobramycin was used, it was almost always used in combination with a second IV antibiotic. Of the 17,544 IV-treated exacerbations, 2% were treated with tobramycin alone, 24% tobramycin plus ceftazidime (\pm a third antibiotic), 8% tobramycin

plus cefepime, 8% tobramycin plus meropenem, 28% tobramycin with other IV antibiotics, and 30% included other IV antibiotic combinations without tobramycin.

The proportion of non-IV to IV treated PExs decreased with patient age, with under 6 year olds being 4.1 times more likely to receive oral and/or inhaled antibiotics than IV antibiotics, while adult patients were slightly more likely to be treated with IV antibiotics (Figure 3A). The decision to treat with IV antibiotics or not was also associated with the degree of lung function limitation and the magnitude of decline in lung function prior to the PEx (Figure 3B). Exacerbations occurring in patients with less advanced disease ($FEV_1 > 100\%$ predicted) were 4.0 times more likely to be treated with inhaled and/or oral than IV antibiotics whereas PExs in patients with the most advanced disease ($FEV_1 < 40\%$ predicted) were treated with IV antibiotics 52% of the time.

PFT results for evaluating the short-term impact of treatment were available for 13,673 exacerbations. Overall, treatment with antibiotics was associated with an average short-term improvement in FEV_1 of $3.4 \pm 12.3\%$ predicted (mean \pm SD) (Table 2, Figure 4). Treatment with IV antibiotics was associated with a significantly lower FEV_1 prior to the PEx compared with non-IV treated exacerbations (53.6 ± 22.8 vs. $71.5 \pm 24.1\%$ predicted, $p < 0.001$). Average short-term improvement in FEV_1 was significantly greater for events treated with IV antibiotics than for those that were not (5.1 ± 12.7 vs. $2.0 \pm 11.6\%$ predicted, $p < 0.001$).

There were 27,251 exacerbations with related PFT results available for evaluating long-term impact of therapy (Table 3, Figure 4). The average long-term loss of FEV_1 associated with a treated PEx was $3.8 \pm 10.5\%$ predicted. Similar to the short-term results, use of IV antibiotics was associated with lower baseline lung function (FEV_1 66.8 % predicted for IV treated vs. 84.9 % predicted for non-IV treated PExs), however over the long term both IV and non-IV treated exacerbations were associated with similar FEV_1 losses (-4.0 and -3.7% predicted).

There were 2016 patients with long-term PFT results included in the sub-group with only one PEx during the 3-year study. Comparing these patients with the 4139 patients who had PFT results and no reported exacerbations, the long-term fall in FEV_1 was almost identical (-2.4 ± 9.9 vs. $-2.4 \pm 10.6\%$ predicted). Similar to the results for all exacerbations, patients treated with IV antibiotics had significantly lower baseline lung function (77.2 ± 23.7 vs. $90.6 \pm 22.3\%$ predicted FEV_1 , $p < 0.001$) compared with non-IV treated patients. Short-term PFT results demonstrated an average FEV_1 increase of $6.2 \pm 12.4\%$ predicted, with patients whose treatments included IV antibiotics improving an average of $8.6 \pm 13.2\%$ predicted, whereas those treated without IV antibiotics averaged only $4.2 \pm 11.3\%$ predicted ($p < 0.001$).

DISCUSSION

Patients with CF experience frequent PExs and based on our data, most clinician-defined exacerbations are treated with oral antibiotics. Only one third of reported exacerbations were treated with IV antibiotics, and as expected, this treatment was more likely to occur in older patients with more advanced lung disease and/or a greater recent fall in lung function. Immediately following treatment for a PEx there was generally an improvement in

pulmonary function, however over a longer time period there was a drop in lung function associated with the average exacerbation. One important finding was that there was no difference in the drop in pulmonary function between patients with only a single treated exacerbation during the 3-year study and patients with no recorded exacerbations.

This study differs from most previous studies in that we include all clinician declared exacerbations, regardless of whether the exacerbation was treated with IV antibiotics or not. Much debate has arisen over the definition of a pulmonary exacerbation in patients with CF. (1, 4, 32) Using the ESCF dataset, Rabin and coworkers(33) identified specific risk factors associated with IV treated PExs, but noted that even in patients experiencing all of these risk factors, clinicians did not always initiate IV antibiotic therapy. Previous studies, both epidemiologic and randomized controlled trials, have employed IV antibiotic administration as a marker for a PEx.(8, 9, 17-19, 22, 23) Although these past observations are important, our results suggest that including IV therapy to define an exacerbation will bias the results towards the minority of clinician-defined PExs which occur predominately in the older patient population with more advanced lung disease. Our results indicate that more PExs are treated without IV antibiotics than are treated with IV antibiotics and the use of non-IV antibiotics is strongly weighted towards younger children who are earlier in their lung disease process. This is particularly important since children less than 6 years old have a greater incidence of reported antibiotic-treated PExs than any other age group.

There are likely multiple reasons that IV antibiotic use increases with age. Although viral infections are associated with PExs at all ages, they are reported more frequently in younger patients and would be less likely treated with antibiotics, particularly IV.(34-36) Furthermore, the composition of a CF patient's microbial community changes over time, with bacteria such as *Pseudomonas aeruginosa* being more common in older patients and necessitating a different selection of antibiotics.(37) Finally, clinical experience is greater for the older patient and prior response to antibiotics will influence antibiotic choice and route for treating a PEx. It is important to note that while our data is limited to age and lung function, it suggests that the clinician's decision to use IV antibiotics is influenced by the patient's baseline FEV₁ and the degree of their pulmonary function drop prior to presenting with a PEx. One risk of this apparent reliance on FEV₁ and lung function loss to gauge therapy is that clinicians may inaccurately estimate the severity of a PEx in patients too young to reliably perform PFTs.

There have been several, relatively small prospective studies looking at antibiotic treatment of PExs in CF.(38-41) Most have involved the use of IV antibiotics for varying durations and in varying combinations. We did not analyze the duration of treatment, but did find that most of the time when IV therapy was used, the clinician decided to treat with multiple antibiotics. This was not true when oral or inhaled antibiotics were used; they were generally used alone and to treat younger patients and patients with better lung function. Of interest, there were a few reported exacerbations that were not treated with any antibiotics. Given the epidemiologic nature of this study, we are unable to know whether these patients were considered to have viral infections (ie. not requiring antibiotic therapy) or to have mainly an obstructive problem due to secretions (ie. possibly treated with increased airway clearance therapy without antibiotics), or whether an error was made in reporting. The existence of

these events, however, suggests that the definition of a PEx should probably not be limited by requiring the use of antibiotics.

When we separated the antibiotic choices into three groups: 1) oral only, 2) inhaled with/without oral, and 3) IV with/without other antibiotics, the resulting groups were at different stages of lung disease and clinicians treated the patients with more advanced disease more aggressively. However, the difference in short-term improvement was a little surprising. As shown in Table 2, oral antibiotics were associated with a relatively small improvement in pulmonary function compared with IV, with inhaled \pm oral being intermediate. This was true for both absolute and relative changes. The degree of pulmonary function improvement may be related to many aspects of treatment for a PEx. Patients with the largest drop in lung function prior to a PEx are the most likely to show the largest improvement, and they were also the most likely to be treated with IV antibiotics. Additionally the size of improvement could be related to the availability of more effective antibiotics for IV use, or could possibly indicate that other therapies (ie. inpatient care) used at the time of IV therapy have added benefit.(16) The long-term average change in lung function was not different between treatment groups and showed a discouraging average 3.8 ± 10.5 % predicted absolute and 4.9% relative drop in FEV₁ associated with each exacerbation. This average drop may indicate the harmful impact of a PEx in all patients or more likely represents improvement in some and failure to improve in others (Figure 4). Recently, Sanders and colleagues(26-28) reported that about one-fourth of patients fail to recover lost lung function to within 10% of baseline following treatment with IV antibiotics. Our data on long-term pulmonary function shows a similar finding with 21.1% of patients failing to regain within 10% of their prior year best FEV₁. However this observation, as well as others describing health outcomes associated with PExs, may be complicated by the inclusion of patients who experience multiple exacerbations. Patients who have multiple IV-treated exacerbations in a prior year are at greater risk for a near-term decline in FEV₁ as well as future PExs.(10, 42) In our analysis we treat each exacerbation as a unique event and we determined the average change associated with that one event. Our results may show a more severe average drop in lung function associated with a PEx than previously reported since in some cases there was a second PEx during the 180 day follow-up period. However in general this impact is small since these patients averaged just over three exacerbations during the 3-year period.

To further eliminate the contribution of patients experiencing multiple PExs, we studied a subset of patients that had only one exacerbation during the 3-year study. Average FEV₁ increased 6.2 ± 12.4 % predicted over the short term following treatment and the average improvement in patients treated with IV antibiotics was greater than in patients treated with oral and/or inhaled antibiotics (13.4% vs. 5.3% relative improvement). These results are consistent with the changes in FEV₁ % predicted in the overall study involving all exacerbations. However the average long-term drop in FEV₁ of 2.4 ± 9.9 % predicted over 18 months was almost identical to the 2.4 ± 10.6 % predicted fall seen in a comparator group of patients with no exacerbations. Importantly, these patients were at an early stage of their disease with baseline FEV₁ values frequently in the normal range. This result suggests that PExs are not the only reason for pulmonary deterioration in patients with CF and that, although antibiotic treatment is associated with improved short-term pulmonary function, it does not prevent a drop in long-term lung function. It is also possible that the patients with

no reported exacerbations may have experienced acute events similar to the treated patients, but these events were not recognized, or if recognized were not treated or reported. Regardless of the reason, it appears there is an opportunity for better or more frequent therapy to reduce this fall in lung function, a conclusion consistent with the findings of Johnson and colleagues(43) which indicate that CF care sites with greater reporting of exacerbations and greater use of antibiotics have overall better lung function in their patients.

As with all epidemiologic studies, these results are limited by the data collected and what the clinician reports. Conclusions must be considered hypothetical and not proven. However the strength of an epidemiologic study is that it more closely represents “real life” experience than is the case with a highly selected randomized controlled trial. In this study we chose to be descriptive in our analyses and avoid constructing a multivariate model since we had limited data about other patient characteristics. Additionally, we felt that this descriptive approach better represented the clinician’s decision making. Even with these limitations we identified interesting differences between routes of antibiotic use and were able to compare pulmonary function outcomes following PExs.

In summary we found that PExs are frequent in patients with CF at all ages. Antibiotic treatment choice varies greatly between clinicians, with oral antibiotics used to treat the majority of PExs and used most commonly in younger patients with less advanced lung disease. There is an acute improvement in FEV₁ following treatment with antibiotics, however PExs are associated with a long term loss of lung function. In patients with infrequent PExs, this loss is not greater than the general loss of lung function in patients who are not reported as having an exacerbation and who are at a comparable early stage of lung disease. Importantly our results show that limiting the definition of a PExs to those treated with IV antibiotics will bias the results toward older patients in a later stage of disease. A better understanding of the impact from these less aggressively treated PExs may aid in developing improved, earlier care in CF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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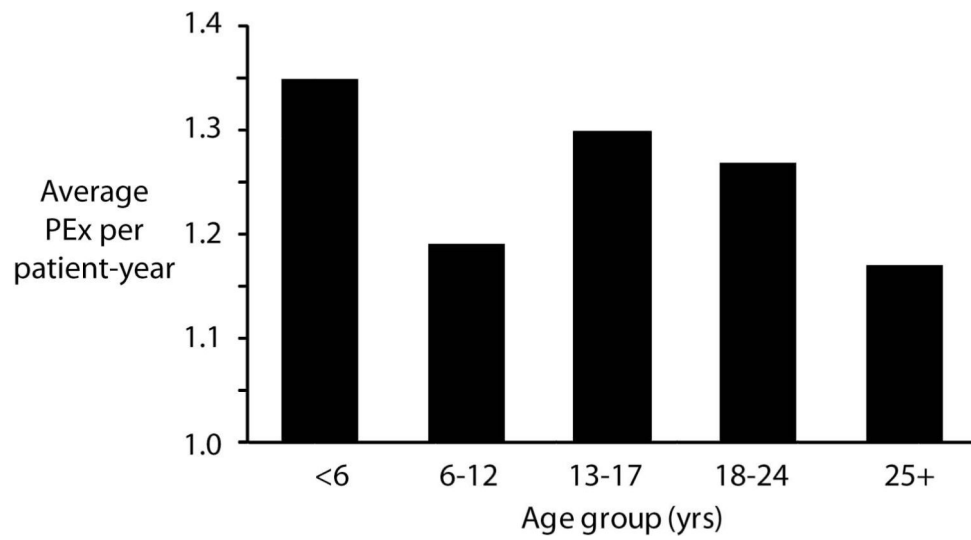


Figure 1. Incidence of PExs stratified by age group. Significant comparison differences ($p<0.001$) include: <6 vs 25+, 6-12 vs 13-17, 6-12 vs 18-24, 13-17 vs 25+, and 18-24 vs 25+.

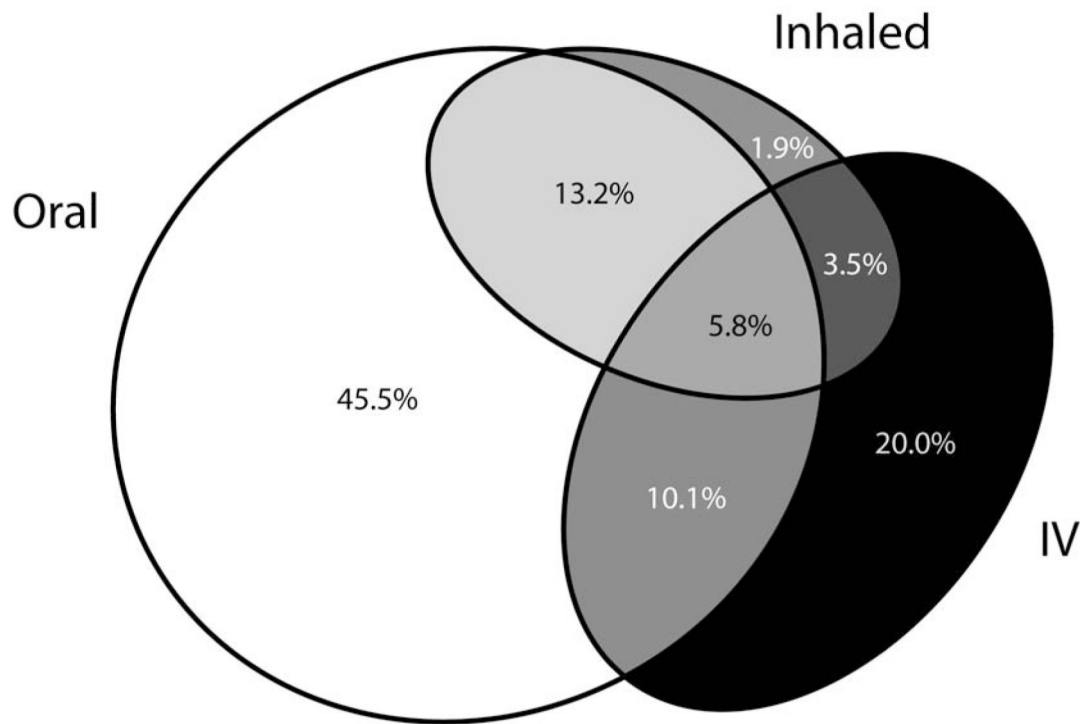


Figure 2.

Oral, inhaled, and IV antibiotics prescribed for PEXs from 2003 through 2005. Route of administration for 88,839 antibiotic treatments (Supplement Table) during 45,374 clinician-diagnosed pulmonary exacerbations. Areas reflect the number of treatments by route of administration: Oral only – 45.5%, Inhaled only – 1.9%, Inhaled plus oral – 13.2%, IV only – 20.0%, IV plus oral – 10.1%, IV plus inhaled – 3.5%, and IV plus oral and inhaled – 5.8%. (Figure created with eulerAPE <http://www.eulerdiagrams.org/eulerAPE/>).

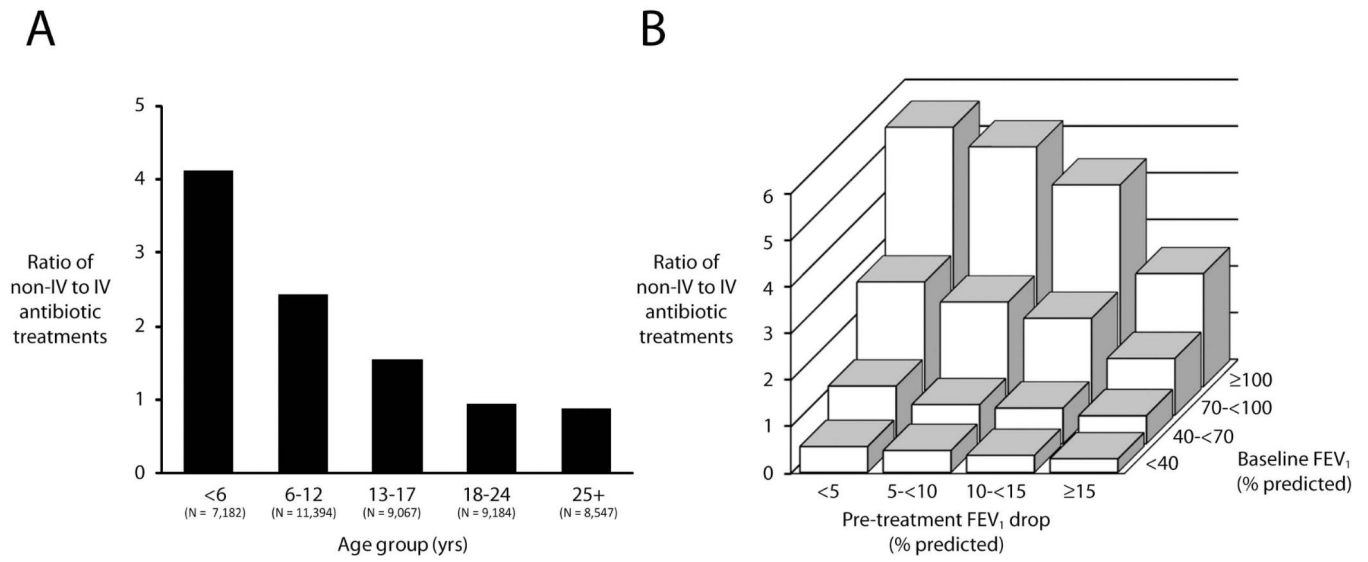


Figure 3. Ratio of non-IV to IV antibiotic treatment routes. Panel A: Ratio of treatment without or with IV antibiotics stratified by the patient age. Panel B: Ratio of treatment without or with IV antibiotics stratified by lung disease stage (based on best FEV₁ within the year prior to the PEx) and the drop in FEV₁ during the year prior to the exacerbation.

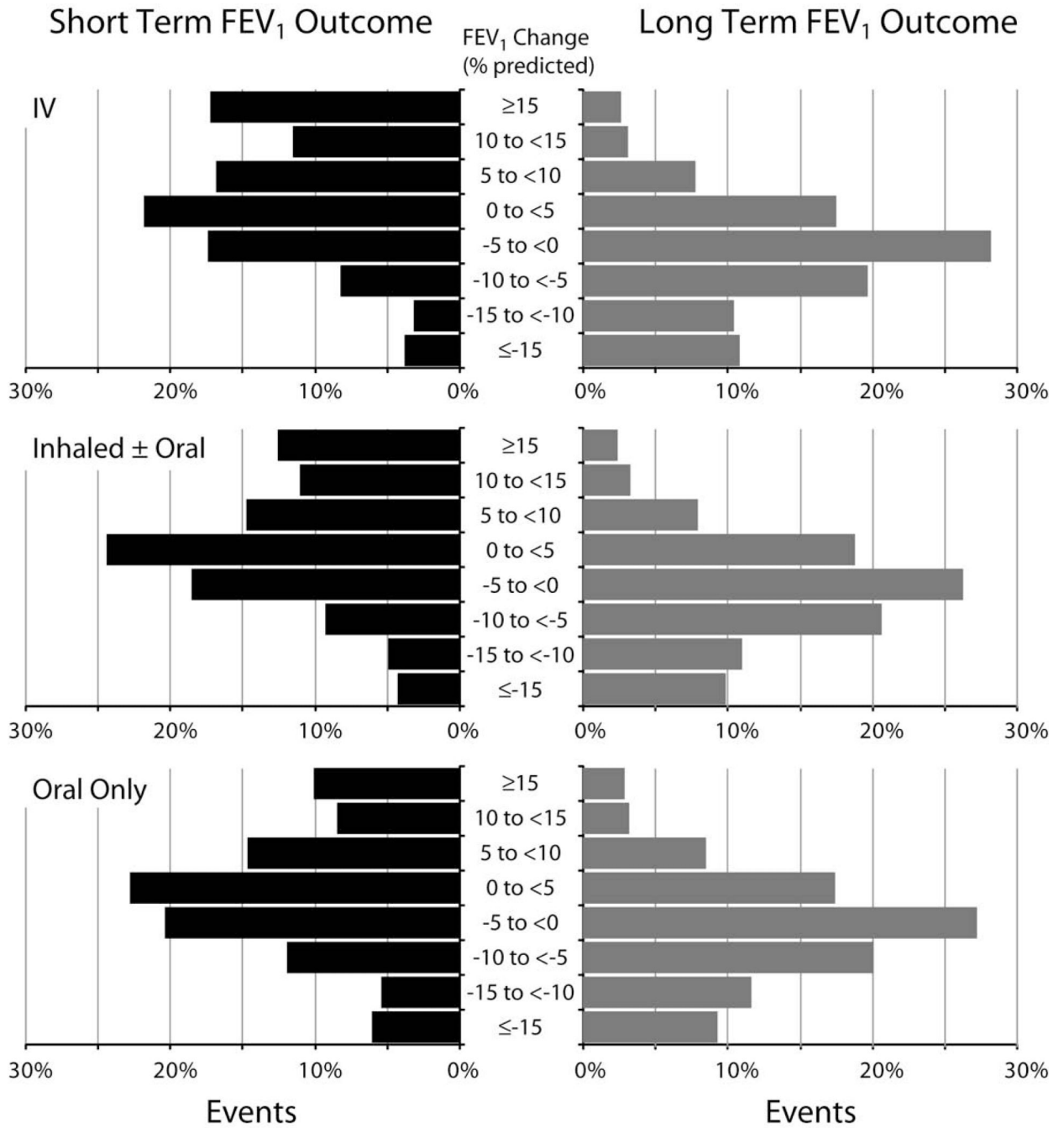


Figure 4. Distribution of short-term (left panel) and long-term (right panel) absolute % predicted change in FEV₁ associated with antibiotic treatment of PExs, separated by route of administration (IV on top, oral on bottom, and inhaled ± oral in the middle). Bars represent percent of PEx events divided into groups of 5 % predicted change in FEV₁. Short-term and long-term patient groups are not identical.

Table 1

Exacerbation demographics by age group including gender, weight, and pulmonary function.

Age Group at onset of PEx (years)	<6	6-12	13-17	18-24	25+
Number of PExs	7,182	11,394	9,067	9,184	8,547
Gender (% female)	53.5	52.7	51.0	52.7	50.4
Weight for age percentile at baseline *	33.5±28.7	31.0±26.9	27.7±26.1	24.6±25.0	36.0±29.1
Best stable FEV ₁ prior to PEx (within 1 year) #	NA	93.4±20.7	83.5±22.4	68.0±23.0	63.1±25.2
FEV ₁ prior to PEx (within 30 days) #	NA	77.8±22.6	66.7±23.1	54.2±22.0	45.4±19.3
Best FEV ₁ after PEx (within 90 days) #	NA	81.5±22.4	70.4±23.6	58.3±22.9	47.4±20.1
Best stable FEV ₁ after PEx (within 180 days) #	NA	90.2±21.3	78.6±23.1	63.7±23.5	52.1±21.5

Definition of Abbreviation: FEV₁ = forced expiratory volume in 1 second; PEx = pulmonary exacerbation; NA = not applicable

* mean ± SD

percent predicted mean ± SD

Table 2

Short-term Pulmonary Function Data for PEXs with PFT Results Within 30 Days Prior to and 90 Days after Antibiotic Treatment

	All	IV antibiotics	Inhaled ± Oral antibiotics	Oral antibiotic only
Sample Size	13,653	6,375	2,227	4,862
Closest FEV ₁ within 30 days prior to treatment*	63.1±25.2	53.6±22.8	69.1±23.9	72.9±24.0
Closest FEV ₁ within 90 days after treatment*	66.6±25.7	58.7±24.4	72.3±24.8	74.4±24.7
Absolute change*	3.4±12.3	5.1±12.7	3.2±11.3	1.5±11.6
Relative change	5.4%	9.5%	4.6%	2.1%

Definition of Abbreviation: FEV₁ = forced expiratory volume in 1 second; IV = intravenous;

SD = standard deviation.

* FEV₁ % predicted ± SD

Table 3

Long-term Pulmonary Function Data for PEXs with PFT Results Within One Year Prior to and 180 Days after Antibiotic Treatment

	All	IV antibiotics	Inhaled ± Oral antibiotics	Oral antibiotics only
Sample Size	27,251	11,252	4,225	11,339
Best FEV ₁ within 1 year prior to treatment*	77.4±26.2	66.8±25.0	82.0±24.8	86.3±23.9
Best stable FEV ₁ within 180 days after treatment*	73.6±26.6	62.7±25.4	78.3±24.9	82.7±24.3
Absolute change*	-3.8±10.5	-4.0±11.1	-3.7±10.1	-3.6±10.1
Relative change	-4.9%	-5.9%	-4.5%	-4.2%

Definition of abbreviations: FEV₁ = forced expiratory volume in 1 second; IV = intravenous;

SD = standard deviation.

* FEV₁ % predicted ± SD