Susceptibility Testing of *Pseudomonas aeruginosa* Isolates and Clinical Response to Parenteral Antibiotic Administration

Lack of Association in Cystic Fibrosis

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**Study objective:** To determine the relationship between the antibiotic susceptibility of *Pseudomonas aeruginosa* isolated from the sputum of patients with cystic fibrosis (CF) and the patient’s response to parenteral antibiotic administration, we performed a retrospective analysis using data from patients in the placebo arm of a phase 3 trial of tobramycin solution for inhalation. All patients were chronically infected with *P aeruginosa*. Seventy-seven of the 262 patients receiving placebo experienced a pulmonary exacerbation during the trial for which they received therapy with IV tobramycin and ceftazidime. The susceptibility of the *P aeruginosa* isolates to ceftazidime and tobramycin was determined at trial enrollment by broth microdilution.

**Design:** The clinical response to combination antibiotic therapy was assessed by analyzing differences in spirometry before and after antibiotic administration. The FEV₁ percent predicted at the first visit after the conclusion of antibiotic administration was compared to the FEV₁ percent predicted prior to antibiotic therapy. The results were analyzed both descriptively and by regression analyses.

**Results:** The conditions of 54 patients improved, and those of 9 patients worsened, and in 14 patients there was no change in FEV₁ with antibiotic administration. No correlation was observed between the susceptibility of *P aeruginosa* to tobramycin or ceftazidime and clinical response. Only the three following variables were observed to significantly correlate with FEV₁ after antibiotic treatment on regression analysis: FEV₁ prior to treatment (p < 0.0001); number of days elapsed between the previous FEV₁ measurement and the initiation of IV antibiotic therapy (p < 0.002); and the number of days elapsed between the determination of the minimum inhibitory concentration and the initiation of IV therapy (p < 0.03). No significant trends were observed between the antibiotic susceptibility of *P aeruginosa* isolates and treatment outcomes.

**Conclusion:** While lack of statistical significance for a trend between bacterial susceptibilities and the response to parenteral antibiotic administration does not mean that no such trend exists, the precision of the confidence intervals allows us to conclude that even if isolate antibiotic susceptibilities affect outcome, the impact would be small and not clinically relevant.

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**Key words:** antibiotic administration; cystic fibrosis; *Pseudomonas aeruginosa*; pulmonary exacerbation

**Abbreviations:** CF = cystic fibrosis; MIC = minimum inhibitory concentration; PFT = pulmonary function test; PFT₁ = most recent pulmonary function test prior to the IV administration of tobramycin and ceftazidime; PFT₂ = the pulmonary function test performed after the conclusion of IV antibiotic administration

Cystic fibrosis (CF) is an autosomal-recessive disease that is characterized by the abnormal movement of salt and water across the respiratory epithelium, which leads to the production of abnormally viscous mucus and reduced mucociliary clearance in the lung. In addition, the activity of the innate host defense systems is reduced. As a result, CF patients develop a chronic bacterial bronchitis and bronchiectasis, with *Pseudomonas aeruginosa* being the predominant pathogen.¹ This infection is accompanied by a progressive decline in pulmonary function, with intermittent, acute pulmonary exacerbations. Pulmonary exacerbations are associated with a decline in lung function, which in most patients returns to baseline with treatment. The treatment of an exacerbation consists of IV antibiotic administration, intensive chest physiotherapy, and attention to nutrition. A combination of a β-lactam and an amino-
glycoside are commonly administered. Administering an aminoglycoside and a β-lactam that are active against *P. aeruginosa* is significantly better than single antibiotic administration and has become a cornerstone of treatment for pulmonary exacerbations. This therapy produces significant clinical benefits. There is improvement in FEV₁ and FVC, less air trapping, as well as weight gain and lessening of subjective symptoms. However, the efficacy of antibiotic therapy for exacerbations has been questioned, and it has been suggested that at least some of the clinical response observed following IV antibiotic administration may result from intensive chest physical therapy, improved nutrition, and better compliance with medications as patients are usually hospitalized for the treatment of an exacerbation.

Unlike pulmonary infections in non-CF patients, in whom a clinical cure is predicated on the eradication of the infecting organism, *P. aeruginosa* is rarely eradicated from the sputum of CF patients with parenteral antibiotic administration. As their lung disease progresses, CF patients experience more frequent pulmonary exacerbations and receive repeated courses of IV antibiotics. As a result, there is a strong selective pressure for the emergence of bacterial strains with reduced antibiotic susceptibility. All bacteria infecting the CF airway are capable of manifesting resistance, but resistance is of particular concern in *P. aeruginosa*, as its prevalence is greatest in patients with severely compromised pulmonary function.

It is common practice for bacteria that have been isolated from the sputum of CF patients to be tested for antibiotic susceptibility. Since most CF patients carry multiple morphotypes of *P. aeruginosa*, susceptibility tests often are performed on multiple isolates from a single sputum specimen. While the utility of *in vitro* susceptibility tests has been demonstrated for directing the choice of antibiotic in the treatment of acute pulmonary infections in non-CF patients, there is evidence that susceptibility testing is not a reliable predictor of clinical success in the treatment of pulmonary exacerbations in patients with CF.

The question of whether *in vitro* susceptibility tests are predictive of future responses to antibiotic therapy is particularly important to clinicians who are trying to weigh the risks and benefits of long-term antibiotic administration to patients with CF, since these patients will receive multiple courses of antibiotics and will ultimately produce cultures of antibiotic-resistant bacteria. Clinicians commonly ignore the results of susceptibility tests generated during treatment if a patient shows improvement following the IV administration of antibiotics (independent of whether the patient’s *P. aeruginosa* strains are scored as resistant or susceptible). The question of whether it is appropriate to treat a patient with an antibiotic if a patient has previously cultured a resistant bacterial isolate is more difficult to address.

Prospective, controlled studies of the relationship between antibiotic susceptibility results and clinical response are difficult to design and implement, due in part to the ethical dilemma of prospectively treating patients with an antibiotic regimen that has been predicted (by *in vitro* testing) to be clinically ineffective. Thus, the available evidence regarding the predictive value of antibiotic susceptibility tests is largely observational.

We conducted a retrospective analysis of data from patients in the placebo arm of a randomized trial of a tobramycin solution for inhalation to evaluate the relationship between *in vitro* antibiotic susceptibility and the pulmonary function response to IV antibiotics that have been administered for a pulmonary exacerbation. We sought to define the relationship of the quantitative antibiotic susceptibility of *P. aeruginosa* to tobramycin and ceftazidime to the change in FEV₁ percent predicted following the IV administration of these antibiotics.

**Materials and Methods**

Five hundred twenty CF patients with chronic *P. aeruginosa* infection were enrolled in two identical, double-blind, simultaneously conducted, phase 3 clinical trials. Patients were randomized to treatment with aerosol administration of either a tobramycin solution for inhalation (n = 258) or a taste-masked placebo (n = 262). The study drug was administered in a series of cycles consisting of 28 days of drug administration followed by 28 days off drug administration. The selection criteria, the study drug formulation, and delivery have been described. During the trial, patients could receive any and all standard therapy for CF, with the exception of any inhaled antibiotics other than the study.
drug. It is important to note that this population represented a subset of the CF population, since only patients with moderate-to-severe lung disease (ie, FEV₁, 25 to 75% of predicted) whose sputum cultured P aeruginosa, and not Burkholderia cepacia, were eligible.

There were a total of 11 scheduled visits during the studies. During the screening period and the first treatment cycle (ie, study weeks 4 to 8), visits occurred every 2 weeks. During the second and third treatment cycles (ie, study weeks 8 to 24) visits occurred every 4 weeks. Pulmonary function was measured at each visit, with spirometry (FEV₁) performed according to American Thoracic Society standards, expressed as a percentage of the value predicted based on age and height according to the method of Knudson et al.15

Quantitative sputum cultures were performed on all patients at treatment initiation and after weeks 20 and 24 of treatment. Sputum specimens were refrigerated and shipped on ice (within 48 h of collection) to the microbiology laboratory at Children’s Hospital and Regional Medical Center (Seattle, WA) for quantitative cultures on selective media and quantitative susceptibility testing.16 The determination of the minimum inhibitory concentrations (MICs) of tobramycin and ceftazidime was performed on all morphotypes of P aeruginosa present in the sputum. This procedure permitted the determination of the strain that was present in greatest density, as well as the definition of the density of the individual morphotypes. Isolates were categorized as susceptible or resistant to tobramycin and ceftazidime according to National Committee on Clinical Laboratory Standards criteria.16 These criteria define a tobramycin-susceptible organism as one having an MIC ≤ 4.0 µg/mL, while a resistant strain has an MIC ≥ 16 µg/mL. For ceftazidime, a susceptible organism has an MIC ≤ 8 µg/mL, while a resistant isolate has an MIC ≥ 32 µg/mL (National Committee on Clinical Laboratory Standards Performance Standards M100-S12).

Study Population

A total of 119 patients from the placebo arm of the trial were hospitalized for a pulmonary exacerbation during the trial. Of those 119 hospitalized patients, a majority (77 of 119 patients; 64.7%) were treated with IV tobramycin and ceftazidime. These 77 patients were chosen as the sample population.

Individual patient response to parenteral tobramycin/ceftazidime administration was estimated by calculating the relative change in FEV₁ (expressed as a percentage) from the most recent pulmonary function test (PFT) results prior to tobramycin/ceftazidime administration (PFT1) to the PFT performed after the end of antibiotic treatment (PFT2). The relative change in FEV₁ percent predicted was calculated as follows.

Binary relationships between the response to antibiotic therapy and the tobramycin or ceftazidime susceptibility of the most prevalent and the least susceptible isolate were analyzed graphically. The patient response to IV antibiotic administration (expressed as the percentage change from pretreatment FEV₁, percent predicted) was plotted vs either the tobramycin or ceftazidime MIC of both the most prevalent P aeruginosa isolate at baseline as well as the isolate with the lowest susceptibility to either tobramycin or ceftazidime at baseline.

To examine the relationships of three important variables (ie, antibiotic response, tobramycin MIC, and ceftazidime MIC) simultaneously, the patient response to IV antibiotic administration was first qualitatively stratified as “improvement,” “no change,” or “worsening.” Improvement was defined as an increase in the FEV₁ of > 5%, no change was defined as no change in pulmonary function from an FEV₁ ± 5%, and worsening was defined as an FEV₁ of < 5% of the pretreatment value following parenteral antibiotic administration. The tobramycin and ceftazi-

dine susceptibilities of the P aeruginosa isolates then were plotted for the three subgroups. Plots were generated both for the most prevalent P aeruginosa isolate in the spectrum and for the isolate that was least susceptible to each antibiotic.

Regression Modeling

To adjust for potential confounding among variables (eg, delay in time between PFT1 and the initiation of antibiotic therapy) impacting the observed response to antibiotic therapy, a backward elimination regression model was run for the dependent variable PFT2 (Proc Reg, SAS Institute; Cary, NC). Independent variables included patient age, sex, height, PFT1, the number of days between PFT1 and the initiation of IV therapy, and the number of days between the cessation of IV antibiotic administration and PFT2, and the number of days between MIC determination and the beginning of the administration of IV antibiotics (called IV start). Independent variables with significance of > 0.10 were eliminated from the model in a stepwise fashion. Parameter estimates and 95% confidence intervals for variables with significance of < 0.1 were calculated.

After insignificant variables were removed from the regression model, possible associations between the antibiotic administration effect, treatment response and the antibiotic susceptibilities of the isolate were tested. MIC variables were converted to base-10 logarithms and added in various manners to the model to test for the significance of the variable and to determine 95% confidence intervals for parameter estimates. Analyses were performed by the addition of a single MIC variable to the established regression model. First, four individual MIC variables (ie, log10 tobramycin MIC and log10 ceftazidime MIC of the highest density isolate and log10 highest tobramycin and ceftazidime MICs) were tested. Next, the sums of each pair of variables (ie, log10 highest density isolate tobramycin MIC plus log10 highest density isolate ceftazidime MIC and log10 highest tobramycin MIC plus log10 highest ceftazidime MIC) were studied. Finally, the products of each pair of isolate MICs was studied (ie, log10 highest density isolate tobramycin MIC multiplied by log10 highest density isolate ceftazidime MIC and log10 highest tobramycin MIC multiplied by log10 highest ceftazidime MIC). Parameter estimates and 95% confidence intervals were analyzed to understand the greatest possible magnitude of relationship between MIC variables and treatment response.

Results

The response of 77 CF subjects receiving combination IV tobramycin and ceftazidime therapy for pulmonary exacerbations were analyzed. Treatment responses among the 77 subjects ranged from a relative decrease of 40.3% in FEV₁ percent predicted to an increase of 139.9%. The mean relative change was an increase of 17.7%. This improvement, which was expressed as an average change in FEV₁, is of the same order of magnitude as that seen with antibiotic treatment of a pulmonary exacerbation seen in other studies.2–4,13 Absolute changes in lung function ranged from a decrease of 23.5% of the predicted FEV₁ to an increase of 39.3% of the predicted FEV₁, with a mean change of 6.9% predicted (Fig 1).

When treatment outcomes were plotted against tobramycin or ceftazidime MICs of patients’ least suscep-
tible or most predominant *P. aeruginosa* isolates, there was no obvious correlation between the isolate antibiotic susceptibility and the patient response (Fig 2).

The relationships between tobramycin and ceftazidime MICs and patient responses were studied by first dividing patient responses into the following three categories: improvement (ie, > 5% relative increase); worsening (ie, > 5% relative decrease); or

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**Figure 1.** The change in pulmonary function following IV antibiotic therapy is shown. Clear bars represent the distribution of absolute responses (FEV1 percent predicted). Gray bars represent relative responses (percentage change in FEV1% predicted). Response categories for relative change in lung function are highlighted at the top.

**Figure 2.** Changes in pulmonary function vs tobramycin or ceftazidime susceptibility of the *P. aeruginosa* isolate are shown. Tobramycin susceptibilities are shown in the left panel, and ceftazidime susceptibilities are shown in the right panel. ○, isolates with the highest antibiotic MIC; □, each patient’s most prevalent isolate; dotted lines, parenteral breakpoints; horizontal gray bars, range of ± 5% change (ie, the “no-change” category of response).
no change (ie, change of ≤ 5% of the pretreatment value). Figure 3 compares tobramycin and ceftazidime susceptibilities of the most prevalent sputum \( P \ aeruginosa \) isolates (Fig 3, left) and of the least antibiotic-susceptible isolates (Fig 3, right) for the three categories of patient response.

Overall, 54 of 77 patients (70%) responded to the IV administration of tobramycin and ceftazidime, and hospitalization, as defined by an improvement in \( \text{FEV}_1 \) of ≥ 5%. Twenty-four of these 54 patients had \( P \ aeruginosa \) isolates with MICs above the parenteral resistance breakpoint for tobramycin, ceftazidime, or both antibiotics and were therefore designated as resistant. Seventeen isolates that had been shown to be resistant to one or both antibiotics represented the most prevalent strain found in the patients’ sputum (Table 1).

Twenty of the 24 patients with isolates that were resistant to one or both antibiotics responded to treatment of the exacerbation. All four patients with \( P \ aeruginosa \) isolates resistant to both antibiotics responded to treatment (Fig 3). In two of these patients, the isolate that was multiply resistant was also the most prevalent isolate (Fig 3, right).

Of the 14 unchanged patients (ie, those patients whose posttreatment \( \text{FEV}_1 \) percent predicted was ≤ 5% of the value before treatment of the exacerbation), only 4 had ceftazidime-resistant \( P \ aeruginosa \), and none had tobramycin-resistant \( P \ aeruginosa \). In contrast, quantitative susceptibility testing of \( P \ aeruginosa \) isolates from the nine worsened patients (ie, those patients whose posttreatment \( \text{FEV}_1 \) percent predicted was < 5% of the prior value) demonstrated that no patients had tobramycin-resistant \( P \ aeruginosa \) and only one patient had a ceftazidime-resistant isolate (MIC, 64 \( \mu \)g/mL). For the remaining isolates, tobramycin MICs ranged from 0.25 to 4.0 \( \mu \)g/mL and ceftazidime MICs ranged from 2.0 to 16 \( \mu \)g/mL (Fig 3), all within the susceptible range.

Regression modeling was performed to uncover the potential relationships between patient response and antibiotic susceptibilities of \( P \ aeruginosa \) isolates and to find any additional confounding variables (Table 2). The following three variables were identified that significantly predicted a patient’s pulmonary function after antibiotic therapy: the patient’s pulmonary function measured prior to the exacerbation (\( p < 0.0001 \)); the number of days that had elapsed between prior measurement and the initiation of antibiotic therapy (\( p < 0.002 \)); and the num-

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**Table 1—Numbers of Patients with \( P \ aeruginosa \) Isolates Exceeding Parenteral Breakpoints for Tobramycin and Ceftazidime**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Least Susceptible Isolate Exceeding Breakpoint (n = 24)</th>
<th>Most Prevalent Isolate Exceeding Breakpoint (n = 17)</th>
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<tbody>
<tr>
<td>Tobramycin</td>
<td>6 (7.8%)</td>
<td>3 (3.9%)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>22 (28.6%)</td>
<td>16 (20.8%)</td>
</tr>
<tr>
<td>Both</td>
<td>4 (5.2%)</td>
<td>2 (2.6%)</td>
</tr>
</tbody>
</table>
Table 2—Parameter Estimates for Regression Modeling of Variables Significantly Impacting Pulmonary Function (PFT2) Following Parenteral Antibiotic Therapy

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Parameter Estimate</th>
<th>SE</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFT1, L</td>
<td>1.028</td>
<td>0.052</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time from PFT1 to IV start, d</td>
<td>-0.013</td>
<td>0.004</td>
<td>0.002</td>
</tr>
<tr>
<td>Time from MIC to IV start, d</td>
<td>0.0015</td>
<td>0.0007</td>
<td>0.030</td>
</tr>
<tr>
<td>Intercept, L</td>
<td>0.175</td>
<td>0.086</td>
<td>0.046</td>
</tr>
</tbody>
</table>

number of days that had elapsed between the determination of isolate MICs and the initiation of therapy (p < 0.03). No other variables were observed to significantly impact patient outcome, including individual antibiotic MICs of the most resistant or most prevalent \( P. aeruginosa \) isolates. The combination of ceftazidime and tobramycin MICs by either addition or multiplication also failed to demonstrate a significant association with patient response, a result that is consistent with the qualitative graphing of responses vs antibiotic MICs (Fig 3).

**Discussion**

At one time, antibiotic resistance was defined as the persistence of the bacterium in the infectious focus despite standard, nontoxic doses of the antibiotic.\(^{17,18}\) Subsequently, quantitative antibiotic susceptibility testing revealed that bacteria persisting in infectious foci during antibiotic therapy had the ability to grow \textit{in vitro} in antibiotic concentrations that were toxic to mammalian cells.\(^{19}\) In these early studies with Gram-negative bacilli, including \( P. aeruginosa \), the definition of a bacterial strain as susceptible meant that the growth of that strain was inhibited by antibiotic concentrations that were predicted to be nontoxic to humans. The breakpoint for resistance was the concentration above which the bacteria could grow and persist in the infectious focus despite standard doses of the antibiotic. As the concept of the quantitative nature of resistance was applied to other antibiotics, it was recognized that infections caused by susceptible bacteria (ie, those with an MIC lower than the breakpoint) were likely to be eradicated with the administration of that antibiotic. These infections were pneumonia or soft-tissue infections in which the antibiotic concentration in the blood was thought to represent the concentration in the infectious focus.\(^{20}\) Despite the artificial nature of \textit{in vitro} antibiotic susceptibility testing (ie, pH, osmolality, and nutrients available) in comparison to the infectious focus, there is a good correlation between the susceptibility of the infecting bacteria and the clinical efficacy for Gram-negative bacteremia.\(^{21}\) Using this paradigm, tobramycin-susceptible bacteria fail to grow \textit{in vitro} at a concentration \( \geq 4.0 \mu g/mL \),\(^{6}\) while for ceftazidime that concentration is \( 32 \mu g/mL \).

The current study provides insight into the value of antimicrobial susceptibility testing of \( P. aeruginosa \) isolates in predicting the clinical response to combination antibiotic therapy for the treatment of pulmonary exacerbations in patients with CF. It should be noted that these retrospectively analyzed data could not be controlled for timing of the MIC determinations and PFTs relative to pulmonary exacerbations. However, our analysis mirrors the manner in which antibiotics are chosen for the treatment of a pulmonary exacerbation. Physicians routinely review the results of the last susceptibility testing performed on the \( P. aeruginosa \) isolated from sputum and choose an antibiotic combination based on those results.

There are several limitations to our analysis. The definition of \textit{pulmonary exacerbation} was not standardized during the trial, and we also assumed that the dose, the duration of IV infusion, and the dose interval were appropriate and standardized. This study also used only one response variable for this large group of patients (ie, the change in pulmonary function). It can be argued that the response to treatment for an exacerbation includes changes in other important clinical parameters such as decreased cough and sputum production, and subjective improvement in well-being. In addition, only 77 patients were available for analysis. A study with a larger group of patients with a wider variation in tobramycin and ceftazidime MICs may yield different results.

Despite these caveats, both the qualitative and regression analyses presented here indicate that there are no significant trends linking antibiotic susceptibility and response to parenteral antibiotic administration as indicated by a change in pulmonary function. While a lack of statistical significance for a trend does not mean that no trend exists, adequate precision of confidence intervals was observed from regression modeling. This suggests that even if such a trend does exist, the impact would be very small and not clinically relevant.

One explanation for an apparent lack of correlation between antibiotic susceptibility and the response to antibiotic therapy observed in this study could be the variable time between isolate susceptibility testing and IV antibiotic administration. However, differences in observed timing among those patients whose conditions improved, those patients with no change in \( FEV_1 \), and those patients whose conditions worsened following treatment were small (Table 3), and regression modeling suggested that
this independently significant variable (Table 2) had a modest parameter estimate that did not interact with any antibiotic susceptibility variables. Delays between susceptibility testing and antibiotic treatment were uniformly distributed among patients with various antibiotic susceptibilities, removing this variable as a possible explanation for the observed lack of correlation between antibiotic susceptibility testing and treatment response.

Regression modeling suggested that there was a significant (p < 0.002) negative correlation between patient response as measured by change in pulmonary function and elapsed time between PFT1 and the initiation of treatment, with longer delays correlating with lower relative responses. A similar trend can be observed when comparing the mean length of time between PFT1 and the initiation of antibiotic administration for the three categories of treatment response (Table 3). This result is intuitively logical, since a subject’s lung function would be expected to decrease during the interval from PFT1 to treatment for the exacerbation, thus impacting the subsequent response that can be achieved.

In vitro antibiotic susceptibility testing determines the concentration of an antibiotic that is required to inhibit bacterial growth in culture. This technique tends to be a reliable predictor of antibiotic efficacy for clinical situations in which bacterial eradication is essential for clinical response, such as Gram-negative bacteremia.21 In these situations, clinical resistance is characterized by an inability to eradicate organisms and is often predicted by in vitro antibiotic resistance. However, even in this situation, there is not a perfect correlation between the presence of a resistant isolate and the sterilization of the blood.

Another potential shortcoming of this retrospective analyses is the lack of in vitro antibiotic synergy testing data, which might demonstrate that doubly-resistant organisms were in fact susceptible to the combination of tobramycin and ceftazidime. While it may be true that synergy existed for a subset of resistant isolates, this would not explain why susceptibility testing was not predictive of outcome in patients whose conditions worsened despite the presence of doubly-susceptible isolates (Fig 3), unless antibiotic antagonism is invoked for these patients.

In contrast to the treatment of acute systemic infections, such as bacteremia or meningitis, the primary goal of antibiotic therapy in the management of acute CF pulmonary exacerbations is the reduction of pulmonary symptoms, not bacterial eradication. In fact, chronic pulmonary infections in CF patients are rarely, if ever, microbologically cured by antibiotic therapy, independent of the in vitro antibiotic susceptibility. In patients with CF, there is a reduction in symptoms without the eradication of bacteria from the lower respiratory tract. Given the unique treatment end point of antibiotic therapy in patients with CF, it is perhaps not surprising that antibiotic susceptibilities and breakpoints that have been established for acute bacterial infections (such as bacteremia or meningitis) in non-CF patients did not appear to correlate with the response to IV antibiotic therapy in this retrospective study.

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Table 3—Comparisons of Elapsed Times Among Susceptibility Tests, Pulmonary Function Tests, and Parenteral Therapy for Patients With Different Treatment Outcomes

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>Time From MIC to Treatment, d</th>
<th>Time From PFT1 to Treatment, d</th>
<th>Time From End of Treatment to PFT2, d</th>
<th>Duration of Parenteral Therapy, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement (n = 54)</td>
<td>63.5 ± 6.1</td>
<td>7.5 ± 1.0</td>
<td>9.2 ± 1.0</td>
<td>16.2 ± 1.0</td>
</tr>
<tr>
<td>No change (n = 14)</td>
<td>60.0 ± 12.2</td>
<td>9.0 ± 2.0</td>
<td>12.7 ± 2.7</td>
<td>12.5 ± 1.6</td>
</tr>
<tr>
<td>Worsening (n = 9)</td>
<td>59.3 ± 15.2</td>
<td>11.2 ± 2.6</td>
<td>9.3 ± 2.9</td>
<td>14.6 ± 1.2</td>
</tr>
<tr>
<td>All patients (n = 77)</td>
<td>62.4 ± 5.1</td>
<td>8.2 ± 0.9</td>
<td>9.9 ± 0.9</td>
<td>15.4 ± 0.8</td>
</tr>
</tbody>
</table>

*Values given as mean ± SEM.
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