Timing of Referral for Lung Transplantation for Cystic Fibrosis: Overemphasis on FEV1 May Adversely Affect Overall Survival

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Timing of Referral for Lung Transplantation for Cystic Fibrosis*
Overemphasis on FEV₁ May Adversely Affect Overall Survival

Carl F. Doershuk, MD; and Robert C. Stern, MD

Study objectives: (1) Report our experience with referral for lung transplantation. (2) Review survival in cystic fibrosis (CF) patients without lung transplantation after FEV₁ remains < 30% predicted for ≥1 years.

Design: Retrospective review.

Setting: A university hospital CF center.

Patients: (1) Forty-five patients referred for lung transplantation evaluation, and (2) 178 patients without Burkholderia sp infection, with the above FEV₁ criterion.

Main outcome measure: Survival.

Measurements and results: (1) One- and 2-year survival after transplantation was 55% and 45%, respectively. However, among patients without transplants with FEV₁ < 30% predicted, median survival, 1986 to 1990, ie, before the transplant era, was 4.6 years with 25% living > 9 years (before 1986, 25% lived > 6 years). (2) Survival after transplantation was not correlated to any of the following: age, sex, genotype, FEV₁ percent predicted, insulin-dependent diabetes mellitus, or with waiting time before transplantation, and did not seem to be correlated to serum bicarbonate or percent ideal body weight. Four of five patients already infected with Burkholderia species died within 5 months of transplantation; the fifth died at 17 months. All five died of pulmonary or extrapulmonary infection with Burkholderia species

Conclusions: Use of FEV₁ < 30% predicted to automatically establish transplantation eligibility could lead to decreased overall survival for CF patients. Referral for evaluation and transplantation should also be based on oxygen requirement, rate of deterioration, respiratory microbiology, quality of life, frequency of IV antibiotic therapy, and other considerations. If pulmonary status has unexpectedly improved when the patient is at or near the top of the waiting list, total survival may be improved by “inactivating the patient” until progression is again evident.

(CHEST 1999; 115:782–787)

Key words: cystic fibrosis; FEV₁; lung transplant; survival

Abbreviations: AF = Aspergillus fumigatus; BC = Burkholderia cepacia; BG = Burkholderia gladioli; BSLT = bilateral single lung transplant; CF = cystic fibrosis; %IBW = percent ideal body weight; IDDM = insulin-dependent diabetes mellitus; PA = Pseudomonas aeruginosa; SA = Staphylococcus aureus

Lung transplantation is now a widely accepted option for treating cystic fibrosis (CF) patients with end-stage pulmonary disease.¹ ² Reports of lung transplantation outcomes have come from the transplantation centers. To our knowledge, there has been only one report that is based on the referral and transplant outcome experience from a CF clinical center.³ In addition, the timing of transplantation (and, therefore, the timing of referral for evaluation) is critical. If referral is unduly delayed, the patient risks dying before a donor becomes available. However, approximately 40% of CF patients transplanted in the United States still die within 2 years of the procedure.⁴ Therefore, premature referral and transplantation may compromise overall survival. Kerem et al,⁵ reporting on 145 patients, suggest that since FEV₁ < 30% of predicted implies a 50% chance of death within 2 years, patients with this degree of pulmonary impairment should be considered for

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lung transplantation. This observation was supported by Grasemann et al., but, more recently, Milla and Warwick indicated a better prognosis.

Assessment of the potential usefulness of FEV₁ < 30% predicted as a criterion for transplantation eligibility requires estimating how these patients might have done if they had not undergone transplantation. We report our center’s experience with survival after FEV₁ falls below 30% predicted in patients without transplants and our survival data after lung transplantation. Our data suggest that, if all CF patients with FEV₁ consistently < 30% were listed for transplant, overall life expectancy may be adversely affected.

**Materials and Methods**

CF was diagnosed by a positive sweat test together with typical pulmonary or digestive disease, or a positive family history. From 1991 to 1997, our patients have been referred to one of three lung transplant centers for evaluation. Twenty of these patients have subsequently undergone bilateral lung transplantation. The decision to refer for evaluation for transplantation candidacy included the results of pulmonary function tests, especially the percent predicted FEV₁, the rate of deterioration of pulmonary function test scores, and the patient’s overall morbidity (frequency and duration of hospitalizations; severity of pulmonary symptoms).

The following data were collected on all patients who subsequently underwent transplantation: age; gender; genotype; pulmonary microbiology; FEV₁ 1 year before, at, and 1 year after referral; waiting time until transplantation; serum bicarbonate; percent ideal body weight (%IBW); and presence of diabetes at referral; survival after transplantation; and cause of death. FEV₁ was measured by standard technique and expressed as percent of predicted value. Survival data were also gathered on all patients at referral with a range of 24 to 40 mmol/L. Four were normal; the rest showed mild-to-moderate elevations (range, 28 to 40) (Table 1). Whether serum bicarbonate level was elevated at referral did not seem to be correlated with outcome, in that elevation levels were almost equally distributed between > 2 years and ≤ 1 year survival.

Five of the 20 patients (cases 3, 4, 11, 14, and 15) had insulin-dependent diabetes mellitus (IDDM) at transplant, including two who survived > 2 years. None of our patients had preparatory sinus surgery or sinus irrigation procedures. %IBW did not seem to be correlated with survival, and there was no value that offered firm predictive value. Six of eight patients with %IBW values > 85% survived for < 1 year, including the two patients with the highest values (cases 17 and 20; %IBW = 105% and 106%, each of whom survived < 1 month), whereas two of eight patients with levels < 85% (including the patient with the lowest value (case 1; %IBW = 64%) survived > 2 years.

During the year prior to referral, all but two patients (cases 1 and 9) had *Pseudomonas aeruginosa* (PA) recovered from sputum cultures and 18 had yeast. Ten had *Staphylococcus aureus* (SA), only one of which (case 6) was methicillin resistant. Of note, five had either *Burkholderia cepacia* (BC) (cases 1, 9, 15, 16) or *Burkholderia gladioli* (BG) (case 19). Although 10 of the 20 patients repeatedly had *Aspergillus fumigatus* (AF) recovered from sputum, this usually did not influence overall outcome as six were long-term survivors (> 45 months for five patients; 19 months for one other), and another 3 did not have further problems with this organism. However, one patient (case 20), whose pretransplant cultures had revealed AF, did die 3 weeks following transplant when there was erosion by this organism into one of the great vessels.

Bronchiolitis obliterans contributed to death in the two patients (cases 1 and 8) who died after 2 years (24 and 30 months) (Fig 2). Ten deaths occurred within the first 18 months; nine of these patients died within 10 months. Five (cases 12, 15, 17, 18, and 20) died within 1 month of transplantation from...
severe bilateral pleural adhesions with postoperative hemorrhage, disseminated cytomegalovirus, fungal sepsis, AF erosion into an artery, and BC with sepsis, respectively. Three others died of BG (case 19) or BC (cases 14 and 16) and one (case 13) of bronchiolitis obliterans at 5, 2, 10, and 5 months after BSLT, respectively. The tenth patient (case 9) died of BC complications at 17 months.

Valid pulmonary function studies for at least 2 consecutive years were available on 978 CF patients. Of the 338 who ever had an FEV$_1$ < 30% predicted, 178 met the following criteria: (1) no history of BC

### Table 1—Summary of Demographic and Laboratory Data on 20 Patients With CF Who Underwent BSLT*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr/ Gender</th>
<th>Genotype</th>
<th>Wait to Tx, mo</th>
<th>FEV$_1$ % pred</th>
<th>%IBW</th>
<th>HCO$_3^-$, mEq/L</th>
<th>Bacterial Pathogen (Suscept)</th>
<th>Fungal Pathogen</th>
<th>Diabetes (IDDM)</th>
<th>Survival, mo</th>
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<tbody>
<tr>
<td>1</td>
<td>16/F</td>
<td>ΔF508/ΔF508</td>
<td>&lt; 01</td>
<td>18</td>
<td>64</td>
<td>35</td>
<td>BC/SM (R)</td>
<td>Yeast</td>
<td>No</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>32/F</td>
<td>ΔF508/ΔF508</td>
<td>07</td>
<td>20</td>
<td>92</td>
<td>27</td>
<td>FA/SM/SA (R)</td>
<td>AF/yeast</td>
<td>No</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>11/F</td>
<td>ΔF508/ΔF508</td>
<td>03</td>
<td>18</td>
<td>88</td>
<td>34</td>
<td>FA/SA (S)</td>
<td>AF/yeast</td>
<td>Yes</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>27/M</td>
<td>ΔF508/ΔF508</td>
<td>01</td>
<td>07</td>
<td>87</td>
<td>35</td>
<td>FA/SA (S)</td>
<td>None</td>
<td>Yes</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>17/M</td>
<td>ΔF508/ΔF508</td>
<td>18</td>
<td>22</td>
<td>89</td>
<td>39</td>
<td>FA/SA (R)</td>
<td>AF/yeast</td>
<td>No</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>31/F</td>
<td>ΔF508/ΔF508</td>
<td>16</td>
<td>31</td>
<td>97</td>
<td>28</td>
<td>PA/MRSA (R)</td>
<td>AF/yeast</td>
<td>No</td>
<td>47</td>
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<tr>
<td>7</td>
<td>17/F</td>
<td>ΔF508/ΔF508</td>
<td>08</td>
<td>31</td>
<td>86</td>
<td>26</td>
<td>PA (R)</td>
<td>AF/yeast</td>
<td>No</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>29/F</td>
<td>3849 + 10KB/Unknown</td>
<td>07</td>
<td>16</td>
<td>79</td>
<td>34</td>
<td>PA/SA (S)</td>
<td>None</td>
<td>No</td>
<td>24</td>
</tr>
</tbody>
</table>

Patients with survival > 2 yr

9           | 22/M            | ΔF508/ΔF508 | 01             | 46             | 80   | 30              | BC/SA (R)                  | Yeast          | No            | 17          |

Patients with survival > 1 but ≤ 2 yr

10          | 22/M            | ΔF508/ΔF508 | 17             | 19             | 80   | 40              | PA/SA (S)                  | AF/yeast       | No            | 19          |

Patients with survival ≤ 1 yr

11          | 25/F            | ΔF508/ΔF508 | 01             | 28             | 76   | 36              | PA (R)                     | None           | No            | 1 d         |

Patients with survival > 2 yr

12          | 36/M            | ΔF508/ΔF508 | 01             | 28             | 76   | 36              | PA (R)                     | None           | No            | 1 d         |

Patients with survival > 1 but ≤ 2 yr

13          | 18/M            | ΔF508/ΔF508 | 09             | 16             | 88   | 25              | PA (S)                     | AF/yeast       | No            | 05          |

Patients with survival ≤ 1 yr

14          | 23/M            | ΔF508/ΔF508 | 10             | 17             | 86   | 35              | PA/SM (R)                  | AF/yeast       | Yes           | 10          |

Patients with survival > 2 yr

15          | 29/F            | ΔF508/ΔF508 | 03             | 28             | 87   | 36              | BC/PA (R)                  | Yeast          | Yes           | 3 wk        |

Patients with survival > 1 but ≤ 2 yr

16          | 23/M            | ΔF508/ΔF508 | 05             | 23             | 81   | 24              | BC/PA (PR)                 | Yeast          | No            | 02          |

Patients with survival ≤ 1 yr

17          | 39/M            | ΔF508/ΔF508 | 05             | 09             | 105  | 38              | BC/PA (PR)                 | Yeast          | No            | 2 wk        |

Patients with survival > 2 yr

18          | 29/M            | ΔF508/ΔF508 | 05             | 23             | 94   | 32              | PA/SM/SA (R)               | AF/yeast       | No            | 02          |

Patients with survival > 1 but ≤ 2 yr

19          | 22/M            | ΔF508/ΔF508 | 16             | 26             | 76   | 35              | BG/BA/PA (S)               | Yeast          | No            | 05          |

Patients with survival ≤ 1 yr

20          | 41/M            | ΔF508/ΔF508 | 17             | 21             | 106  | 36              | PA/SA (S)                  | AF/yeast       | No            | 3 wk        |

*BF = Burkholderia fluorescens; MRSA = methicillin-resistant SA; PR = at least one pathogen susceptible to no known antimicrobial agent; (R) = at least one pathogen susceptible to only one class of antimicrobial; (S) = all pathogens susceptible to at least two classes of antimicrobials; SM = Stenotrophomonas maltophilia; SEM = Serratia marcescens; Suscept = in vitro antimicrobial susceptibility; Tx = Transplant. Waiting time to transplant and survival after transplant given in months unless otherwise stated.

†Transplant center No. 1.
‡Transplant center No. 2.
§Survival before death.

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infection; and (2) FEV$_1$ < 30% predicted for ≥ 1 year. Survival data on these patients were analyzed further.

Survival (without transplant) ranged from a few months to > 20 years. The 178 patients were divided into three groups: those who reached the FEV$_1$ criterion before 1980; between 1980 (when cefazidime became available to us) and 1986; and from 1986 (when oral quinolones began to be used extensively here, starting with the introduction of norfloxacin) through 1990 (Table 2). The latter period ended just prior to our referring our first patient (case 12) for transplant evaluation.

Table 2 shows the numbers of patients and the percent surviving for periods > 3 years for each of these groups. Of the 21 patients whose FEV$_1$ dropped to and remained < 30% predicted for 1 year during 1986 to 1990, 15 (71%) had a > 3-year survival, and the median survival time improved to 4.6 years, with 25% living at least 9.2 years. The longest survivors to date are still alive at 11 years (Table 2). Male survival (mean ± SD, 5.7 ± 4.7 years) was not statistically different than female survival (mean, 4.7 ± 3.6 years) (p = 0.369) for 1980 to 1990.

Ideal body weight (percent predicted) was not different for male and female patients at the point when FEV$_1$ fell < 30% predicted. Furthermore, there was no difference between the %IBW of “short survivors” (below the median) vs “long survivors” (above the median) for either male patients (short survivors, 81.7%; long survivors, 80.3%) or female patients (short survivors, 82.8%; long survivors, 80.8%).

**DISCUSSION**

To our knowledge, this is the first US-based report of survival data for CF patients with and without transplants. Our number of patients with transplants and survival was very similar to that of the Birmingham (Great Britain) Center, which is the only other report from a CF Clinical Center, to our knowledge. Their patients with transplants were > 18 years, while our patients with transplants included three patients who were < 18 years of age. All our surviving patients are ≥ 12 months posttransplant; four of their patients were at ≤ 7 months. Both centers’ 1- and 2-year survival (Cleveland, 55% and 45%; Birmingham, 58% and 52%) are worse than reported elsewhere. This may be due in part to the relatively large incidence of BC/BG infection (five in our series; six in Birmingham), which amounted to almost 25% of the combined patients.

The International Society for Heart and Lung Transplantation 1995 data indicated 1-, 2-, and 3.5-year survival for all double-lung transplantation of 67%, 60%, and 47%. The St. Louis International Lung Transplant Registry 1997 7-year survival data for 5,910 patients revealed 1-, 2-, and 5-year survivals of 71%, 63%, and 46%.

![Figure 1: Length of survival and cause of death for each patient who died after lung transplantation for CF.](https://example.com/figure1)

![Figure 2: Survival following lung transplantation (55% at 1 year, and 45% at 2 years).](https://example.com/figure2)

Table 2—Survival of Patients With CF After the FEV$_1$ Remained < 30% Predicted for 1 Year*

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<tr>
<td>&gt; 3</td>
<td>69/122 (57)</td>
<td>18/35 (51)</td>
<td>15/21 (71)</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>49/122 (40)</td>
<td>15/35 (43)</td>
<td>12/21 (57)</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>36/122 (30)</td>
<td>15/35 (43)</td>
<td>10/21 (48)</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>27/122 (22)</td>
<td>13/35 (37)</td>
<td>09/21 (38)</td>
</tr>
<tr>
<td>Median survival, yr</td>
<td>3.4</td>
<td>3.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Upper quartile, yr</td>
<td>5.4</td>
<td>6.7</td>
<td>9.2</td>
</tr>
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</table>

*Patients with Burkholderia species omitted.
For CF patients, one center has reported a 1- and 2-year survival of 85%/67%.12 Three centers reported 1-year CF survivals of 58%,13 64%,14 and 65%.15 The combined 1996 St. Louis Registry Data for CF revealed 1- and 2-year actuarial survival of 72% and 64%.4

Our poor survival in BC/BG-colonized patients with transplants is consistent with transplant center reports.16,17 Survival in our patients (Table 1) did not seem to be correlated with any of the following: genotype, sex, age, presence of multiply resistant pathogens (other than Burkholderia species), yeast, aspergillus, SA, or Stenotrophomonas maltophilia on cultures, serum bicarbonate, IDDM, FEV1 percent predicted, or rate of FEV1 decline. Unexpectedly, %IBW also did not seem correlated to posttransplant survival.

To assess the potential impact of lung transplantation on overall survival, we compared our non-BC-colonized patients with transplants with all BC-negative patients without transplants whose FEV1 remained < 30% predicted for at least 1 year. %IBW was not predictive of survival in male or female patients without transplants.

Our criteria of FEV1 < 30% predicted for at least 1 year and the absence of BC differs from Kerem et al5 (who included only patients who had died and did not exclude BC) and from Milla and Warwick7 (who did include surviving patients, but did not have the 1-year FEV1 criterion or the BC exclusion). Thus, Kerem et al5 would not have included surviving patients with FEV1 < 30% predicted. Furthermore, our requirement that the FEV1 stay < 30% predicted for 1 year excludes patients whose pulmonary function rapidly deteriorated and then recovered after resolution of an acute illness.

At our center, survival of these patients with very advanced pulmonary disease has continued to improve recently (1986 to 1990), quite possibly related to our extensive use of the oral quinolones. During that time, we observed survival percentages of 57% for ≥ 4 years and 48% survival for > 5 years. The median survival and upper quartile survival both increased for each time period reaching almost 7 years for 1980 to 1985 and over 9 years for 1986 to 1990.

Based on the St. Louis Registry data4 (64% 2-year survival), we would predict that the average CF patient from our center referred for transplantation evaluation when the FEV1 fell < 30% predicted for at least 1 year, and who then receives a transplant 2 years later, would, at that point, have had approximately a 64% chance to survive an additional 2 years (4-year total). An identical patient from our center who was not referred for transplant actually had a 57% chance of surviving the same 4 years. The St. Louis 5-year posttransplant survival data (46%) is no better than our survival for similar patients without transplants (48%). Of course, some patients with transplants would have a markedly increased quality of life and some would have the possibility of truly long survival. However, those who would die within 2 years anyway would probably have had considerable pretransplant stress (waiting for the donor, perhaps moving to a strange city, additional expense, etc) and would have undergone considerable postoperative pain, not to mention the expense of the procedure itself and follow-up treatment. Similar considerations apply to those patients who “die waiting.”

There is no doubt that the fall of the FEV1 < 30% predicted is a measurable marker for more severe pulmonary involvement18 and, in two centers’ reports,5,6 predicts 50% mortality within 2 years. In such centers, this finding should certainly prompt consideration for transplant. However, our experience, like that of Milla and Warwick,7 differs, and suggests that, at least at some other centers, this degree of pulmonary function abnormality is not as ominous and should not necessarily qualify the patient for consideration for transplantation. Additional medical considerations, recommended by others,12,19,20 include gender, the rate of FEV1 decline, the frequency of IV antibiotic therapy, response to intensive treatment, oxygen requirement, weight loss, presence of resistant or multiply resistant organisms, quality of life, and perceived life expectancy. Evaluation of psychological factors, availability of supportive persons, and short- and long-term financial support are also thought to be important for successful outcome.

At our center, a fall of FEV1 to < 30% predicted for at least 1 year is not as ominous as previously reported,5,6 but it may still be a reasonable point for initiation of discussion about lung transplantation.21 However, since a substantial number of our patients have survived for long periods after that event, the decision to accept such a patient for transplantation candidacy should not be considered automatic or immutable. If the patient’s condition improves or stabilizes while waiting for a donor, temporary removal from the “active” transplant list may be prudent. The length of survival of such a patient may be better without transplant, and “reactivation” can be done when disease progression is again evident.

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