

# Lung Transplantation in Cystic Fibrosis

Randall L Rosenblatt MD

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## **Summary**

Lung transplantation has become a viable option for those cystic fibrosis (CF) patients with end-stage lung disease. Despite the challenges that the CF patients present, the survival seen after lung transplantation is more favorable than seen in patients with chronic obstructive pulmonary disease and pulmonary fibrosis. Although the CF patients with severe respiratory disease usually are infected with organisms that display in vitro resistance to the commonly used antibiotics, these patients usually have successful outcomes with transplantation. The other challenges include the presence of nontuberculous mycobacteria, the significant incidence of liver involvement, the development of an ileus or the development of the distal intestinal obstruction syndrome, and the presence of gastroesophageal reflux. Most of the patients have metabolic bone disease, even preoperatively, that warrants treatment, especially with the significant loss of bone density seen in the first year after transplant, thought to be related, in part, to the high dose of corticosteroids. Diabetes mellitus and its consequences are not uncommon. The malabsorption of fat seen in the pancreatic-insufficient patients complicates the absorption kinetics of the anti-rejection drugs. In May 2005 the United Network of Organ Sharing instituted a lung-allocation score to better distribute the donated lungs to those patients who would achieve the most benefit. This score uses several variables to balance the likelihood of the patients living one year with a transplant versus one year without a transplant. With this change in the allocation of organs, the median waiting times have significantly decreased, the mortality on the waiting list has decreased, and the number of CF patients transplanted has not changed. With substantial experience, more programs are now transplanting patients who require constant mechanical ventilation or patients who have undergone previous pleural procedures, especially in the treatment of a pneumothorax. The limiting factor now in lung transplantation is the number of organs available. Efforts to increase the donor pool, such as alveolar recruitment strategies to improve gas exchange, have been effective in allowing more

**patients to be transplanted. Lung transplantation is now an accepted form of therapy in those patients who are developing progressive respiratory failure.** *Key words: lung transplantation, cystic fibrosis, determinants of survival, Burkholderia cepacia complex, guidelines for referral, guidelines for lung transplantation, United Network for Organ Sharing, malabsorption, nontuberculous mycobacteria, cystic fibrosis liver disease, gastroesophageal reflux disease, lung-allocation score, retransplantation.* [Respir Care 2009;54(6):777–786. © 2009 Daedalus Enterprises]

## Introduction

Cystic fibrosis (CF) impacts the function of multiple organ systems, but respiratory failure remains the most frequent cause of death and impairment. With the development of new therapies, important strides have been made in improving the lives of these patients. The median life expectancy of the CF patients now approaches 38 years of age, in contrast to just 27 years of age approximately 20 years ago.<sup>1</sup> The lung function of the CF patients has also significantly improved. In the last 15 years the median forced expiratory volume in the first second (FEV<sub>1</sub>) has improved about 10 percentage points. In 2007 approximately 41% of the patients 18 years and older had an FEV<sub>1</sub> more than 70% of predicted, 39% had an FEV<sub>1</sub> between 40% and 69% of predicted, and 20% had an FEV<sub>1</sub> less than 40% of predicted.<sup>1</sup> However, when our medical therapies fail and lung function declines, lung transplantation becomes a viable option to improve the quality of life and prolong survival.

In 2006, 2,168 patients underwent lung transplantation, an increase from 3 years earlier (Fig. 1).<sup>2</sup> Over the last 12 years, approximately 16% of the patients underwent lung transplantation because of end-stage CF (Table 1).<sup>2,3</sup> The survival rate in all patients who have undergone lung transplantation has improved but still is less than that seen in other solid-organ transplants. The benchmark survival rates in all lung-transplant recipients from January 1994 through June 2006 are approximately 78% at one year, 63% at 3 years, and 51% at 5 years.<sup>3</sup> The CF patients who have undergone lung transplantation tend to have a more favorable long-term survival than patients with chronic obstruc-

tive pulmonary disease (COPD) or pulmonary fibrosis, most likely secondary to their younger age and the lack of the other comorbidities seen in the older population<sup>3</sup> (Fig. 2).

The causes of death in the lung-transplant population vary with the time period after transplantation. In the first month, technical problems, graft failure, and cytomegalovirus infections account for a significant amount of the deaths, whereas after the first year, chronic rejection or bronchiolitis obliterans syndrome and non-cytomegalovirus infections account for approximately 67% of the deaths.<sup>3</sup> The CF population presents several unique challenges when considering lung transplantation. The goal of lung transplantation in all patients is to prolong survival and to improve the quality of life. This review focuses on the indications for transplantation, emphasizing the determinants of survival in the CF population, the specific factors unique to lung transplantation in the CF patients, the impact of the lung-allocation score that is now used to determine the ranking order on the list to receive lungs, and methods to increase the pool of donors acceptable for transplantation.

## Determinants of Survival

In general, most lung-transplant centers recommend evaluation for transplantation in patients who have less than a 50% 2-year predicted survival or who have functional limitations that would be classified as New York Heart Association class III or IV. Predicting survival using objective data has been difficult, and no single factor has been sufficiently predictive of poor survival in CF patients. However, measurements of lung function, especially over a certain time period, such as a yearly decline, have been the most useful predictors.<sup>4</sup>

The FEV<sub>1</sub> has been the most frequently used variable in assessing early mortality. In 1992, Kerem et al reported that an FEV<sub>1</sub> < 30% of predicted was associated with a 2-year mortality rate of approximately 40% in men and 55% in women. The mortality was higher in individuals ages 6–17 years, in contrast to those older than 18 years.<sup>5</sup> Mayer-Hamblett and colleagues utilized the Cystic Fibrosis Foundation registry to develop a model identifying the best clinical predictors of mortality in the CF patients. They found that age, height, FEV<sub>1</sub>, respiratory microbiology, number of hospitalizations, and the number of home intravenous antibiotic courses were significant predictors

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## LUNG TRANSPLANTATION IN CYSTIC FIBROSIS

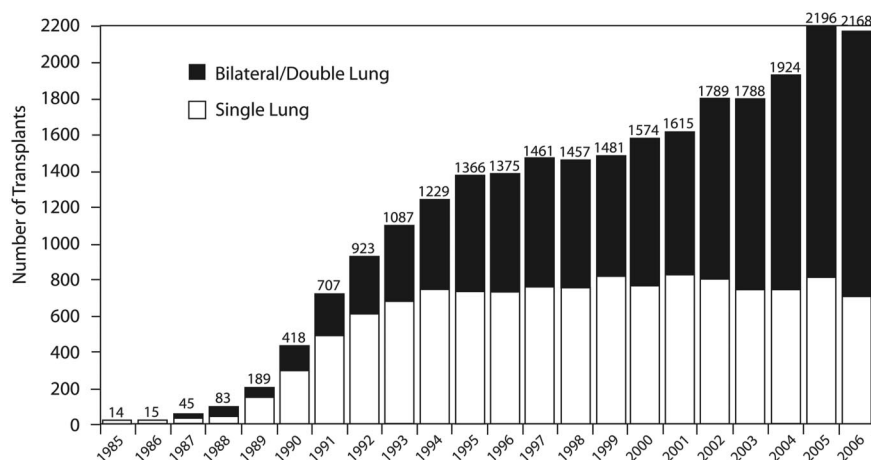


Fig. 1. Number of lung transplants, reported by year and procedure type. This figure includes only the lung transplants that are reported to the International Society for Heart and Lung Transplantation transplant registry. As such, this should not be construed as representing changes in the number of lung transplants performed worldwide. (Adapted from Reference 3, with permission.)

Table 1. Adult Lung Transplantation: Indications 1995–2006

Diagnosis	Number of Patients (%)
COPD/emphysema	6,530 (37)
Pulmonary fibrosis	3,410 (19)
Cystic fibrosis	2,889 (16)
Alpha-1-antitrypsin	1,412 (8)
Pulmonary hypertension	640 (4)
Sarcoidosis	438 (2)
Bronchiectasis	503 (3)
Re-transplant	342 (2)
Other	1,543 (9)
Total	17,616 (100)

COPD = chronic obstructive pulmonary disease  
(Data from Reference 2.)

of 2-year mortality, but their multivariate logistic regression model was no better a predictor of early mortality than the FEV<sub>1</sub> alone.<sup>6</sup> Another study evaluated CF patients referred for transplantation at 4 lung-transplant centers. Using a univariate analysis, they found a relationship between early mortality and an FEV<sub>1</sub> less than 30% of predicted and an elevated P<sub>a</sub>CO<sub>2</sub> > 50 mm Hg. They also noted the need for and the use of nutritional supplements as an indicator of increased early mortality. In their population, those patients who had an FEV<sub>1</sub> > 30% of predicted had an increased early mortality only when their P<sub>CO</sub><sub>2</sub> was > 50 mm Hg.<sup>7</sup> Other investigators not only evaluated the absolute FEV<sub>1</sub> but also the rate of decline in the lung function as a predictor of early mortality and as an indication for referral for lung transplantation. Rosenbluth et al in their center concluded that observing the rate of decline would have led to an earlier referral in their model.<sup>4</sup> Milla and Warwick in their single-center study also

found that the rate of decline was a better predictor of early mortality than the FEV<sub>1</sub> < 30%.<sup>8</sup>

Using the Cystic Fibrosis Foundation database, Liou and colleagues developed a 5-year survivorship model.<sup>9</sup> They evaluated the impact of various variables on survival and correlated it to a change in the FEV<sub>1</sub> percent predicted. Using the Cystic Fibrosis Foundation database, they found that the female sex, diabetes mellitus, *Burkholderia cepacia* infection, and the number of exacerbations negatively impacted the survival of the CF patient. Their model adjusted the FEV<sub>1</sub> to a lower value, based on the presence of these factors. They found that the FEV<sub>1</sub> percent predicted alone was not a sufficient predictor of early mortality. Using their model, 18% of the patients predicted to have a 5-year survival of 70–90% had an FEV<sub>1</sub> < 30% of predicted, and 8% of the patients with a predicted 5-year survival of less than 30% actually had an FEV<sub>1</sub> > 30% of predicted.<sup>9</sup> Thus, the FEV<sub>1</sub> alone was not a reliable predictor of survival.

As has been suggested, survival in CF is usually determined by multiple factors involving the respiratory system, and each factor alone is not specific enough to indicate the need for transplantation. Other diagnostic considerations that may impact survival include exercise tolerance and pulmonary hypertension. A 6-min walk distance less than 400 m and a pulmonary-artery systolic pressure > 35 mm Hg both have been associated with a poorer prognosis.<sup>10–12</sup>

### Guidelines for Transplantation

Without a specific factor to determine prognosis, the International Society for Heart and Lung Transplantation published the following guidelines for referral of CF patients to lung-transplant centers: (1) FEV<sub>1</sub> below 30% of

## LUNG TRANSPLANTATION IN CYSTIC FIBROSIS

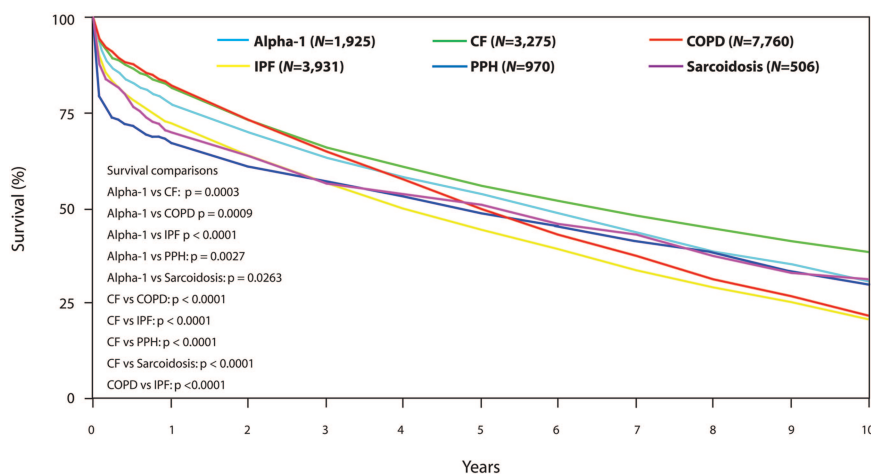


Fig. 2. Kaplan-Meier survival by diagnosis in adult lung-transplantation patients, for transplants conducted January 1990 through June 2006. (Adapted from Reference 3, with permission.)

predicted or a rapid decline in FEV<sub>1</sub>, particularly in young female patients; (2) exacerbation of pulmonary disease requiring an intensive-care-unit stay; (3) increasing frequency of exacerbations requiring antibiotic therapy; (4) refractory and/or recurrent pneumothorax; and (5) recurrent hemoptysis not controlled by embolization (Table 2).<sup>13</sup> Their guidelines for transplantation included: (1) oxygen-dependent respiratory failure; (2) hypercapnia; and (3) pulmonary hypertension.<sup>13</sup> As will be discussed later, the United Network for Organ Sharing evaluated several factors in determining the likelihood of survival for one year without a transplant. The forced vital capacity, rather than FEV<sub>1</sub>, was a better measurement in their data and explains its use in the lung-allocation score that is used in the listing of patients for lung transplantation.<sup>14</sup>

### Specific Issues Related to Transplantation in Patients With Cystic Fibrosis

#### Specific Organisms Seen in Patients With Cystic Fibrosis

As the patients with CF become more ill and suffer more lung destruction, they become infected with more resistant and pathogenic organisms. Both mucoid and non-mucoid *Pseudomonas aeruginosa* frequently colonize the respiratory tract in these ill patients and, many times, are resistant to our commonly used antibiotics.<sup>1</sup> However, the presence of these organisms, which have been referred to as “pan-resistant,” has not been shown to have a significant impact on long-term survival after lung transplantation. Although the use of in vitro synergy testing of commonly used antibiotics to determine the response to antibiotic therapy has been advocated and is frequently used in many CF and lung-transplant centers, its real value

Table 2. Guidelines for Referral of Cystic Fibrosis Patients for Transplantation

1. FEV<sub>1</sub> below 30% predicted or a rapid decline in FEV<sub>1</sub>, in particular in young female patients
2. Exacerbation of pulmonary disease requiring an ICU stay
3. Increasing frequency of exacerbations
4. Refractory and/or recurrent pneumothorax
5. Recurrent hemoptysis not controlled by embolization

FEV<sub>1</sub> = forced expiratory volume in the first second  
 ICU = intensive care unit  
 (Data from Reference 13.)

is yet to be determined. Thus, despite the “pan-resistance” of many of the mucoid pseudomonas organisms to the frequently used antibiotics, the presence of these organisms should not be considered a contraindication to lung transplantation.<sup>13,15</sup>

The presence of both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* also has not been a significant factor in impacting survival in the lung-transplant population. The impact of other Gram-negative organisms, such as *Achromobacter xyloxidans* or *Stenotrophomonas maltophilia*, on post-transplant survival still needs to be examined.<sup>15</sup> However, by and large, most lung-transplant programs do not consider the presence of these organisms in their potential lung-transplant recipients or their resistance profile as a factor in determining the patient’s eligibility for transplantation. On the other hand, these patients do receive combinations of antibiotic therapy in the preoperative and postoperative periods.

*B. cepacia* infection has been linked with a poor prognosis in CF patients, and especially in those patients who have undergone transplantation.<sup>16</sup> More recently it has been better appreciated that organisms classified as *B. cepacia*

comprise a number of distinct species of the *B. cepacia* complex. Initially all patients with *B. cepacia* complex in their sputum were thought to be at increased risk for lung transplantation; a more recent evaluation indicates that only those patients with *B. cenocepacia* (previously known as genomovar III) have a significant increase in mortality.<sup>16-18</sup> Patients with *B. gladioli* also seem to have an increased number of postoperative complications and mortality.<sup>19</sup> Thus, *B. cenocepacia* colonization remains a contraindication for lung transplantation in most programs, whereas those patients with infection with the other burkholderia species may be considered for lung transplantation.<sup>20,21</sup>

Nontuberculous mycobacteria occur in 13–15% of patients with CF. The exact impact of these organisms on the survival in lung-transplant patients is not clear.<sup>22,23</sup> Most programs attempt treatment prior to transplantation but do not consider these organisms as an absolute contraindication. *Mycobacterium abscessus* infection in the lung-transplant patient, however, remains more challenging. In an international survey, most of these infections occurred in the pulmonary allograft, with the remainder involving the skin. Treatment consisted of multiple antibiotics for at least 4–6 months and surgical debridement when skin lesions were present. Of the 17 patients with *M. abscessus*, death occurred in 2 patients, apparent cure was noted in 10 patients, and control of the disease occurred in five of the patients.<sup>24</sup>

### Gastrointestinal Complications

CF liver disease develops in 8–17% of CF patients.<sup>1</sup> Usually the CF liver disease manifests as portal hypertension and abnormalities in liver function, but severe hepatocellular dysfunction with synthetic failure is unusual in the adult patients. Most lung-transplant programs will consider patients with portal hypertension for transplant, as long as the hepatocellular function is intact, which usually means fairly normal liver-function tests. More sophisticated tests, such as computed tomography scans or magnetic resonance imaging will show liver disease, but the major decisions in regard to lung transplantation are related to the liver function and the presence of portal hypertension. In a small single-institution study of lung-transplant patients there was no significant difference in the 5-year survival and the lung function in those CF patients with substantial liver disease, in comparison to those without liver disease.<sup>25</sup>

The combination of liver and lung transplantation at the same time has been discouraged. Although the postoperative mortality was 24% in the combined procedure, the 10-year survival was approximately 50%, which was equal to the survival of CF patients without substantial liver involvement.<sup>26</sup>

Nausea remains the most common gastrointestinal complaint. This usually is secondary to the numerous medications that are necessary after transplant, which include but are not limited to the calcineurin inhibitors, mycophenolate mofetil, and ganciclovir.

Gastroparesis is fairly common in the postoperative period, in part related to the impact of the surgery on vagal nerve function.<sup>27</sup> This usually improves with time and with the addition of the prokinetic agents.

Gastroesophageal reflux disease is a common finding in patients with CF and all end-stage lung diseases. Gastroesophageal reflux disease has also been linked to the development of bronchiolitis obliterans syndrome. A Nissen fundoplication has been proposed to address the reflux, in an attempt to decrease the development of bronchiolitis obliterans syndrome.<sup>28</sup> Many programs have become much more aggressive in addressing this reflux, either preoperatively or 3–6 months after the lung transplant.

CF patients are susceptible to the development of the distal-intestine-obstruction syndrome in the postoperative period, which has been found in about 20% of CF patients, and is, in part, related to the postoperative ileus, the attempts to achieve a low intravascular volume to minimize the alveolar capillary leak, narcotics, and the tenacious intestinal secretions. Early ambulation, judicious use of narcotics, and prophylactic regimens of electrolyte solutions have been used to prevent the distal-intestine-obstruction syndrome.<sup>29</sup>

The pancreatic insufficiency and malabsorption commonly seen in the CF patients significantly impact the absorption of the medications used in the post-transplant patients. The calcineurin inhibitors are in a lipid-based solution. Thus, they must be administered with pancreatic enzymes in order to obtain adequate levels. Some centers will use concomitant azole medications, not as an antifungal agent, but to interfere with the metabolism of the calcineurin inhibitors, in an attempt to reduce the amount of calcineurin inhibitor needed to obtain an adequate serum level.

### Bone Disease

All solid-organ transplantation has been associated with a higher incidence of osteopenia and osteoporosis. Patients with CF have additional risk factors of malnutrition, impaired absorption of vitamin D and calcium, hypogonadism, previous use of corticosteroids, and increased bone-resorbing cytokines. Approximately 32% to 54% of patients awaiting lung transplantation have bone densities compatible with osteoporosis.<sup>1</sup> After transplant, an accelerated loss of bone occurs in the first 3–6 months. The reported loss of bone, as measured by a bone mineral density, is 4–12% in the first year.<sup>30,31</sup> Thus, aggressive measures, including vitamin D supplementation, use of calcium, and

antiresorptive agents, are important even while awaiting transplantation.<sup>32</sup>

### Diabetes Mellitus

As the CF population has aged, diabetes mellitus has increased in prevalence. Approximately 30% of the CF patients over 30 years old have CF-related diabetes.<sup>1</sup>

Even in non-CF patients, diabetes occurs rather frequently after lung transplantation, with a reported incidence of 24% one year after transplant and 33% 5 years after transplant.<sup>3</sup> The presence of diabetes prior to transplant confers an increased relative risk of mortality of 1.24 (95% confidence interval 1.07–1.04).<sup>3</sup> In patients with CF the presence of diabetes, even in those patients who do not undergo transplant, portends a poorer survival.<sup>33</sup> The development of diabetes after transplant, however, has not been shown to impact the survival, but this just may be secondary to the poor long-term outcomes and patients dying from infection and chronic rejection prior to developing complications related to diabetes.<sup>3</sup> Nevertheless, aggressive treatment of diabetes is encouraged in the pre-transplant and post-transplant periods.<sup>33</sup>

### Sinus Disease

Although nasal and sinus disease are almost always present in the CF patient, especially if endoscopic or radiographic studies are performed, this should not be considered a contraindication to lung transplantation. There has been concern that the organisms cultured in the chronically infected sinuses would then invade the lung and contribute to infection in these immunosuppressed patients or contribute to the development of chronic rejection. Some programs have been very aggressive in treating sinus disease with surgery and nasal washes prior to transplant.<sup>34</sup> However, there have not been any randomized controlled trials in the treatment of sinus disease, and most programs now use aggressive measures, including surgery and antibiotic washes, only in those patients who are substantially symptomatic.

### Previous Pleural Procedures

In the past, previous pleural procedures were considered a relative contraindication to patients undergoing lung transplantation. With more experience and improved techniques, this remains a concern but should no longer be considered a contraindication. However, those patients who had undergone a previous pleural procedure did require more blood products during the surgery, because of bleeding. On the other hand, those patients who had previous pleural procedures who required cardiopulmonary bypass had markedly poorer outcomes.<sup>35</sup> Thus, each patient should be

Table 3. Factors Predicting Wait-List Survival

Forced vital capacity
Pulmonary artery systolic pressure
Oxygen requirement
Age
Body mass index
Insulin-dependent diabetes mellitus
Functional status
6-min walk
Ventilation use
Diagnosis
P <sub>CO<sub>2</sub></sub>

Data from Reference 36.

considered individually when evaluating the impact of the previous pleural procedure on the candidacy for lung transplantation.

### Impact of the Lung-Allocation Score

Until May 2005, lungs were allocated in the United States only by the amount of time spent on the waiting list, without regard for the severity of the illness or likelihood of survival. Consequently, the United Network for Organ Sharing developed a lung-allocation score to better distribute the organs to those who would receive the most benefit.<sup>36</sup> The goals in creating this allocation system included a reduction in patients dying while on the list, a demonstrable increased benefit for the transplant recipient, an efficient and equitable allocation system, and improved access for pediatric and adolescent patients. The factors identified as predictors of improved benefit for survival of lung-transplant patients include the type of lung disease, the forced vital capacity, the pulmonary artery systolic pressure, the amount of oxygen being utilized, the age of the patient, the body mass index, the presence of insulin-dependent diabetes mellitus, the functional status of the patient, the 6-minute walk distance, the use of mechanical ventilation, and the P<sub>CO<sub>2</sub></sub> (Table 3).<sup>36</sup>

Because the pediatric patients undergoing lung transplantation were so few in number, had a heterogeneous group of diagnoses, and had an unpredictable natural history of survival, patients less than 12 years of age were not included in the lung-allocation system. Adolescent patients between the ages of 12 and 17 years old were also found to be less likely to be offered a lung and consequently more likely to die on the waiting list.

Thus, as of 2005, children less than 12 years of age are prioritized on the basis of time on the waiting list alone. Patients between the ages of 12 and 17 years have a lung-allocation score but receive a preference for all pediatric donors. Patients 18 years and older are prioritized on the waiting list solely on the basis of the lung-allocation score.

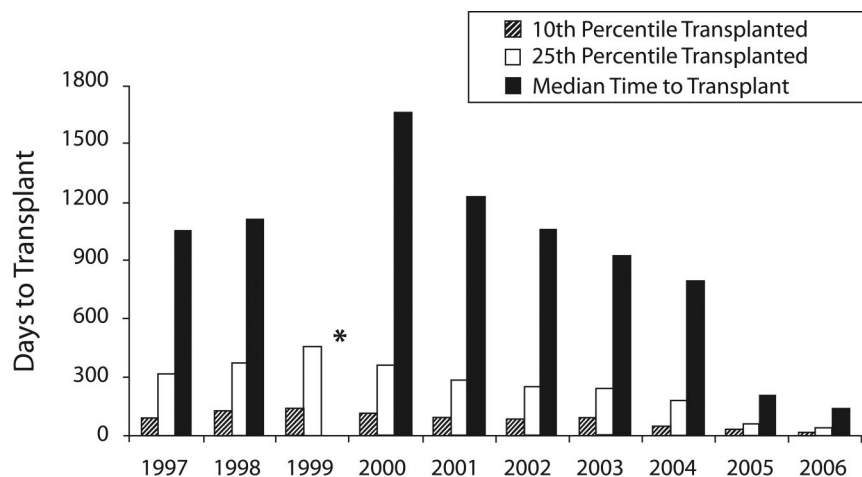


Fig. 3. Time to transplant for new lung-waiting-list registrations, 1997 through 2006. \* The median was not determined in 1999 because fewer than 50% of patients received a transplant. (Data from Reference 37.)

Table 4. Lung and Heart-Lung Registrations on February 2008

Disease	Ages (y)			Total (%)
	12–17	18–34	>34	
COPD	0	7	495	502 (50)
Pulmonary hypertension	8	23	47	78 (8)
Cystic fibrosis	12	81	30	123 (12)
Pulmonary fibrosis	4	22	271	297 (30)

COPD = chronic obstructive pulmonary disease  
(Data from Reference 38.)

Overall, the lung-allocation system factors both the urgency of the transplant and the predicted post-transplant survival into the score. The algorithm is dynamic and continuously adapts to the patients being listed and the patients being transplanted. As patients' clinical status changes, their scores will change.

The lung-allocation score has benefited the patients with interstitial lung disease, COPD, and CF. The median time waiting for a transplant has dropped from near 900 days in 2004 to less than 300 days in 2006 (Fig. 3). As of February 2008, the number of patients on the active waiting list was 1,000, with 50% having COPD, 7.8% having pulmonary hypertension, 12.3% having CF, and 30% having interstitial pulmonary fibrosis (Table 4). The median lung-allocation scores for the CF patients and the interstitial-lung-disease patients were higher than the scores in the COPD or pulmonary hypertension patients.<sup>37,38</sup>

With the change in the allocation system, the number of patients with COPD undergoing transplantation has decreased, the number of patients transplanted with interstitial lung disease has increased, and the number of patients with CF transplanted has stayed approximately the same (Table 5). However, the mortality on the waiting list has significantly decreased in all categories. Thus, the lung-

allocation system seems to be achieving its goal to distribute organs to those most in need.<sup>37,38</sup>

### Controversial Topics in Lung Transplantation

#### Patients Requiring Mechanical Ventilation

Patients who continue to deteriorate and require mechanical ventilation have not previously been considered for lung transplantation in many programs. According to the International Society for Heart and Lung Transplantation database, the relative risk for 1-year mortality in 2007 for patients requiring mechanical ventilation prior to lung transplantation was 1.75 (95% confidence interval 1.36–2.24,  $P < .001$ ).<sup>3</sup> Patients with CF who require mechanical ventilation may have an improved survival after transplantation, in comparison to patients with other end-stage lung diseases that require transplantation. The United Network of Organ Sharing database suggests that mechanical ventilation in CF patients may not be a significant risk factor, in contrast to the database of the International Society for Heart and Lung Transplantation.<sup>38</sup> However, in a single institution in a pediatric population, pre-transplant mechanical ventilation was a predictor of poor short-term outcomes, including 1-year survival, after transplant.<sup>39</sup>

The 1-year survival for patients requiring the combination of mechanical ventilation and extracorporeal membrane oxygenation is estimated to be 45%, whereas the normal 1-year survival after lung transplant is approaching 80%.<sup>40</sup> Those who favor transplanting these individuals cite the near 100% mortality without transplantation, whereas others cite the need to transplant only those who have the highest likelihood of having a successful transplant.

More programs will now offer transplantation for ventilated patients if they are able to maintain adequate nutrition, manifest a satisfactory metabolic status, and have adequate strength. Thus mechanical ventilation is not con-

Table 5. Diagnosis Grouping for All Lung and Heart-Lung Transplants

Diagnosis Group	Transplants (time period, n, %*)							
	5/4/2004–5/3/2005		5/4/2005–5/3/2006		5/4/2006–5/3/2007		5/4/2007–11/3/2007	
	n	%	n	%	n	%	n	%
A: COPD	652	52	546	37	496	34	258	35
B: Pulmonary hypertension	75	6	89	6	62	4	33	4
C: Cystic fibrosis	173	14	215	14	217	15	88	12
D: Pulmonary fibrosis	352	28	632	43	674	46	355	48
Not classified	7	<1	2	<1	0	0	0	0
Total	1,259	100	1,484	100	1,449	100	734	100

\* Because of rounding, percent values do not necessarily sum to exactly 100. (Data from References 37 and 38.)

sidered a contraindication for lung transplantation in the CF patient.

These data do not apply to the use of noninvasive ventilation in CF patients. Noninvasive ventilation has been difficult to evaluate objectively in the CF population, but a recent Cochrane review concluded that it may improve gas exchange during sleep but could not comment on its impact on reducing the number of exacerbations or its effect on altering the progress of the disease.<sup>41</sup>

### Lung Transplantation and Survival in Children With Cystic Fibrosis

Most CF physicians have assumed that lung transplantation afforded their patients both an improvement in survival and a better quality of life. In a recent study aimed at addressing the impact of lung transplantation on CF patients younger than 12 years of age, Liou et al used data from the Cystic Fibrosis Foundation patient registry and from the Organ Procurement and Transplant Network to perform a proportional-hazards survival model.<sup>42</sup> They concluded that only 5 of 514 patients had a significant estimated benefit, 102 patients had an insignificant benefit, 124 patients had an insignificant risk of harm, and 283 patients had a significant risk of harm with lung transplantation.<sup>42</sup> However, others certainly disagreed with the study and conclusions. The data in this statistical study were felt to be biased because the covariates were obtained early in the patients' course, and the post-transplant survival used was lower than reported elsewhere. The calculated hazard ratios in the study were based on factors obtained early in the patients' course and did not reflect the true benefit. There was no consideration if the patients got sick. These findings are different than what has been seen in other studies and others' interpretation of the data. This study did not evaluate or consider the quality of life after transplantation. Finally, this study was performed prior to the development of the lung-allocation score, which allocates the organs to those who would obtain the most benefit.<sup>43</sup>

Thus, most CF physicians still recommend lung transplantation to their pediatric patients when they are deemed to have a poor life expectancy and feel that Liou's study was faulty in design.

### Retransplantation in Patients With Cystic Fibrosis

According to the International Society for Heart and Lung Transplantation data, between 1995 and 2006, 17,616 lung transplants were performed, of which only 342 (1.9%) were considered retransplants. The risk factor for 1-year mortality with retransplantation was significantly increased, at 1.53 ( $P = 0.01$ , 95% confidence interval 1.10–2.11).<sup>3</sup> Utilizing the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients data on lung transplantation in the United States from 1996 to 2005, retransplantation was also shown to be associated with poor outcomes, in contrast to the initial transplant. Overall the death rate in these retransplanted patients was higher than in first-time recipients (427 vs 161 per 1,000 patient-years at risk), and they had a much lower unadjusted graft survival at one year, 3 years, and 5 years (59%, 43%, and 23%, respectively).<sup>44</sup>

Thus retransplantation clearly results in poor outcomes. Because of these data and the number of patients who are on the waiting list, most centers do not routinely retransplant these patients. The specific data for outcomes in CF patients who have been retransplanted alone were not published.

### Methods to Increase the Donor Pool

Lung transplantation is still limited by the shortage of suitable lungs from donors. Only about 15–20% of lungs from potential donors are considered to be adequate for use. The standard criteria used to determine if the patient is a potential donor include age < 55 years, a clear chest radiograph, relatively normal gas exchange ( $P_{aO_2} > 300$  mm Hg on a fraction of inspired oxygen [ $F_{IO_2}$ ] of 1.0, and positive end-expiratory [PEEP] 5 cm H<sub>2</sub>O), the absence of chest trauma, no evidence of sepsis or aspira-



tion, absence of purulent secretions seen at bronchoscopy, absence of organisms on Gram-stain, no history of previous pulmonary disease, less than 20-pack-year history of smoking, and no previous cardiopulmonary surgery.<sup>45</sup> However, efforts are now being made to improve the organ availability. Most programs have liberalized their criteria and will accept donors with some purulent sputum, as long as there is no radiographic evidence of pneumonia. Others have individualized the use of "marginal" donors (extended-criteria donors).

The proper ventilatory strategy to maintain lung integrity and to meet the gas-exchange criteria for transplantation has not been adequately studied. Although low-tidal-volume ventilation appeared to be beneficial in acute lung injury and the acute respiratory distress syndrome, there are no studies in the brain-dead donor.<sup>46</sup>

Although there is concern about the use of large tidal volumes exacerbating lung injury in the donors, this seems to be a more theoretical discussion. Recruitment strategies to improve gas exchange and to prevent atelectasis have increased the number of lungs judged suitable for transplant. In a recent study using pressure-controlled ventilation with 25 cm H<sub>2</sub>O pressure and PEEP of 15 cm H<sub>2</sub>O for 2 hours, followed by volume-controlled ventilation with a tidal volume of 10 mL/kg and PEEP of 5 cm H<sub>2</sub>O, there was an increase in the mean P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub> ratio of 131 mm Hg, compared to 87 mm Hg using the standard ventilating technique. More importantly, instead of being able to use the lungs from 60 donors out of 336 consented donors, 90 donors were available.<sup>47</sup> Thus, the lung-recruitment strategy is one method to increase the donor availability.

### Summary

Lung transplantation is now an accepted therapy in patients with end-stage lung disease. The survival after transplantation is acceptable; the quality of life is good; but the overall survival still lags behind other solid-organ transplants. Despite the higher incidence of diabetes mellitus, poor nutrition, and colonization with both multi-resistant and pan-resistant Gram-negative organisms, the patients with CF clearly benefit from lung transplantation. The lung-allocation system appears to have resulted in a better distribution of organs to those who most likely will benefit. Presently our efforts both to increase the number of donors and to improve the lung function in these donors should be expanded.

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## Discussion

**Rubin:** You can pop in new lungs, so to speak, but the sinuses still have CF<sup>1</sup>; there's still a lot of bugs there. Very aggressive sinus drainage, antibiotics, and the like, do slightly reduce infections, and you showed a high rate of death from infection: almost half in those with resistant organisms.

A problem is that we don't really have a good way of eradicating the

bugs from the sinuses. Perhaps the development of new delivery devices that will really allow reliable delivery of antimicrobials to the sinuses may help. We also tell patients that when you get a lung transplantation, it is not a cure for CF. We've had newly-diagnosed patients say, "I want new lungs right away." What you're doing is trading the complications of CF and the disease of CF for the complications of being a solid organ recipient. The ther-

apist has very little to say about who goes for transplant and when, but they do see these people back again, and when they say, "Gosh, I feel like crud," the question is, how do you sort out what's going on?

Post-transplant complications can include rejection of the organ, which would require more immunosuppression; graft versus host disease, particularly in the lung, where you can get obliterative or constrictive bronchioli-

tis, which require even more immunosuppression; infection, which may require less immunosuppression and adding antimicrobials; post-transplant lympho-proliferative disease, which is a type of cancer in the lung, triggered by Epstein-Barr virus, that requires less immunosuppression; and even secondary organ problems.

Diabetes is a problem. These patients are getting prednisone, which markedly increases their risk for diabetes. Liver disease is a problem in CF, and some of these drugs are hepatotoxic. What do you do when a patient comes in for their therapy and they say, "I just feel like crud." Can you give us practical guidelines for sorting out what that means?

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**Rosenblatt:** What it means when you "feel like crud"? We tell patients that when they get a lung transplant they still have CF, but not involving the lung. Usually what this means is that they still take all of their CF medicines but have to add about 6 more medications. However, the important thing is that they are no longer doing any respiratory therapy after the first 30 days, so they don't have to worry about nebulizers or chest physiotherapy.

It is important for them to realize that they are "trading one disease for another." They are trading CF lung disease for being an organ recipient, which basically means that they are going to have to take anti-rejection medication for the rest of their life, and those have a lot of adverse ef-

fects. Despite that, we do improve their survival, by approximately 50% at 5 years in CF patients. When we list someone for a transplant, we have to ask ourselves, what is the survival with versus without the transplant? In our program I can confidently say that we prolong their life.

We also address the quality of life after a transplant. None of the data I presented address the quality of life after a transplant. Patrick just showed me a picture of a woman whom we both took care of who received a transplant and won 3 medals at the Transplant Olympic Games. After lung transplantation, patients can resume their normal activities; they can get a job or go back to school. In our program approximately 85% of the CF patients went back to school or work. They do have complications, but I would say in the CF population most of them would say they feel great, not "like crud," and that's because they couldn't breathe before.

The majority of the patients who now undergo transplantation are on some form of noninvasive ventilation. Some of them have been intubated, and most of them were essentially living in the hospital. Their nutritional status was terrible. So I think that it's an easy tradeoff in the CF population, given how sick they were, and in terms of who is now getting transplanted with the institution of the lung-allocation score. So they're not "normal" after a transplant, but they certainly have a better quality of life.

**Marshall:** That paper by Kerem et al<sup>1</sup> in *The New England Journal of Medicine* still gets cited quite a bit, and I just want to remind everybody that it came out of Toronto, from the

mid-1980s, and I'm not sure it's relevant any more. It was an important first paper, but there've been a lot of refinements. It's more than the FEV<sub>1</sub>. I want to point out the paper by LiPuma et al<sup>2</sup> in *American Journal of Respiratory and Critical Care Medicine*, about the impacts of post-transplant *B. cepacia*. Most centers exclude patients with *B. cepacia*. However, *B. multivorans* did not negatively impact post-transplant outcomes, so we're optimistic that some centers will start to consider those patients. A surprising finding was that *B. gladioli* negatively impacted post-transplant survival.

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**Rosenblatt:** That has been our experience with *B. gladioli*, and also that it may not necessarily reoccur in the lung but reoccurs elsewhere, especially in the skin and soft tissue, and progresses to be a systemic process. We had a patient with CF and *B. gladioli* who was quite sensitive to antibiotics in vitro, but he developed an abscess in his incision about 4 months after transplant, which grew *B. gladioli* that progressed despite antibiotics and aggressive surgical management. He finally succumbed to liver disease, which was thought to be related in part to the antibiotics used. His lungs were never significantly impacted. *B. gladioli* is a problem.