Heart-Lung and Lung Transplantation for Cystic Fibrosis

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Abstract

End-stage lung disease in Cystic Fibrosis (CF) now is considered to be one of the indications for heart-lung or double lung transplantation. Results of this surgery for 50 or so CF patients in the US and Europe are about the same as for other diseases, although there are some postoperative problems specific for this diagnosis. These include: need for higher oral dosages of cyclosporine, likelihood of precipitation of diabetes mellitus with high dosage corticosteroid therapy for acute lung rejection, constant threat of pathogens remaining in the sinuses, increased likelihood of drug toxicity to the liver and kidneys, and need to make a psychological transition from a patient with a fatal disease to one with optimism about the future. Although improved postoperative management likely will improve postoperative mortality and morbidity, scarcity of donor organs and the high cost of the procedure will limit the impact of this procedure on the general CF population.

Introduction

In spite of the promise of therapeutic breakthroughs and identification of the CF gene, most CF patients must face the inexorable progress

Clinical Reviews in Allergy, vol. 9: Cystic Fibrosis Ed: E. Gershwin

of their lung disease to a slow death by respiratory failure. Although this may take several decades for some patients, a feeling of hopelessness and deterioration accompanies each milestone in the progression of disease; the need for oxygen, the need for diuretics, the need for frequent hospitalizations. Curiously, as mentioned elsewhere in this monograph, the main focus of pathology in CF is the respiratory tract. When Quinton, in 1983, demonstrated that the basic defect in CF was located in the individual cell and not the result of some sort of circulating "factor," marked interest developed in the newly described art of lung transplantation *(1)*. This meant that it was quite possible that the new lung would not have CF, and that the recipient might be able to look forward to several decades of good health. The CF community, never a timid lot, began to put pressure on transplantation centers to include CF patients in lists of potential recipients. The results of this successful campaign are discussed below.

Background

The first human heart-lung transplantation occurred at Stanford University in 1981 *(2)*. Since then, approx 800 patients have undergone this procedure in a number of centers in the US and Europe. Although the initial results of this operation were somewhat disappointing, the one-, two-, and three-yr survival of recipients at Stanford since 1986 are 72, 72, and 63%, respectively *(3)*. The procedure is very labor intensive, requiring a five-h operation, a one-mo stay in the intensive care unit, and then a stay of about another month in the hospital. The recipient must take a combination of immunosuppressive drugs (currently cyclosporine, prednisone, and azathioprine) daily for the rest of his life. This results in an increased susceptibility to infection, a process not easily distinguished from the constant specter of allograft rejection. The patient also must take an array of drugs to control hypertension, cardiac failure, and other cardiovascular events. A total of 14 or 15 different medications daily is not unusual. The operation and aftercare costs about $200,000 (in 1989), and the *monthly* medication bill may total hundreds of dollars.

In spite of all of the drawbacks mentioned above, there are always more potential recipients than donor organs available. Less than 1% of the 25,000 traumatic deaths annually provide lungs suitable for transplantation. Since the current maximal ischemic time for a heart-lung block is less than four h, it is necessary for potential recipients to live close

enough to the transplant center so that they can arrive within two and one-half h of being called. Recipients are matched by ABO blood type, thoracic dimensions, height, and weight. No attempt is made to match by HLA antigens, although a close match seems to be associated with a better result *(4)*.

Transplantation of the heart and lungs as a tissue block is the preferred procedure at most centers for emphysema, pulmonary hypertension, and bronchitic lung disease (including CF). The Toronto Lung Group have preferred to leave the heart in place and transplant both lungs, arguing that this will prevent competition for the heart with the 150 or so heart transplant centers and thus make organs more available *(5)*. It generally is agreed that it is not desirable to leave an infected lung connected to a transplanted lung, so single lung transplants for CF are not an option at this time.

Transplantation for Cystic Fibrosis

The first Heart-Lung Transplantation (HLT) for CF in the US was performed by Griffith in Pittsburgh in 1984 *(6)*. The recipient died of cytomegalovirus pneumonia six wk after the procedure. Since then, approx 150 patients have received such surgery in the US and Europe. Results of the surgery, for the most part, have been similar for CF patients as for other patients at each center. In some patients, the degree of improvement seems little short of miraculous (Fig. 1, Table 1). Since approx 2000 CF patients die of lung disease in the US and Europe annually, competition for spots on potential recipient lists would be thought to be particularly fierce, especially since CF patients have to compete for donor blocks with patients with other lung diseases. As it turns out, there is interest, but not particular enthusiasm, for patient referrals from many CF centers. CF patients have to meet the same criteria as other potential recipients, plus some additional ones that have considerable bearing upon their possible acceptance as candidates. Clinical characteristics of 44 CF candidates accepted as potential recipients at four US centers are listed in Table 2.

Requirements for Transplant Candidates

Candidates for HLT or lung transplantation must have cardiopulmonary disease that would classify them as NYHA Class III or IV. They

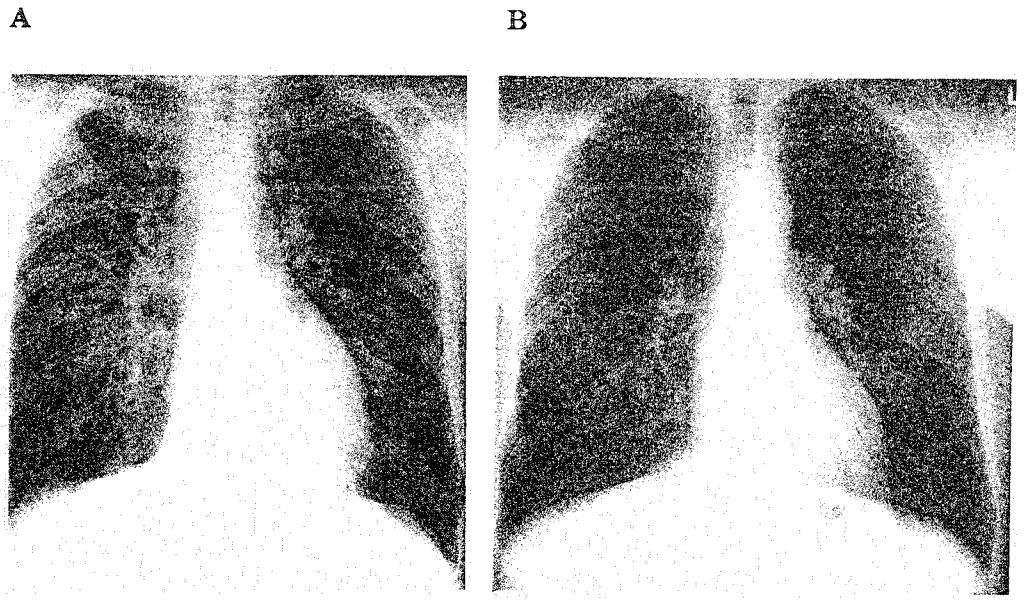

Fig. 1. Chest roentgenograms obtained shortly before (A) and 10 mo after (B) heart-lung transplantation in a 29-yr-old man with CF.

Table 1
Pulmonary Function Before and 10 Months After Heart-Lung Transplantation in a 29-Year-Old Man with Cystic Fibrosis

	Pre	(%pred.)	Post	(% pred.)
Forced vital capacity	1.27 L	(25%)	4.62 L	(94%)
Forced expiratory volume One second	0.55	(14)	4.01	(101)
Forced expiratory flow 25–75	0.17 L/sec	(4)	5.84 L/sec	(134)
PaO2	36 torr		95 torr	
PaC02	66 torr		34 torr	

should have a predicted survival of between 12 and 24 mo because of the extent of their basic disease, but be in otherwise fairly good health. They must have demonstrated evidence of good social support, with the guarantee of an adult caretaker who can stay with them for the waiting period, the postoperative hospitalization, and the postoperative period during which they are at risk for acute rejection. They must be extremely well-motivated individuals who have the stamina and the courage to cope with the transplant surgery. Finally, they must be free of any of the contraindications for transplant surgery.

Table 2
Clinical Characteristics of CF Patients Chosen for Heart-Lung Transplantation*

	Center A	Center B	Center C	Center D
Number	14	21	4	5
Age in yr	25.9 + 7.2	27 + 7	27.3 + 15	20.7 + 5.7
% ideal wt/ht	81 + 7.7	85 + 3	85.3 + 8.5	86 + 12.6
% pred. FEV1	15.5 + 6.3	20 + 6.3	25.1 + 5.3	28.3 + 7.5
$PaCO_2$	57 + 12	~55	60 + 15	~45
O_2 use >8h	92%	90%	100%	100%
# transplanted	4	3	4	1
Months wait for HLT (for those done)	7.8 + 5.3	4.3 + 2.9	5.1 + 4.7	0.8
Pretransplant mortality	36%	33%	25%	0

*Clinical characteristics of 44 patients with CF selected as active candidates for heart-lung transplantation at four university medical centers in the US.

Contraindications for a Transplantation Candidate

Previous Chest Surgery or Pleurodesis

With the exception of a midline sternotomy or a small incision for lung biopsy, chest surgery resulting in a pleural scar is a contrain-dication to transplant candidacy. The reason for this is that the bleeding from lysis of pleural adhesions has been a significant cause of morbidity and mortality in the immediate postoperative period, frequently requiring a trip back to the operating room for control of bleeding in the immediate postoperative period. Chemical or surgical pleurodesis for the treatment of pneumothorax is included in this category. This has caused considerable debate about the proper means of treating pneumothorax in the CF individual. Although the goal in the past has been to reinflate the lung as quickly as possible by using chemical pleurodesis early in the course of the illness, prevention of pleural scarring has now dictated the more conservative approach of prolonged tube drainage without pleurodesis.

Corticosteroid Therapy in the Two Months Prior to Surgery or Adrenal Suppression Secondary to Prolonged Corticosteroid Treatment

One of the most serious complications of the early postoperative period is dehiscence of the tracheal anastomosis. For this reason, it is imperative

that the patient not receive corticosteroids between operative days one and ten, the critical period of tracheal healing. This implies, of course, that the patient's endogenous production of corticosteroids is adequate for postoperative stress. For this reason, patients must not have received corticosteroid therapy for two mo prior to the operation. If, in fact, they have been treated for prolonged periods with corticosteroids, patients must show evidence of adrenal competence prior to acceptance as a candidate. If they require such treatment for an acute exacerbation of disease, their candidacy is temporarily postponed until they have achieved the required time interval off this class of drugs. Cyclophosphamide does not seem to have the same deleterious effect upon healing, so patients with certain types of lung disease can be managed with this drug during the pretransplant period.

Insulin-Dependent Diabetes Mellitus

Although there is some controversy about the importance of this requirement, many centers still will not accept as a candidate a patient who requires daily insulin. The reason for this is the relative poorer healing and increased susceptibility to infection of the diabetic individual. This requirement is of particular concern to CF candidates who may wish to consider enteral or parenteral hyperalimentation in the pretransplant period.

Presence of Liver Disease

Since many of the drugs utilized in the post-transplant period are potentially hepatotoxic, it is important that presurgical liver function be within normal limits. For practical purposes, this is defined as a serum total bilirubin concentration of less than 2.5 mg/dL. Individuals with passive congestive heart failure secondary to *cor pulmonale* may have considerable improvement in liver function with brisk diuretic therapy. CF individuals with evidence of periportal fibrosis and early cirrhosis would not be eligible for transplant candidacy. Cox, et al., have described liver transplantation in CF individuals, but only one individual to date has had successful transplantation of heart, lungs, and liver *(7,8)*.

Impaired Renal Function

Cyclosporine and trimethoprim/sulfamethoxazole are particularly toxic to the kidneys, but play vital roles in the postoperative management

of transplant patients. The possible necessity of using parenteral amphotericin B for fungal infections is another reason for a need for some reserve renal function. For this reason, evidence of normal renal function is required for active candidacy. This is defined as a creatinine clearance of greater than 50 mL/1.73 m^2.

Poor Nutritional Status

CF patients with long-standing lung disease frequently are poorly nourished. Moderate to severe loss of muscle mass and body fat are poor prognostic signs for wound healing and postoperative rehabilitation. A cachectic individual usually is counselled to try to gain some muscle mass by hyperalimentation before considering transplant candidacy. This runs the risk of making the patient acutely diabetic, particularly if a high carbohydrate load is prescribed.

Poor Psychosocial Status

This is one of the most important factors in the assessment of a potential transplant recipient. The waiting period for a donor organ is particularly stressful, more so since the individual must be on beeper call on a 24 h basis for an average waiting period of several months. The surgery itself is stressful and the "ICU syndrome" of patients who have survived extensive cardiac surgery frequently is seen. The drugs used for immunosuppression have neurological effects, causing everything from tremors to frank psychosis *(9)*. Finally, adherence to a complicated regimen of 15–20 drugs is extremely important in the optimum management of the allografted organ. The requirement of an adult companion for the postoperative period is as much for psychological support as it is for medical logistics.

Recent History of Aspergillus *Sp. Colonization of the Respiratory Tract, Including the Presence of Allergic Bronchopulmonary Aspergillosis (ABPA)*

Although ABPA is not usually thought of as common in the CF population, Nelson et al. have found that as many as 25% of CF patients may meet the diagnostic criteria for this disorder *(10)*. Invasive aspergillosis is one of the dreaded complications of profound immunosuppression. This organism is so feared by transplant physicians that the presence of only a few colonies of *Aspergillus* sp. obtained from bronchial lavage or sputum

culture will indicate a course of amphotericin B therapy. The presence of IgG serum antibodies against this agent is not a contraindication to transplantation since a high percentage of individuals with bronchiectasis will have this finding. CF patients also have a high prevalence of IgE antibodies to *Aspergillus fumigatus*, the significance of which is not well understood *(11)*.

Evidence of Active Viral Infection, Especially HIV or Hepatitis B

Immunosuppression of individuals with active viral infections does not seem to be desirable, so the presence of active infection is a contraindication. Patients are screened for the presence of cytomegalovirus (CMV) antibodies. Patients who are CMV negative are not transplanted with CMV positive donor organs. The recent availability of Gancyclovir™ for the treatment of CMV infections has added considerably to the armamentarium of the transplant physician. Alpha-interferon has been suggested as useful in the treatment of non-A and non-B hepatitis. In the transplanted patient, however, use of this agent has been associated with increased incidence of allograft rejection *(12)*.

Colonization of the Respiratory Tract with Pan-Resistant Organisms

Another problem common to CF patients with severe lung disease is the emergence of respiratory flora resistant to antimicrobials. *Pseudomonas cepacia* and *P. maltophilia* are notorious in this regard, although *P. aeruginosa* also can develop resistance to the entire antimicrobial list. Since the individual is immunosuppressed and still harbors these organisms in his upper respiratory tract, patients who have flora resistant to all available antimicrobials are not selected as transplantation candidates.

Presence of a Tracheostomy

The presence of a tracheostomy stoma adds considerably to the difficulty of establishing a tracheal anastomosis. The area immediately around the stoma becomes colonized with bacteria, there is hypertrophy of the mucus glands distal to the site, and (almost always) a certain degree of granuloma formation that can produce a relative tracheal stenosis. Unfortunately, this is the case even for the increasingly popular "minitrachs," transtracheal catheters designed to deliver oxygen directly into

the trachea. Delivery of water, antimicrobials, and mucolytic agents by this route to facilitate hydration of the airway mucosa has been proposed as a means of delaying the development of CF lung disease. Patients who may wish to consider transplantation should avoid any form of tracheostomy. Candidates who have had a tracheostomy in the past should have direct visualization of the trachea by the transplant surgeon who will need to be satisfied about the degree of health of the trachea at the site of proposed anastomosis.

Selection of Candidates for Transplantation

In virtually all transplantation centers, patients with CF must compete for donor organs with all other candidates. Because of the desirability of matching donor organ with recipient thorax size, patients at Stanford are placed in a "best-fit" category (ABO blood type and thoracic dimensions) rather than by priority or date or ranking on a list. Patients are referred to the center by their physicians. A worksheet for transplantation suitability is prepared, including a very important psychosocial assessment (Table 3). If the patient appears to be a good candidate, he/she is invited to the center for an assessment. Blood is drawn for metabolic studies and for immunological suitability for transplantation (transfusion antibodies, Coombs test, etc.). Patients who meet these criteria and who are still interested in a transplantation are placed on an active waiting status. This means that the patients and an adult family member carry beepers and must be able to arrive at the hospital within 2 1/2 h after being called. If the patient is not available at the time an organ is found, the next most suitable donor will be called. Since the average wait for a donor organ is around 12 mo, the waiting period is a source of considerable anxiety. Whether a heart-lung or double lung transplantation is to be performed is a matter of preference of the center. Single lung transplantations are not appropriate for CF since the remaining lung would serve as a source of massive infection to the allograft.

Medical and Surgical Problems After Transplantation

The noninfectious complications can be categorized by time period:

Mechanical (The First Few Days)

Approximately one-quarter of patients who have HLT must be taken back to the operating room in the first few hours following surgery because

Table 3
Psychosocial and Financial Planning Assessment
Prior to Candidacy for Heart-Lung or Lung Transplantation

1. Please provide a factual and complete psychosocial history (family background, education, work history, current family constellation, available support system, etc.) of the patient and his/her family.
2. Please specifically address the following issues:
   a. How does the patient deal with medical procedures and how much responsibility does he/she take for medical routines?
   b. What is the patient's understanding of his/her illness and prognosis?
   c. Please characterize the patient's predominant mood or affect and emotional stability.
   d. What are the patient's patterns of alcohol use, cigaret smoking, and other drug use?
   e. What are the patient's and the family's expectations of transplant?
   f. What have been the reactions of the patient and the family to the possibility of a cardiac transplant procedure, the survival statistics, and potential risks of transplant?
   g. Is there a family member or person willing to make the commitment to stay with the patient in the Stanford area throughout the transplant process for both emotional support and practical help?
   h. Are financial resources available for medical insurance and travel and living expenses in the Stanford area?

of postoperative bleeding. This is especially important for CF patients who have a high prevalence of pleural adhesions because of the history of numerous bacterial lung infections. Bleeding from the site of adhesions and suture lines and air leaks from small leaks in the tracheal anastomoses require very close monitoring in an intensive care unit that has considerable experience in the care of transplanted patients. Since there are massive fluid shifts and physiological compensations from the transplanted lungs and heart, arrhythmias and problems with electrolytes are common.

Acute Rejection (Weeks 1–16)

Undoubtedly the most serious complication from heart-lung transplantation is an acute rejection of the allograft. This may occur at any

time after the first few postoperative days, but usually occurs within the first three or four mo following transplantation. The body mounts a ferocious immunological attack on an organ perceived as foreign tissue. Clinically, this may be manifested by fever, dyspnea, malaise, or the sudden onset of respiratory failure. The chest X-ray may show a variety of changes, including pleural effusion, patchy infiltrates, or complete opacification of one side of the chest. The patient may manifest hypoxemia. Pulmonary function will show the onset of obstructive disease beginning in the small airways, indicating a propensity of these as sites of acute rejection. Overall pulmonary function rapidly deteriorates with further progression of rejection *(13)*. Biopsy of the lung will show a perivascular infiltrate of lymphocytes, progressing to fibrosis and destruction of the alveolar bed. If treated vigorously with high dosage corticosteroids, the patient may recover completely *(13)*, but if left unchecked, the he/she can die in a matter of hours.

Chronic Rejection (Weeks 12 Onward)

After the first few postoperative months, the patient usually has achieved a successful regimen of immunosuppression. Acute allograft rejection then is unlikely as long as the patient continues to follow this regimen in a scrupulous fashion. Approximately 50% of long-term survivors (defined as surviving more than three mo posttransplantation) develop a condition the Stanford group has named obliterative bronchiolitis (OB). This is the insidious onset of obstructive lung disease, beginning with the small airways and progressing to severe to fatal obstructive lung disease. It is believed to represent chronic or smouldering rejection *(14)*. This may be precipitated or associated in some way with viral lower respiratory infections, or may be some other result of the transplantation process. In this condition, the earliest lymphocytic infiltrate involves the alveolar sub-epithelium as well as the capillary endothelium *(15)*. Although this, too, can be reversed with augmented immunosuppression, it can progress to fixed obstructive disease in a relatively short time *(16,17)*. Recent changes in the maintenance regimen of immunosuppression and a willingness to perform lung biopsy for very early signs of obstruction or hypoxemia have reduced the prevalence of this disorder at Stanford from 50 to 22% and also reduced significantly the mortality from this complication *(3,13)*.

Infection with a variety of agents, especially CMV, *Pneumocystis carinii*, *Pseudomonas aeruginosa*, and *Aspergillus fumigatus* are possible

at any time following the transplantation. The clinical presentations of the infectious processes are virtually identical to the signs and symptoms of rejection, making the diagnosis of infection extremely difficult and decisions about therapy even more so. Scrupulous culturing of fluid from bronchoalveolar lavage (BAL) and a willingness to obtain transbronchial biopsies of the airways and lung tissue are critical in making the proper diagnosis. The prevalence of *Pneumocystis carinii* pneumonia (PCP) is sufficiently high that many centers place transplant recipients on prophylactic pentamidine aerosol or oral trimethoprim/sulfamethoxazole therapy during the winter months. Patients are encouraged to wear paper masks when in crowds, virtually for the rest of their lives. Younger patients face a dilemma about whether to return to school following transplantation, balancing a need for social interaction with an extremely high risk of developing a viral respiratory infection. No hard and fast rules have been adopted for this problem, but the youngsters usually manage to obtain permission to attend school on at least a part time basis.

There are a number of additional problems. Virtually all of the transplant recipients are hypertensive and need medication for this. They also have a rather startling elevation of serum cholesterol (even the patients with CF) suggesting that this is a complication of the medical regimen. A significant percentage of cardiac transplant recipients have developed coronary artery disease over the course of one or two yr. Since the myocardium now is denervated, there is no anginal pain and any ischemia is necessarily silent.

Results of Transplantation in CF Patients

When the criteria of acceptance of transplantation candidates mentioned above are observed, patients with CF who receive transplantation do about as well as those transplanted for other conditions. Smythe et al. reported that 15 of 17 CF patients who received transplantation at the Papworth Hospital in Cambridge, England, were still living, having survived 1–41 mo after the surgery *(18)*. Noirclerc reported that five of seven patients who had received bilateral lung transplantation at Marseille were living and well *(19)*. The results of the five patients with CF who have received heart-lung transplantation at Stanford are listed in Table 4. In a number of cases, at least in the US, compassion dictated an attempt at surgery for a patient who probably was too ill to be a truly appropriate candidate.

Table 4
Results of Heart-Lung Transplantation for CF at Stanford

1.	30-yr-old-male –20 mo posttransplantation. Health is excellent, and he has returned to work and school.
2.	29-yr-old-male –16 mo posttransplantation. Health is excellent, and he has returned to work.
3.	32-yr-old-male –6 mo posttransplantation. Health is excellent.
4.	24-yr-old-female –5 mo posttransplantation. Many complications of surgery because of unforeseen pleural and pericardial adhesions. She currently is ventilator dependent but is in fair health.
5.	7-yr-old-male –Died 3 mo posttransplantation. The technical aspects of the surgery were successful but he died of *Pseudomonas* pneumonia after a stormy course of rejection which required lymphocytic tissue irradiation.

As far as can be determined, the new lungs do not have CF. Wood et al., used technology described by Knowles et al., to measure the electrical potential difference across respiratory membranes *(20,21)*. They determined that the allograft lungs had the same transbronchial potential as normal lungs and allografts in individuals who did not have CF. Of interest, CF recipients maintained the diagnostic elevated potential difference in respiratory tissue proximal to the graft. This has now been confirmed in a number of laboratories. Only a small percentage of transplant recipients have had lower respiratory infections attributable to *Pseudomonas aeruginosa*. These infections appear to respond to antimicrobial therapy in the same fashion as lungs of other immunosuppressed patients rather than those of CF patients.

Problems Specific to CF Transplant Recipients

In spite of optimum patient selection and successful surgery, there are several problems after transplantation that are specific to CF recipients. Each of these will require a solution before the transplantation of CF individuals will be accepted as an appropriate means of therapy.

CF Patients Require Considerably More Oral Cyclosporine Than Do Other Transplant Recipients

Cyclosporine, a cyclic polypeptide derived from the swamp fungus *Tolycladium inflatium*, has been a critical addition to the armamentarium

of immunosuppressive agents. It is of particular interest because it acts specifically on lymphocytes and does not seem to affect other arms of the immune system. Unfortunately, it is extremely lipophilic and, as such, must be delivered in an olive oil-based medium usually mixed with chocolate milk or orange juice. Since most CF patients have some degree of exocrine pancreatic insufficiency, their ability to digest an oily medium is impaired. Even with increasing the dosage of pancrelipase, most CF patients require oral dosages four to five times as great as patients who were transplanted for other reasons. The extreme cost of this drug (more than $50.00/d for most CF patients) may in time make this a critical factor in the acceptability of these patients as transplantation candidates. Since the metabolism of this drug by the liver can be affected by some of the same agents as affect the breakdown of theophylline, these agents may permit lower dosages and thus lower daily costs. The use of agents for this purpose is in the earliest stages of investigation.

The Sinuses Serve as Reservoirs of Infection with CF Specific Organisms

As discussed elsewhere in this monograph, the sinuses of CF patients are packed with a thick gel of CF mucus, cellular debris, and a rich flora of *Pseudomonas aeruginosa*. Unfortunately for the CF transplant recipient, sinusitis remains after the bacterial burden of the lungs is removed by transplantation and, worse, drains into the allograft. Surgical drainage of the maxillary and ethmoid sinuses by large antral windows are required of all CF patients prior to transplantation surgery in the Stanford program. Repeated tobramycin flushes via these antral windows are needed by most CF transplant recipients to prevent recurrent *Pseudomonas* bronchitis (*see* paper by King, this issue).

Many CF Patients Become Overtly Diabetic After Pulse Corticosteroid Therapy for Allograft Rejection

Pulse corticosteroid therapy, usually one g of methylprednisolone intravenously daily for three d, is an important modality in the treatment of acute allograft rejection. Since even the endocrine pancreatic status of many CF patients is precarious, this large dosage of corticosteroid may precipitate insulin-dependent diabetes mellitus. There has been some benefit in the use of oral hypoglycemic agents, such as

glyburide, for maintenance regulation of blood sugar with occasional need for insulin during periods of increased corticosteroid therapy.

CF Patients May Have Underlying Latent Liver and Kidney Disease

Most CF patients have some degree of cholestasis almost certainly the result of a relative dehydration of bile duct mucus as part of the basic physiologic prdcess of the disease. They also may have received repeated courses of aminoglycoside antimicrobials as therapy for lung disease. The continued assault on both of these organs by pharmacological, immunosuppressive, and biological agents may amplify any underlying damage. Cyclosporine, sulfamethoxazole, and most of the diuretics are potentially toxic to the kidneys. Many of the agents are potentially hepatotoxic. The current risk of non-A, non-B hepatitis from a blood transfusion is about one in 200 transfusions, a very significant risk for someone who must undergo cardiopulmonary bypass and have repeated transfusions for chronic anemia. Extreme care should be exercised in the selection of CF patients, especially those with any elevation of total bilirubin or borderline creatinine clearance values.

Most CF Patients Must Change Their Attitudes About Health Care

The underlying principle guiding the current management of CF is that it is a FATAL disease and that therapy is aimed at ameliorating, not curing, the symptoms. Implicit in this attitude is the surrender of considerable control of therapy to the patient, in essence a partnership whereby hospitalizations, therapies, and even drug regimens are negotiated between the physician and the patient *(22)*. By gaining this control, the patient believes that he/she has some control over his/her destiny, an important factor in the care of devastating illness. Whereas this attitude is beneficial in certain chronic illnesses, it is not viable in a posttransplantation situation. The patient must cooperate fully with the physician and submit to endless uncomfortable and potentially dangerous procedures to detect and reverse early signs of infection or rejection *(23)*. The "spunky" individual who has won the respect of the medical community prior to surgery may cause a good deal of consternation after transplant by arguing with staff, procrastinating with therapy, trying to negotiate biopsies, and so on. It is extremely important to stress this need for an

"about-face" that will be required in the posttransplantation period and to reinforce it throughout the period of waiting for a donor organ.

Cardiac Status

Most CF patients are extremely "barrel-chested," making it somewhat difficult to assess the status of the pulmonary artery by Doppler echocardiogram. This latter procedure becomes important when CF individuals are considered as heart donors in the so-called "domino" procedure. The heart-lung recipient donates his/her heart to an individual awaiting a heart transplant. CF persons have been found to be particularly appropriate for this procedure since the coronary arteries usually are pristine and the small amount of right ventricular hypertrophy is clinically beneficial in the posttransplantation period. The emotional reaction of having donated one's heart to another person usually is one of extreme delight, and several of the "domino" pairs have become fast friends.

Summary

Heart-lung or double lung transplantation has shown promise as "last-chance" therapy for individuals with CF who have severe lung disease. Most of these do about as well posttransplantation as do patients who receive this surgery for other conditions. A number of problems remain to be solved before this procedure can receive blanket recommendation to the entire medical community. These include: a) the tremendous cost of the surgery and posttransplant care (in 1989 dollars, about $150,000 for the surgery and $15,000–20,000/yr for maintenance), b) a critical shortage of organ donors, currently enough only for around 60 transplantations/yr in the US for patients with ALL lung diseases, c) residual sinus flora that serves as a nidus for infection for an immunosuppressed patient, and d) complications of the posttransplantation medications on the liver, kidneys, and cardiovascular system. Any therapy that is cost-beneficial in the treatment of CF likely will need occur prior to the development of severe lung disease. It is probable, though, that continued refinement of the techniques of transplantation will make this appropriate for a certain segment of the CF population, resulting in long-term improvement with acceptable side-effects from this therapy.

Acknowledgment

This work was supported in part by NIH Grant HL 13108–20.

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