



consensus conference

Lung Transplantation in Cystic Fibrosis*

Consensus Conference Statement

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The first successful heart-lung and lung transplant operations in cystic fibrosis (CF) patients were performed in 1983 and 1987, respectively. Lung transplantation is now available at dozens of centers in North America, Europe, and Australia. Recent technical developments and the major limitations of donor organ availability prompted the CF Foundation to sponsor a meeting of 37 experts to evaluate the state of the art in lung transplantation for CF, highlighting areas of consensus, practice variations, and controversy. This document summarizes the work of that group. (CHEST 1998; 113:217-26)

Key words: cystic fibrosis; lung transplantation; respiratory failure

Abbreviations: CF=cystic fibrosis; CMV=cytomegalovirus; EBV=Epstein-Barr virus; MRSA=methicillin-resistant *Staphylococcus aureus*; NHBD=nonheart-beating donor; NTM=nontuberculous mycobacteria; OPO=organ procurement organization; UNOS=United Network of Organ Sharing

Since the mid-1980s, nearly 400 cystic fibrosis (CF) patients in the US have undergone thoracic transplantation. More than 300 additional CF patients have undergone lung or heart-lung transplantation in Canada, the United Kingdom, and France over the same period. Today the predominant operative approach to end-stage CF lung disease is the bilateral (double) lung transplant. In 1990, the first living-donor lobar lung transplantation took place, with >50 completed to date. Most of the living-donor lobar lung transplants have been performed in patients with CF.

EPIDEMIOLOGY

There are three sources of data that document lung transplants performed in the United States or worldwide: (1) the St. Louis International Lung Transplant Registry—a voluntary registry of lung

transplants performed worldwide with 5,208 lung transplants total and 746 (14%) in CF recipients through April 1996; (2) the CF Foundation National Patient Registry—a required registry for the network of 113 CF Foundation accredited-care centers within the United States that currently includes 20,100 CF patients in whom 348 lung transplants have been reported between 1985 and 1995; the number of sites performing lung transplantation for CF has grown to 62 sites in 1995 with 10 sites performing nearly half of all CF transplants; (3) the United Network of Organ Sharing (UNOS) has collected US data on transplants and organ procurement since 1988, but CF-specific data are not currently available from UNOS. Data from the two available registries show an equal distribution of male and female patients with CF receiving transplants. The mean age of patients receiving transplants is 26 years (range, 5 to 59 years), with 83% of patients aged 18 years and older. Further analysis shows the following.

1. Survival rates are improving; current estimates of 3-year survival are 56% for patients with transplants since 1992, compared to 46% for those with transplants prior to 1992. The current 5-year survival rate for CF patients is 48%.

2. No significant differences in survival are attrib-

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utable to differences in gender, age group (children compared to adults), blood group (A, O, and AB/B combined), donor/recipient cytomegalovirus (CMV) status (positive or negative), or US compared to outside US locations.

3. Survival rates are higher at the sites that perform more transplants. Three-year survival rates were 55% at centers that performed >10 transplants compared to 46% ($p < 0.009$) at centers that performed <10 transplants to date (CF Foundation Patient Registry).

Most importantly, survival rates in CF lung transplant recipients are comparable to those from other diagnostic groups (Fig 1). Emerging survival statistics for living-donor lung transplantation appear comparable to bilateral transplantation, but most of these procedures have been performed since 1993.

Members of the CF transplant community should work aggressively with registry personnel to ensure more comprehensive lung transplant data collection. Current demographic and clinical information should be supplemented by data to elucidate the impact on survival of pretransplant and posttransplant antibiotic use, mechanical ventilation, preoperative sinus surgery, Epstein-Barr virus (EBV), CMV, allergic bronchopulmonary aspergillosis, *Burkholderia cepacia*, *Burkholderia gladioli*, *Alcaligenes xylosoxidans*, *Stenotrophomonas maltophilia*, and other organisms resistant to multiple antimicrobial agents. Careful documentation of prior compli-

cations, such as diabetes and previous chest surgery, is recommended. In addition, it is recommended that infectious and immunologic data, potentially predictive of obliterative bronchiolitis, be collected to facilitate further research on this critical long-term issue.

REFERRAL AND EXCLUSION CRITERIA

Candidates for lung transplantation should have progressive respiratory insufficiency that will likely lead to death shortly after the expected waiting period for donor lung availability (Table 1).¹ Their health should otherwise permit survival to, and through, the transplant operation and not limit post-operative survival. The waiting period for donor organs (currently 6 to >24 months) has increased at all transplant centers. Due to the highly variable clinical course of CF lung disease, prognostication of survival is inexact,² and timing of transplantation referral is difficult. The criteria listed in Table 1 apply to all transplant centers. Individual centers may have additional criteria and standards that are based on specific techniques and experiences. These criteria are subject to modification on the basis of donor organ availability and technical developments. An individual's suitability for lung transplantation may change according to his/her clinical status during the pretransplantation period.

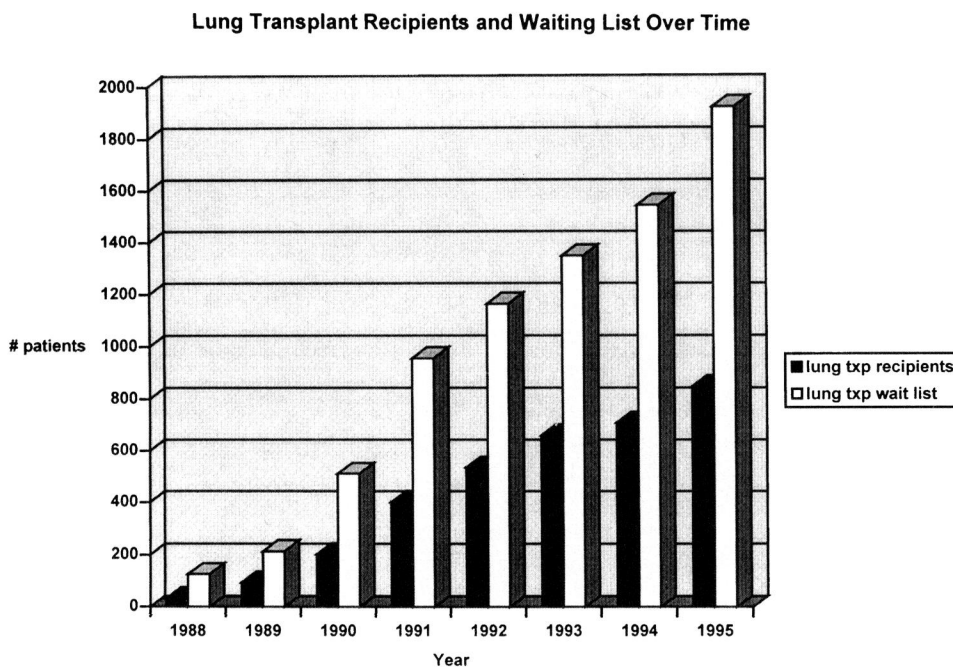


FIGURE 1. Number of lung transplant (txp) recipients and individuals accepted for lung transplantation waiting lists from 1988 to 1995.

Table 1—Referral Criteria

Criteria
1. Progressive pulmonary function impairment manifest by FEV ₁ <30% predicted, severe hypoxemia, and hypercarbia
2. Increasing functional impairment, evidenced by increasing frequency and duration of hospital treatment for pulmonary exacerbations
3. Major life-threatening pulmonary complications, such as recurrent massive hemoptysis
4. Increasing antibiotic resistance of bacteria infecting the lungs

Infections that would preclude perioperative and long-term survival contraindicate lung transplantation. These include HIV infections and bacterial infections that are refractory to treatment with available antibiotics. The infectious exclusion criteria are summarized later. Significant psychological or social dysfunction (Table 2) contraindicates lung transplantation because it severely compromises the likelihood of achieving long-term survival. Frank evaluation of suitability by the referring physician is of paramount importance to the lung transplant team. As with other exclusionary criteria, consistent demonstration of adequate psychosocial performance is required to maintain active transplant candidacy.

The noninfectious medical contraindications (Table 3) are dependent on the severity of the dysfunction, and some may respond to preoperative treatment. Repeated evaluations by the referring physicians and transplant teams are often required to demonstrate continued suitability for transplantation. Others may be amenable to alternative approaches. For example, combined lung and liver transplantations have been performed at a few centers.

Currently, there are no absolute surgical contraindications to lung transplantation. Prior thoracic procedures, such as pleurodesis or lobectomy, are not contraindications. Relative surgical contraindications include major mechanical chest deformities (such as severe kyphoscoliosis) and previous pneumonectomy with severe distortion of the mediastinal anatomy. Severe malnutrition and prolonged mechanical ven-

Table 2—Psychological or Social Dysfunction Contraindications

Contraindications
1. Recent or current abuse of alcohol, tobacco, or other drugs (prescription and other)
2. Psychiatric illness that precludes adherence with the pretransplant and posttransplant medical regimen
3. Inability to adhere to complex treatment plan
4. Lack of adequate social support systems

tilation with endotracheal intubation currently are considered relative contraindications.

In summary, these consensus criteria for referral and exclusion are guidelines. They may change with time and are dependent on repeated clinical evaluations and close interaction between the referring physician and the lung transplant team.

DONOR AVAILABILITY AND ALLOCATION

As survival rates and the quality of life of pulmonary allograft recipients continue to improve, an increasing number of patients are being listed for lung transplantation. Unfortunately, the number of donor lungs available has been relatively fixed over the past several years at a level well below the number of lungs needed (Fig 1). This disparity between donor availability and a growing recipient pool has progressively lengthened the waiting time for organs and has increased the mortality rate for those awaiting lung transplantation. The progressive increase in waiting time and the additional regional variability in waiting times have complicated the referral process for patients, families, and referring physicians.

Increasing the pool of potential cadaveric donors should remain a national priority. There is an ongoing nationwide effort by several organizations to increase public knowledge about the importance of organ donation. Although these efforts are visible and persistent, they have not dramatically changed donor numbers. Nevertheless, these grassroots programs should continue to be encouraged.

Patients with end-stage lung disease secondary to CF have survival after lung transplantation comparable to other diagnostic groups (Table 4). CF patients have at least two distinct disadvantages in the current donor allocation scheme. First, by the nature of the suppurative lung disease in CF, a bilateral lung transplantation is required to remove the primary focus of infection. Patients awaiting bilateral transplants are at a comparative disadvantage to those awaiting single lung transplants. Secondly, not all transplant centers offer lung transplantation to patients with CF because of the increased complexity in management before, during, and after surgery. It is, therefore, appropriate for the CF community to investigate ways to improve donor availability and to reduce regional disparities in lung allocation.

The US Department of Health and Human Services has contracted with UNOS to develop and monitor the organ allocation system. UNOS has divided the nation into 11 geographic regions; each region is further divided into organ procurement

Table 3—Noninfectious Medical Contraindications

Contraindications
1. Significant left ventricular dysfunction
2. Significant hepatic dysfunction or portal hypertension
3. Renal insufficiency
4. Diabetes mellitus with significant end-organ damage
5. Malignancy within 5 years
6. Osteoporosis (<i>ie</i> , below fracture threshold or with symptomatic vertebral fractures)
7. Inability to ambulate
8. Other systemic diseases that compromise long-term survival with or without lung transplantation

organizations (OPOs). Although there are uniform policies nationwide, there are variances in practice among regions and OPOs. The current regional distribution algorithm used by UNOS results in widely varied waiting times among regions of the United States. For patients with CF, this situation is exacerbated by the fact that not all transplant centers will accept them. UNOS should investigate alternative distribution strategies. One alternative would be to eliminate local OPO priority and allocate organs based on listed time and distance from donor site. UNOS should utilize computer modeling to simulate a variety of organ distribution algorithms to derive a system with more equitable waiting times across the country.

Once an appropriate donor is identified, the attribution of the transplantable organs should be minimized. In England, donor management teams are used with the specific intent of preserving all donor organs to serve the maximum number of recipients. In the United States, a donor identified through matching is managed by an informal committee of local physicians, harvesting teams, and OPO nurses. Traditionally, the goal has been to optimize cardiac function with adequate perfusion of other organs, particularly the kidney and liver. Unfortunately, some common clinical techniques (*eg*, intravascular volume expansion and certain ventilator strategies)

can be detrimental to the lungs. In the process, potentially suitable lungs become unusable for transplantation due to undefined infiltrates on chest radiograph and worsening arterial blood oxygenation. Significant progress in the United States would occur if an “organ neutral” donor management protocol were developed and a mechanism for uniform application were implemented. Further advances could materialize if local teams, specialized in standard harvesting of organs, were widely employed. The current system, which requires the recipient center to provide both distant harvest and local implant teams, is burdensome and may lead to wasted organs. A system of local harvesting is gaining acceptance for both liver and kidney transplantation.^{3,4}

ALTERNATIVE DONORS

Living related or unrelated lung donors are being used more often at selected centers across the country. Living-donor approaches have yielded acceptable results for kidney⁵ and liver⁶ transplantation. Short- and intermediate-term results after living-donor lung transplantation are comparable to standard cadaveric lung transplantation with respect to function, incidence of complications, and survival.⁷ Thus far, the predominant indication for living-donor lobar transplantation has been CF. The surgical procedure is performed as a bilateral sequential transplant of a lower lobe from each of two living donors.⁸ The complexity of coordinating three simultaneous operations may discourage some centers from performing this procedure. Nevertheless, this option should be explored with all patients with CF early in the evaluation process rather than being introduced solely as a life-saving option in a gravely ill patient. Patients being considered for living-donor lung transplantation should meet the same criteria as any candidate for a conventional lung transplant. As a general rule, they should also be listed for cadaveric transplant.

The shortage of suitable donors has prompted investigation into a new potential source of human cadaveric organs, the so-called nonheart-beating donor (NHBD). The recovery of organs from NHBDs is based on the principle of rapid intervention after death in an effort to perfuse organs with preservation solutions. This intervention is not practical in most clinical situations. However, the lung may be ideally suited for retrieval in the NHBD since it is unique among solid organs in not relying solely on perfusion for cellular respiration. Clinical investigators have demonstrated the feasibility and success of this

Table 4—Actuarial Survival of Lung Transplant Recipients Based on Primary Disease*

First-Degree Disease	No.	Years After Transplant, Survival, %				
		1	2	3	4	5
CF	738	70	62	53	49	48
Emphysema	2,015	77	69	62	53	45
PF	804	64	55	49	42	38
PPH/Eisen	506	62	56	49	47	38

*No.=number of patients with indicated disease. PF=pulmonary fibrosis; PPH/Eisen=primary pulmonary hypertension or Eisenmenger's complex.

strategy in animal models.^{9,10} This novel approach could add hundreds of potential donors to the lung donor pool.

Other surgical approaches have been implemented to extend the effective donor pool. A general reevaluation of current exclusion criterion, including projected ischemic time, bronchial flora, PaO₂, and chest wall trauma, may further increase the donor pool. Recent work with cadaveric lobar transplant, whereby an adult cadaveric single lung is divided into two lobes for a smaller double-lung recipient, is an encouraging option for selected pediatric candidates.¹¹ Xenotransplantation, *ie*, the use of nonhuman donors, is an exciting prospect for the future, but serious immunologic and physiologic problems must be solved before this becomes a feasible alternative.

INFECTIOUS CONSIDERATIONS

The following infectious considerations are focused on CF patients and should not be considered a complete review of the infectious issues in lung transplantation. At present, there are limited published data for CF transplant recipients and these guidelines should be regarded as “work in progress.” The guidelines are subject to modifications and additions as more clinical experience is accrued and published.

Infectious Exclusion Criteria

Absolute Contraindications: Evidence of infection with the following organisms is an *absolute* contraindication for lung transplantation in patients with CF: HIV, hepatitis B infection as evidenced by a positive test for surface antigen, and active *Mycobacterium tuberculosis* infection. The decision to perform transplantation in patients with previously treated *M tuberculosis* should be made at the transplant center.

Specific Pathogens: Organisms found in the respiratory tract of CF patients pretransplant may cause significant morbidity and mortality following transplant.¹² These include *B cepacia*, multiply antibiotic-resistant *Pseudomonas aeruginosa*, *Aspergillus* species, and nontuberculous mycobacteria (NTM) species such as *Mycobacterium avium-intracellulare* and *Mycobacterium abscessus* (formerly *Mycobacterium chelonae*). While patients may be merely “colonized” with certain NTM or fungi during the pretransplant period, following immunosuppression, these organisms can become invasive. They are capable of causing septicemia and pneumonia and may metastasize to distal sites such as the eye, CNS,

and bone. However, none of these pathogens is necessarily an absolute contraindication to transplant.

***B cepacia*:** To date, published reports on posttransplant infectious complications have largely been limited to *B cepacia*.¹³ Patient-to-patient spread has been documented posttransplant and genotyping studies have shown that *B cepacia* strains, isolated pretransplant, were responsible for posttransplant infections including septicemia and death.¹⁴ It is recommended that transplant centers assess the suitability of each transplant candidate harboring *B cepacia* based in part on the clinical experience of the center, the clinical profile of the patient, and the antibiotic susceptibility of the individual’s strain. At present, many US transplant centers consider *B cepacia* to be an absolute contraindication for lung transplantation.

Multiply Antibiotic-Resistant *P aeruginosa*: Many transplant candidates harbor multiply antibiotic-resistant *P aeruginosa*. Standardized susceptibility testing is crucial for the identification of CF patients infected with multiply resistant isolates. While there is not a universally accepted definition for multiresistance, the CF community has adopted the following definition:¹⁵ resistance to *all* agents in two of the following classes of antibiotics: class I— β -lactams (including imipenem and aztreonam); class II—aminoglycosides (specifically tobramycin); and class III—quinolones (generally ciprofloxacin).

This definition has clinical implications as therapeutic options are limited to one or no antimicrobial agents. Testing multiply resistant strains for antibiotic synergy in a reference laboratory¹⁶ can be performed to attempt to identify optimal drug combinations. This testing often demonstrates that apparently pan-resistant organisms are susceptible to one or more synergistic combinations of antibiotics and/or aerosolized aminoglycosides. Initial studies suggest that the use of such combination therapy may improve posttransplant survival.¹⁶ The use of colistin sulfate or colistimethate sodium by the aerosolized route is commonly employed in the United Kingdom and some US centers. Methods for *in vitro* susceptibility testing of cultured bacteria to these antibiotics have not been standardized, and the clinical value of such therapy has not been rigorously established.

Other Multiply Resistant Gram-Negative Organisms: Additional organisms of potential concern in transplant candidates are other multiply drug-resistant Gram-negative bacilli, including *Burkholderia* species other than *B cepacia*, *Stenotrophomonas* (formerly *Xanthomonas*) *maltophilia*, and *Alcaligenes* (formerly *Achromobacter*) *xylosoxidans*. In general, consensus on these organisms as pathogens

rather than colonizers is lacking and further data must be gathered to determine the role of these organisms in the posttransplant patient.

Methicillin-Resistant *Staphylococcus aureus*: Numerous CF centers report isolation of methicillin-resistant *S aureus* (MRSA) from CF patients. Isolation of this organism has obvious infection control implications, but it should not be considered a contraindication to transplantation. At present, there are effective antimicrobial agents for MRSA and it has not been shown to be more virulent than methicillin-susceptible *S aureus*.

Nontuberculous *Mycobacteria*: The NTM are emerging as potential pathogens in CF patients. The extent of the role of NTM in lung disease is being addressed currently in an ongoing multicenter natural history study. However, it is becoming increasingly clear that some species of NTM, such as *M abscessus*, may be more difficult to treat than other species such as *M avium complex*.¹⁷ At present, the outcome of CF patients colonized/infected with NTM posttransplant is limited to unpublished case reports.

***Aspergillus*:** CF patients colonized with *Aspergillus* species may be at increased risk of invasive disease following transplantation. It has been hypothesized that patients with allergic bronchopulmonary aspergillosis have a larger fungal burden and are at even more risk, but data to support this contention are lacking. Prophylactic treatment options are discussed in the section on posttransplant management.

Future Directions: It is acknowledged that clinical experience with the organisms discussed has varied and many transplant centers have developed their own set of guidelines. It is hoped that as further publications become available, a more effective and uniform approach to management will evolve.

Pretransplant Evaluation

Respiratory Tract Cultures: Respiratory tract cultures should be obtained quarterly from patients listed for transplant and all culture results reported to the transplant center. Changes in pathogens can influence antimicrobial management, and may alter the suitability of a patient for transplant. Patient education about these issues should occur throughout the pretransplant period.

The following organisms should be sought: MRSA, *P aeruginosa*, *B cepacia*, other Gram-negative bacilli, *Mycobacterium* species, and fungi, including molds and endemic fungi such as *Coccidioides* and *Histoplasma* species. In general, most centers aggressively treat these organisms prior to transplant due to concern about potential dissemination of infection after initiating immunosuppression.

Serology and Immunizations: The initial trans-

Table 5—Serologic Tests Obtained During Pretransplant Evaluation*

Serology	Rationale
HIV I/II	Exclude seropositive patients
Hepatitis B surface antigen	Exclude seropositive patients
Hepatitis B surface antibody	Vaccinate seronegative patients
Varicella-zoster IgG	Vaccinate seronegative patients
EBV IgG	Management posttransplant
CMV IgG	Management posttransplant
<i>Toxoplasma gondii</i> IgG	Management posttransplant

*Other serologic tests such as hepatitis A and C, herpes simplex virus, and measles, mumps, and rubella may be done to assess immune/vaccination status.

plant assessment should include serologic tests (Table 5). Vaccinations (Table 6) may be required, based on history and serology results. All transplant candidates should have an intradermal tuberculin skin test (purified protein derivative, 5 tuberculin units) placed by the Mantoux technique. The role of control antigens is unclear, but some patients may be anergic due to ongoing treatment with systemic steroids. It should be noted that NTM may result in a “false-positive” reaction to purified protein derivative.¹⁸

Sinus Disease: In some transplant centers, there is concern that the sinuses are an important reservoir for posttransplant lung infection.¹⁹ Therapeutic options for treating sinus infections include endoscopic sinus surgery with serial antimicrobial lavage or inhaled antimicrobials. The role of these treatment strategies in preventing or decreasing posttransplant morbidity and mortality is not known. Controlled studies assessing the efficacy of this treatment modality are needed.

Table 6—Immunizations Performed During Pretransplant Evaluation

Assure Routine Immunizations Are Up-to-Date Including*
Measles, mumps, rubella [†]
Tetanus
Hepatitis B
If seronegative:
Varicella ^{††}
Suggested:
Influenza (annual)
Pneumovax [§]

*No data on use of acellular pertussis vaccine.

[†]Protective immune responses develop some weeks after immunizations and may be inhibited by earlier immunosuppression.

^{††}Recent experience has shown that enzyme-linked immunosorbent assays (ELISA) have a lower specificity than previously appreciated. It is therefore recommended that if a person has no history of varicella, but has positive titers by ELISA, a latex agglutination should be performed. This test should resolve the discrepancy between the history and the ELISA.

[§]Recommended by some centers.

General: Bacterial, fungal, and viral cultures of both the engrafted and explanted lungs should be done at the time of the transplant. Antimicrobial treatment during the early posttransplant period should be based on the findings of recent preoperative and intraoperative cultures. Treatment strategies for organisms commonly encountered in CF patients have been outlined.¹⁵ The posttransplant lung environment is radically different from the pretransplant environment, and the goal of therapy should be sterility of the lower respiratory tract. The removal of severely obstructed airways and the blunting of the cough reflex by unavoidable denervation of the lower airways may make the use of aerosolized antibiotics particularly useful in the posttransplant period.

Throughout the posttransplant period, respiratory specimens such as sputum, BAL, or sinus cultures should continue to be processed for CF-specific pathogens using the same selective media employed for pretransplant respiratory specimens.^{15,20} The need to treat CF-specific organisms isolated from BAL fluid of clinically well patients is unclear, but consideration should be given to performing quantitative cultures to distinguish colonization from infection.

Standard infection control practices can help prevent the spread of respiratory tract pathogens in the hospital posttransplant. CF patients may be at increased risk due to contact with other CF patients infected with multiply resistant organisms such as *B cepacia*, *P aeruginosa*, or MRSA. Such contact may occur in the hospital, clinic, home, or in social settings. At present, infection control guidelines²¹ exist to minimize patient-to-patient spread of these pathogens and patient education is critical.

Aspergillus: Posttransplant prophylaxis with aerosolized amphotericin B and/or oral itraconazole for *Aspergillus* has been used at some centers, but to our knowledge, no randomized trials have been performed to support this practice. Efforts to minimize exposure to *Aspergillus* and environmental molds should be made during extensive building or renovation projects as the level of airborne fungal spores can increase during construction. Such exposure may occur at home or in the hospital.

Patients must be educated pretransplant and posttransplant about potential environmental pathogens. Organisms such as *Aspergillus*, NTM, and other fungi are ubiquitous; exposure cannot be avoided. To our knowledge, there are no studies of the efficacy of the wearing of a mask in the posttransplant period; however, the wearing of a mask to prevent inhalation of small particles in high-risk settings, such as construction sites, is prudent practice.

Patients with CF who undergo lung transplantation are subject to the same potential posttransplant complications as those of non-CF patients. The most common and serious complications after solid organ transplantation are graft rejection and infection. It is generally agreed that the mechanisms and risks of acute or chronic rejection are similar in CF and non-CF recipients.²² The infectious risks in CF patients may not result in more complications or shorter survival than non-CF patients¹² and do not preclude successful lung transplantation. Treatment for rejection episodes should be based on the strategy of the particular transplant center.

Important complications other than rejection or infection include GI tract motility disorders, osteoporosis, systemic hypertension, renal dysfunction, and diabetes mellitus.²³ These problems may have existed preoperatively and are certain to become more severe in the posttransplant period. Early, aggressive intervention is warranted to minimize the debilitating effects of these complications.

CF affects the pharmacokinetics of many therapeutic drugs through primary renal and hepatic alterations and through secondary changes in absorption and blood volume.²⁴⁻²⁷ Decreases in enteric absorption and increases in volume of distribution mandate higher doses of many drugs to achieve therapeutic concentrations. The renal and hepatic effects may produce compound-specific increases in drug secretion, metabolism, and clearance, amplifying the need for individual dose titration to achieve therapeutic serum levels.

The essential immunosuppressive drugs cyclosporine and tacrolimus have narrow therapeutic indexes and similar toxicity profiles and are predominantly metabolized and excreted by the liver. Drugs that alter, induce, or inhibit intestinal or hepatic cytochrome CYP3A4 activity often significantly alter cyclosporine and tacrolimus serum levels.²⁸ High serum trough levels of either cyclosporine or tacrolimus can decrease glomerular filtration rate and secondarily decrease renal clearance of other drugs. The importance of adequate immunosuppression and the complex drug interactions mandate meticulous management of drug doses and levels through the transplant center.

Significant rejection or infection can produce remarkably modest signs and symptoms in lung transplant recipients. Symptoms such as malaise, GI dysfunction, or cough, and signs such as fever, decline in spirometry, infiltrates on chest radiograph, and mild leukocytosis are nonspecific. It is essential to distinguish innocuous disease from subtle manifestations of graft rejection or infectious pneumonitis

that can cause rapid deterioration and death without proper treatment. All such findings demand immediate attention. Local physicians can often assist the transplant center in determining appropriate diagnostic and treatment strategies and the need to transfer to the transplant center. Vigilance is the key.

Routine or symptom-directed bronchoscopy should be performed by a bronchoscopist who is trained in the care of patients after lung transplantation, and may require transfer to a lung transplant center. The intricacies of performing these procedures and the knowledge of appropriate specimen retrieval and processing mandate this approach for optimal care of the patient. Communication between the bronchoscopist and the lung transplant center is crucial to ensure that the proper specimens are obtained and forwarded to the center when necessary. Decisions on treatment, based on culture results, must be made according to the experience and protocol of the individual transplant center. Deference to the transplant center is particularly important when cultures are positive but the patient is asymptomatic.

General treatment algorithms should be developed that can serve as a guideline for local physicians to assist in the care of their patients. These algorithms should supplement, not replace, the close relationship among patient, local physician, and transplant center.

CARE AFTER LUNG TRANSPLANTATION

The combination of CF and lung transplantation places a large burden on the physical, psychosocial, and financial resources of the patient and family. The patient, family, and referring physician should understand the common complications of lung transplantation in the CF patient. In contrast to the relatively slow changes of most CF complications, clinical status in the immunosuppressed lung transplant recipient may change rapidly and have significant short- and long-term implications. It is important that the referring CF or primary care physician, and the transplant center physician have a clear and mutual understanding of the role and location of regular CF care, emergency care, transplant-related care, and routine health care.

Psychosocial and Communication Issues

Following lung transplantation, CF patients still have CF pathophysiology in other organs and should therefore continue to receive regular CF care. CF-specific medical problems that may arise in the posttransplant period include chronic sinusitis, nasal polyps, diabetes mellitus, pancreatic insufficiency,

distal intestinal obstruction syndrome, and biliary cirrhosis. Communication (written and telephone) between the transplant center and the CF referring physician before and after transplantation should be a high priority. If the patient lives a long distance from the referring CF center, as well as the transplant center, then a primary physician who will follow up that patient should be identified.

After lung transplantation, no matter how uncomplicated the recovery period might be, the patient and family should assume responsibility for timely and detailed communication with the primary physician, the referring CF center, and the transplant center. Any change in patient well-being, in medical therapy, or in other health-related issues is of vital interest to the transplant center. The transplant center needs to have a user-friendly communication system to accommodate prompt contact.

Rehabilitation of the patient toward returning to work or school should be a goal in virtually all CF transplant recipients. Formal education, vocational rehabilitation, and/or school tutoring should be provided. Changes in medical insurance eligibility and coverage may limit some employment opportunities. Such limitations may be prejudicial and require government or industry intervention to assure equitable opportunity for the able-bodied transplant recipient.

Improvement in patient quality of life is commonly reported following lung transplantation.²⁹ Longer-term studies using a variety of measurement tools should be encouraged. Comparisons of objective measures of well-being, such as exercise tolerance, pulmonary function tests, and freedom from hospitalization or antibiotic use in the pretransplantation and posttransplantation periods, will be especially important as lung transplantation techniques (such as living-donor lung transplantation and the use of NHBDs) expand the number of lung recipients.

Medical Issues

As described previously, the transplant center should direct transplant-related care, especially the immunosuppressive regimen. Because complications of lung transplantation may progress rapidly and have major impact on survival, it is crucial that the referring CF or primary physician be willing and able to see the patient on short notice if necessary with rapid communication to the transplant center when any significant medical change is seen in the recipient. Similarly, transplant center personnel must ensure that changes in recipient medical status are communicated rapidly to the referring physician.

Chronic immunosuppression may be associated

with an increased risk for malignancy. CF has been shown to be a risk factor for GI malignancy in older patients.³⁰ It is not currently known whether immunosuppression will further increase the incidence of such malignancies in CF patients. The CF transplant recipient will require ongoing, routine health maintenance "screening" measures including Papanicolaou smears and mammograms for women of appropriate age, stool guaiac determinations, etc. Ideally, such care should be arranged by the referring CF center or primary referring physician.

Unanswered questions deserving further study include the problem of potential complications associated with exposure of CF lung recipients to various endogenous and exogenous pathogens. For instance, it is unknown whether lung recipients should be protected against exposure to other CF patients who harbor certain pathogens. The danger of infection with respiratory syncytial virus, EBV, or CMV may lead to serious illness in the younger, more immunologically naive CF recipients. Another vital area for potential research is the identification of factors that enhance or undermine the transformation of a chronically ill CF patient into a robust individual. These clinical problems should be investigated further.

Financial Issues

Individually, CF and transplantation place an extreme financial burden on families, health-care institutions, insurance companies, and on society as a whole. The combined financial impact of lung transplantation in the CF population is a problem with which society must deal. Limitations in insurance coverage because of "preexisting conditions" and the unavailability of insurance to many chronically ill young adults remain formidable obstacles to CF lung transplantation. The expense of medications (especially drugs that require high doses due to poor absorption by CF patients) can be daunting and may significantly reduce resources for patient care. The resolution of these imposing issues likely will require a concerted and coordinated effort by the CF community.

CONCLUSIONS

Consensus was reached on the following key issues. (1) Lung transplantation is a viable option for progressive respiratory failure due to CF. The survival of CF transplant recipients is as good as that of recipients with other diseases. (2) Referral to a transplant center should be made when the clinical course predicts survival slightly longer than the expected waiting time (currently 6 months to >2

years). (3) Inability to adhere to a complex medical regimen precludes transplant candidacy. (4) Major complications of organ systems other than the lungs may preclude candidacy. (5) The availability of donor organs does not meet the current needs and severely limits lung transplantation for CF. (6) Improvements in donor care before organ harvest and in allocation of suitable donor lungs may modestly improve the donor shortage. (7) Living-donor lobar transplantation is a viable option in some families and in selected centers, with survival as good as that following standard transplantation. (8) Active tuberculosis, hepatitis B infection with surface antigen expression, and HIV infections absolutely contraindicate transplantation. (9) *B cepacia* and multiply drug-resistant *P aeruginosa* infection are relative contraindications to transplantation. Transplant decisions in such cases are center specific. (10) The risks of acute and chronic graft rejection in CF transplant recipients are equivalent to those of recipients with other diseases. (11) The postoperative risks of infectious complications appear to be equivalent for CF and non-CF transplant recipients. (12) CF alters the pharmacokinetics and metabolism of cyclosporine and tacrolimus and many other drugs. Close monitoring of serum levels and adjustment of doses are vital to successful posttransplant management. (13) Symptoms and signs of rejection and/or infection can be subtle and must be evaluated promptly. (14) Close communications among patients, local physicians, and the transplant center are essential to optimal treatment of the transplant recipient.

APPENDIX

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