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A Complete Guide to  
Lung Transplantation

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*Advances in Pulmonary Hypertension* is committed to help physicians in their clinical decision making by informing them of important trends affecting their practice. Analyzing the impact of new findings and covering current information in the peer-reviewed literature, *Advances in Pulmonary Hypertension* is published four times a year. *Advances in Pulmonary Hypertension* is the official journal of the Pulmonary Hypertension Association.

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## Redefining the Window of Opportunity in Lung Transplantation



Our articles in this issue span the spectrum of treatment for severe pulmonary hypertension (PH), not only from a historical perspective through our profiling of the work of Joel Cooper, MD, a true pioneer in the surgical suite, but also in terms of the therapeutic options available, from medical therapy to lung transplantation. The discussion is particularly timely and relevant because the allocation system for donated lungs may soon be changed by the

United Network of Organ Sharing.

Although the options for managing patients with right ventricular failure have expanded significantly through the use of prostanoids and with atrial septostomy, the paramount issue remains in those patients whose disease is no longer adequately responding to these measures: When is it the right time to proceed with transplantation or listing?

Our experts on the Pulmonary Hypertension Roundtable addressed

a multitude of issues surrounding this question. Although outcomes have improved in the 20 years that lung transplantation has been available for PH, the observation of Dr Cooper—that this surgery remains among the most demanding and difficult largely because of postoperative considerations—remains true. Outcomes in general for lung transplantation for PH have been inferior to those for many other diseases, such as chronic obstructive pulmonary disease.

Because of strides made in medical management, however, we have been able to extend the window prior to lung transplantation in many patients. Ironically, this sometimes has proved to be a mixed blessing. The advent of continuous intravenous epoprostenol, a medication that has revolutionized the treatment of pulmonary arterial hypertension, thereby offering the potential to delay transplantation, may have resulted in a higher proportion of extremely sick, higher-risk patients presenting for transplantation.

The articles in this issue offer a comprehensive resource to address these questions as they delineate the practices and policies prevailing at centers of excellence throughout the country. Once again, I wish to congratulate my colleagues who contributed to this issue on a job well done.

Victor F. Tapson, MD  
Editor-in-Chief



### Joel D. Cooper, MD, the Physician Who Launched Lung Transplantation on Its Path to Successful Outcomes



Joel D. Cooper, MD

**Y**ou might say that every patient with pulmonary hypertension whose life has been extended by a lung transplant continues to live and thrive in the long shadow cast by Joel D. Cooper, MD, the physician who performed the first successful lung transplant surgery in 1983. Not that Dr Cooper would seriously consider this metaphor, but there is no doubting the everlasting impact of his research

in lung transplantation.

Dr Cooper no longer performs lung transplantation in PH, yet he remains a towering figure not only in this setting but in his other areas of clinical interest, including general thoracic surgery, lung volume reduction surgery for emphysema, myasthenia gravis, gastroesophageal reflux, and esophageal cancer. Although lung transplantation in PH has evolved significantly since the time when Dr Cooper pioneered the operation, the principles and precepts governing the technique when it was first performed offer insights into how far its evolution has progressed.

Currently Chief of the Division of Cardiothoracic Sur-

gery, Washington University at Barnes-Jewish Hospital, St. Louis, Missouri, Dr Cooper recalls his years in residency at Massachusetts General Hospital where he served under the well-known thoracic surgeon Hermes Grillo, MD, whom he credits as the inspiration for later research on lung transplantation. Moving to the University of Toronto after completing his residency in Boston, Dr Cooper was further encouraged by his colleagues to pursue his interest, particularly by William Nelems, MD, who had studied with surgeons in Europe. By 1978, 38 lung transplant operations had been attempted worldwide, but with no success. “Most of them were deathbed rescue attempts, maybe one attempted every other year around the world,” said Dr Cooper.

“We went back to the lab and we saw that most of these patients had died within 2 weeks and those who lived longer all had complications of the airway connection. We studied these issues in a dog model and came up with a better understanding.” A combination of factors, including poor blood supply, posed obstacles to a successful outcome. “During surgery the bronchial arteries are severed and cannot be reconstructed. High doses of prednisone were also required to prevent rejection. We recognized that it was also sort of a wound-healing problem. Cyclosporin helped and finally we were able to improve the technique in a dog model.” Not long afterward, in 1983, Dr Cooper and his associates performed the first successful lung transplant.

This first successful transplant occurred several years before additional attempts were made in patients with PH. “It was thought at the time that you needed to replace both the heart and the lung. We went back to the lab and working with a dog model we produced a model of right heart

*(continued on page 25)*

# Listing the Patient: Deciding When Transplantation Is the Only Viable Life-Sustaining Option



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Transplantation of the lungs became an acceptable therapeutic option for patients with end-stage lung and pulmonary vascular disease in 1981, following the first successful human heart-lung transplantation performed for a patient with primary pulmonary hypertension.<sup>1,2</sup> At the time no other efficacious therapy was available and the transplantation was performed as an experimental “last ditch” life-saving procedure. Since then, both single and double lung transplantation has become part of the routine armamentarium to treat patients with pulmonary arterial hypertension (PAH) when all other measures fail. For highly selected patients, lung transplantation offers the possibility of improved survival and functional status.<sup>1,3-5</sup>

However, despite major strides in the field of lung transplantation, numerous shortcomings are still associated with this procedure, including lack of available donor lungs, need for life-long immunosuppression, acute and chronic allograft rejection, infection, and extremely high costs of the procedure and post-transplantation care. Furthermore, since the time of that first heart-lung transplantation, treatment options for patients with PAH have changed dramatically. Both calcium channel blockers and intravenous epoprostenol have shown proven benefit and in many cases provide adequate treatment to prevent or prolong the need for transplantation.<sup>6-12</sup> Recently agents such as endothelin antagonists and sildenafil have been added to the medication armamentarium, further broadening therapeutic options. Indeed, lung transplantation has moved from a primary treatment for pulmonary hypertension to a therapy that complements the current medical options to prolong life and improve quality of life.

## Candidate Selection for Transplantation

Appropriate candidates for lung transplantation have end-stage lung disease without concomitant illness that would adversely affect their survival following transplantation. In selecting candidates for this procedure it is important to consider the severity of the patient's illness as it relates to projected survival without transplantation, coexisting medical problems, and the financial cost of the procedure. Although assessing projected survival without transplantation is difficult, it is extremely important with regard to selecting the appropriate timing for lung transplantation, since waiting periods for lung transplants now average 1.5 to 2 years. Although there are ongoing efforts to change the strategy for donor lung allocation, currently in the United States the priority for obtaining a lung transplant is

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**Table 1—Indications for Lung Transplantation in Pulmonary Arterial Hypertension.**

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New York Heart Association functional class III or IV  
Mean right atrial pressure  $\geq 10$  mm Hg  
Mean pulmonary arterial pressure  $\geq 50$  mm Hg  
Cardiac index  $\leq 2.0$  L/min/m<sup>2</sup>  
Failure of medical therapy in the setting of:  
    WHO class III or IV symptoms  
    Mean right atrial pressure  $\geq 10$  mm Hg  
    Mean pulmonary arterial pressure  $\geq 50$  mm Hg  
    Cardiac index  $\leq 2.0$  L/min/m<sup>2</sup>

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WHO = World Health Organization

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based solely on the time accrued on the waiting list, after matching for ABO blood type and body size. This is unlike that for other solid organ transplants, where consideration is given to the severity of the recipient's disease. Therefore, in order to select the appropriate time to list patients for this procedure, one must carefully consider the candidate's projected survival against the waiting period for transplantation.

In order to assure some consistency across transplant centers, international guidelines have been published that are used by many centers to select lung transplant candidates.<sup>13</sup> These criteria are also used by most insurance carriers for coverage purposes. Although these guidelines were proposed to develop standards across centers, individual programs continue to use their own selection criteria, which vary from center to center. Thus, a candidate who is unacceptable at one program may be considered acceptable elsewhere. The guidelines for patients with primary pulmonary hypertension are outlined in **Table 1**.

There are both absolute and relative contraindications to transplantation (**Table 2**). It is important to note that the criteria used for inclusion and exclusion are general guidelines to help select potential candidates. In special circumstances, individual patients may be accepted for transplantation even if they do not meet all of the criteria in these guidelines.

## Timing of Lung Transplantation

Although many patients may improve or remain stable with medical therapy for several years, at some point this therapy may fail, requiring lung transplantation as the only life-sustaining option.

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**Table 2—Contraindications to Lung Transplantation**

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**Relative contraindications**

Age:

- >65 for single lung transplantation
- >60 for bilateral single lung transplantation
- >55 for heart and lung transplantation

Psychosocial instability

Mechanical ventilation

Chest wall deformity

Asymptomatic osteoporosis

History of substance abuse

Weight outside of acceptable range (morbid obesity or severely malnourished)

Prednisone use &gt;20 mg/day or 40 mg every other day

Bilateral pleurodesis (for cardiopulmonary bypass candidates)

**Absolute contraindications**

HIV infection

Bone marrow failure

Cirrhosis of liver or active hepatitis B or C infection

Chronic renal failure (creatinine clearance &lt;50 mL/min)

Malignancy precluding long-term survival

Other life-limiting conditions

Active tobacco smoking or other substance abuse

Significant coronary artery or peripheral vascular disease

Impaired left heart function unless considered for heart-lung transplant

Severe symptomatic osteoporosis

Sputum growing antibiotic panresistant bacteria

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Because of the long waiting periods for lung transplantation in the United States, and the unpredictable response to medical therapy, deciding when to refer these patients for transplant remains a clinical conundrum. Patients who remain stable or improve with medical therapy should not be prematurely exposed to the risks of surgery and long-term immunosuppression. However, some patients may be observed during medical therapy too long, ultimately being referred for transplantation too late to survive the waiting period for a transplant. Additionally, some patients may be referred late enough in their course to have developed additional problems, such as malnutrition and renal insufficiency, placing them at higher risk for surgery.

Carefully monitoring the response to medical therapy at regular intervals is crucial to assess whether the treatment remains effective. For those in whom all forms of medical therapy fail, transplantation should be offered before the patient becomes too ill to enjoy a successful outcome. Lung transplantation should be considered for patients with PAH in whom therapy with vasodilators fails. Because of the long waiting period for

lung transplantation, and the unpredictable rate of decline for some patients, many centers advocate listing patients for transplantation as soon as the diagnosis of PAH is established, while others recommend that listing should occur when and if there is failure of medical therapy (ie, vasodilators and anticoagulation). Accordingly, the overall clinical picture must be assessed for each patient in order to allow ample waiting time for this potential life-saving therapy. Thus it is left to the treating physician and transplant specialist to make some predictions regarding an individual patient's survival with medical therapy.

Resting hemodynamics, 6-minute walk or shuttle test results, and functional class (eg, World Health Organization) status have each been demonstrated to predict survival in PAH.<sup>14-17</sup> Anticoagulation with warfarin, calcium channel blockers, and long-term epoprostenol have each been documented to improve survival in PAH,<sup>8,18-20</sup> and response to these therapies must be considered in relation to the timing of transplantation. Since the prognosis for patients with PAH may change continuously in response to treatment, pretreatment survival predictions using baseline static measurements, such as functional class, are of little value in determining the need for transplantation. Initiation of epoprostenol may dramatically improve symptoms and prognosis, potentially postponing or obviating the need for lung transplantation.<sup>10</sup> Indeed, vasodilator responders with PAH have a 90% to 95% 5-year survival when initiated on oral calcium channel blocker therapy and therefore are generally not initially listed for lung transplantation.<sup>8</sup> Unfortunately, the vast majority of patients with PAH (75% to 85%) are nonresponders, and without therapy face a 5-year survival of less than 40%. It is this latter group that should be considered for continuous intravenous epoprostenol therapy and listing for lung transplantation. Although long-term data with epoprostenol are limited, improved 5-year, or 50 month (50% to 60%) survival, has been reported.<sup>19,20</sup>

Thus, the potential effect of epoprostenol on survival must be considered when evaluating patients for lung transplantation. At our center, we generally begin the evaluation process for lung transplantation when WHO class III symptoms develop. If there are no significant contraindications for transplantation, these patients are listed and symptoms are monitored while time is accrued on the waiting list. If symptoms stabilize during medical therapy, these patients are removed from the active list; reactivation occurs if medical therapy begins to fail.

**Effect of Epoprostenol on Timing of Lung Transplantation for PAH**

Improvement in symptoms and survival with continuous infusion epoprostenol has had a significant impact on the timing of lung transplantation.<sup>10,11,21</sup> Treatment with this therapy may result in three potential clinical responses. (1) A few patients experience no significant improvement, and in this group medical therapy is considered to have failed. In these individuals, transplantation is the only viable life-sustaining option. These patients are usually maintained on epoprostenol in the hope that their disease will stabilize until transplantation. (2) Another potential response, and fortunately the most likely (occurring in >90% of patients), is improvement with

epoprostenol with a demonstrable reduction of at least one point in WHO symptom class within the first 3 to 6 months. However, some patients develop a recurrence of symptoms despite further increases in their epoprostenol dose and require further consideration for transplantation. These patients will have benefited from epoprostenol in the short term by deferring the immediate need for lung transplantation.<sup>10</sup> (3) Some patients develop a substantial and long-lasting (years) benefit from epoprostenol, and lung transplantation will be deferred indefinitely.

Deciding where an individual patient lies within these three groups at an isolated point in time can be a challenge clinically. Serial assessment of functional status together with direct measurement of hemodynamics allows one to best determine the response to therapy. For those who are good long-term responders to epoprostenol, it remains unclear how long the benefit may hold, as the longest survival time of a patient receiving epoprostenol is now well over 10 years. However, it is important to remember that if one waits too long, until functional status markedly declines and hemodynamics begin to fail, the patient may become too sick for a successful transplant.

### Type of Transplant

The operation of choice for primary pulmonary hypertension remains controversial. Combined heart-lung transplantation,<sup>22</sup> single lung transplantation<sup>23-25</sup> and double lung transplantation<sup>10,23</sup> have all been performed successfully. However, combined heart-lung transplantation is rarely necessary for PAH, since the right ventricle tends to recover function relatively quickly following either single or double lung transplantation.<sup>25</sup> Given the success of single and double lung transplantation, coupled with the limited supply of heart-lung donor blocks, single and double lung transplantation has almost completely replaced heart-lung transplantation for PAH in the United States.

Whether one should offer single or double lung transplantation for PAH is not clear, as there are pros and cons for each approach. Single lung transplantation is a less invasive and shorter surgical procedure, allows two recipients to be served from a single donor, and the waiting periods are shorter than for double lung transplants. However, the most recent International Society for Heart and Lung Transplantation (ISHLT) registry data show a slight long-term survival advantage for patients with double lung transplants (all diseases combined) compared to single lung transplants, although the difference is not statistically significant for patients with PAH.<sup>26</sup> There is, however, one important potential problem with single lung transplants for pulmonary hypertension that has influenced many programs to favor double lung transplantation. With single lung transplantation, blood preferentially flows in the pulmonary circuit toward the new lung; little flow goes to the native lung because of the severe pulmonary vascular disease. If the new lung develops infection or rejection, a severe shunt can develop, causing profound hypoxemia and making management extremely difficult.<sup>27</sup>

### Immunosuppression

Following lung transplantation, recipients must receive lifelong immunosuppression to prevent allograft rejection. Unfortunately, numerous side effects are associated with these medications. The major consequence of long-term immunosuppression is an increased rate of infection. Following transplantation there is an increased risk for bacterial, viral (particularly cytomegalovirus), and fungal infections.<sup>28,29</sup> The risk of infection relates inversely to the time from the transplant procedure.<sup>28,29</sup> This is due in part to both mechanical factors and the intensity of immunosuppression.<sup>28,30</sup> Although the risk of infection decreases as the amount of immunosuppression is reduced over time, the risk never returns to that of normal individuals.

Other risks of immunosuppression relate specifically to each drug. Most centers use a triple-drug-based regimen including cyclosporine (Neoral) or tacrolimus (Prograf), with azathioprine (Imuran) or mycophenolate mofetil (CellCept) and prednisone. Both cyclosporine and tacrolimus may induce hypertension and nephrotoxicity, while azathioprine and mycophenolate produce leukopenia. Long-term corticosteroid use is associated with a litany of problems, including osteoporosis, skin bruising, hyperglycemia, cataracts, and myopathy. In addition to these problems, long-term immunosuppression is associated with an increased risk of cancer, particularly post-transplant lymphoproliferative disorder, which has been reported at a rate of around 6% following thoracic organ transplantations.<sup>31</sup>

### Lung Transplantation Outcomes

#### Survival

The success of lung transplantation can be measured according to several criteria, including survival, physiologic function, quality of life, and cost benefit. According to 2003 US Scientific Registry data, overall survival following lung transplantation is currently 77.4% at 1 year and 42.5% at 5 years.<sup>32</sup> Lung transplant recipients with PAH do not fare as well, however, having a 1-year survival of 72%, with much of this mortality due to perioperative deaths.<sup>32</sup> The 5-year survival is 37%.<sup>32</sup> **Figure 1** shows survival outcome by disease in patients from the United Network for Organ Sharing (UNOS)/ISHLT registry (data analysis through 2001).

A number of factors are responsible for early mortality (0 to 30 days). These include infection (23.5%), primary graft failure (30.5%), cardiovascular factors (11.5%), acute rejection (4.9%), bronchiolitis (0.5%), technical factors (8.3%), and other causes (20.5%).<sup>33</sup> The factors responsible for late mortality differ from those for early mortality. Over the long term, chronic allograft rejection, manifested pathologically as obliterative bronchiolitis, is the single most important factor limiting the overall success of lung transplantation. Obliterative bronchiolitis occurs in at least 40% of patients by 2 years and in up to 70% by 5 years,<sup>34</sup> and it is the cause of death in 50% of those affected. Other causes of late mortality include infection, malignancy, and other comorbidities. Prior to the development of epoprostenol, transplantation provided a survival advantage for patients with PAH when comparing transplant survival with

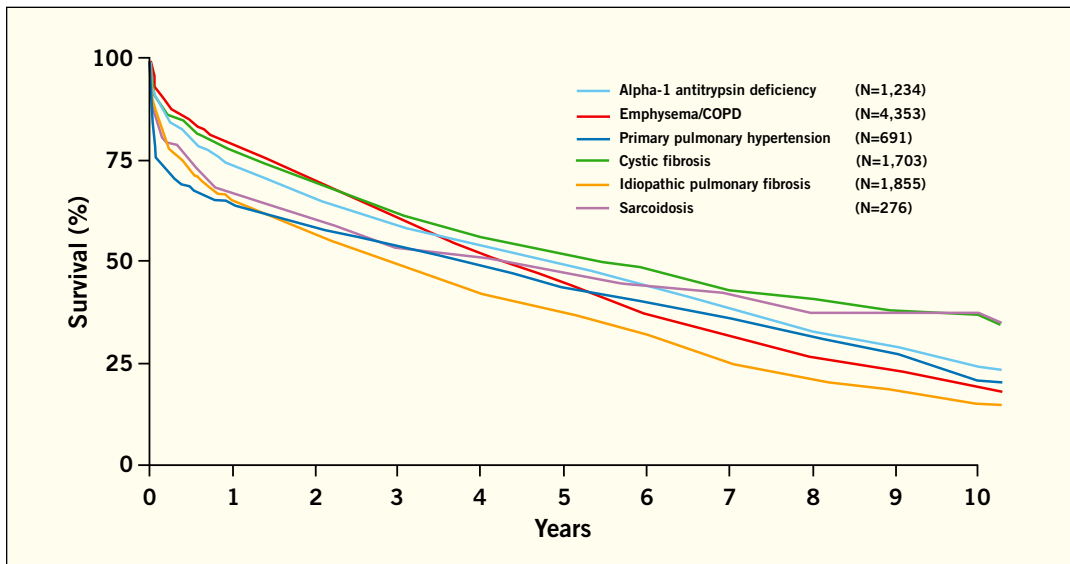


Figure 1. UNOS/ISHLT registry data showing actuarial survival for all lung transplant patients by diagnosis (January 1990 to June 2001). Note higher early mortality for recipients with primary pulmonary hypertension compared with other diagnoses. From [www.isHLT.org](http://www.isHLT.org).

data from the National Institutes of Health primary pulmonary hypertension registry.<sup>25</sup> At this point, however, it makes little sense to compare the outcome of lung transplantation with that of medical therapy. Lung transplantation should be utilized only for patients in whom medical therapy fails.

#### Functional Outcomes of Transplantation

Functional outcomes have been analyzed by the International Society for Heart and Lung Transplantation registry report.<sup>35</sup> At 3 years post transplant, 89.6% of recipients reported no activity limitations, 9.3% were able to perform activity with some assistance, and 1% required total assistance. Despite the functional improvements achieved with transplantation, only a minority of patients (29.1%) were working full time by 3 years post transplant. A majority of patients (54.8%) required repeat hospitalization in the first year of follow-up, although in the third postoperative year this fell to 38.2%. The most common reason for repeat hospitalization was allograft rejection and infection.

#### Quality of Life Following Transplantation

Despite widespread use of lung transplantation as a therapeutic modality, few published studies assess quality of life in recipients of this procedure. Gross and colleagues<sup>36</sup> documented overall improvement in quality of life following lung transplantation assessed by the Medical Outcomes Health Survey (MOS)-20 health profile. Over the long term, the benefit persists except in those patients who develop chronic rejection. Although significant benefits in exercise tolerance, pulmonary function, and quality of life exist following lung transplantation, only a minority of patients return to work on a full-time basis. The reasons why so few recipients return to work are not well known. Following transplantation the majority of patients reach functional levels that should not limit their physical ability to work in a variety of occupations. It is true, however, that many transplant recipients are unable to work because of financial

constraints. For some the choice of returning to work means giving up disability insurance benefits that cover their long-term medications and post-transplant medical care.

#### Cost of Lung Transplantation

The financial cost of lung transplantation is not trivial. In fact, the high cost has been a motivating factor for Medicare and other third party payers to offer reimbursement for this procedure only to approved centers of excellence. Ramsey et al<sup>37</sup> outlined the overall costs of lung transplantation for the University of Washing-

ton Medical Center. The average charges for the procedure and immediate postoperative care were \$164,989 (median \$152,071). The post-transplant average monthly charges during the first 6 months were \$16,628; in the second 6 months they were \$5,440, but fell to \$4,525 thereafter. This compared to the average monthly charges for patients on the waiting list of \$3,395. Although these figures come from a single center, they do not differ substantially from reports of other centers.<sup>38,39</sup>

#### Summary

All potential lung transplantation candidates with PAH should be considered for treatment with epoprostenol where available. In the United States, patients should be listed for transplantation at initiation of therapy; the response to epoprostenol should be reviewed at regular intervals and dosage increased as tolerated. Patients who respond well should be removed from the transplant list and monitored for continued responsiveness. For those in whom medical therapy fails, lung transplantation remains a viable option. Despite the potential for improved survival and function, this procedure is associated with several limitations. These include the lack of available donor lungs, the morbidity and mortality associated with the surgery, high financial cost, lifelong need for immunosuppression, and the risk of infection and rejection. Research is under way to develop better methods for organ tolerance without the need for potent, nonspecific immunosuppression. Potential candidates for lung transplantation should be referred to transplant centers early to maximize their chance for survival.

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# Lung Transplantation: Timing, Perioperative Considerations and Postoperative Outcome



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Lung transplantation has evolved over the past several decades in patients with end-stage lung disease. Single and bilateral lung as well as heart-lung transplantation has been utilized in the setting of severe pulmonary arterial hypertension (PAH) when all other therapeutic measures have been unsuccessful. While transplantation offers the prospect of improved survival and functional status, the potential consequences of lifelong immunosuppression and infection as well as chronic, refractory allograft rejection mandate careful patient selection and close follow-up prior to proceeding to transplantation. Pharmacologic therapy for severe PAH has evolved considerably as well, and survival with this disease in the setting of the best available treatment (continuous intravenous epoprostenol) appears to be approximately 88%, 76%, and 63% at 1, 2, and 3 years, respectively.<sup>1</sup> Because progressive right ventricular failure still occurs, transplantation must be considered in patients with end-stage disease who meet selection criteria. We will focus on timing of the referral and of the procedure, perioperative considerations, and postoperative outcome. Candidate selection, temporizing procedures such as septostomy, and immunosuppressive therapy are discussed in detail elsewhere in this issue.

## Timing of Referral for Transplantation and of Procedure

The physician caring for the patient with PAH must be cognizant of three time-related variables: patient survival on current maximal medical management, approximate projected time on the waiting list, and patient survival after transplantation. Ideally, transplantation occurs when the clinically deteriorating patient has enough reserve to survive long enough to undergo transplantation but is not debilitated enough to jeopardize the graft (**Table 1**). With regard to this ideal there is significant uncertainty. All patients who are in World Health Organization (WHO) class III and IV with refractory right ventricular failure on presentation should be referred for transplantation,<sup>2</sup> as should those with progressive right ventricular failure on maximal medical therapy.<sup>3</sup> Recent evidence from a prospective observational study<sup>1</sup> demonstrated that patients receiving intravenous epoprostenol therapy who had not improved to functional class I or II should be listed because their mortality at 3 years was 38% and 100% for class III and IV, respectively. Patients with class I and II symptoms will likely have better survival with state-of-the-art medical therapy and

referral should be deferred. However, patient characteristics with respect to blood type, size, and panel reactive antibodies should also be taken into account as these factors can significantly prolong time on the waiting list.<sup>4</sup>

Unlike heart or liver transplantation, the lung transplant allocation system does not take into account acuity of illness.<sup>5</sup> The allocation algorithm in this system after matching size and blood group is entirely based on time accrued since listing. Organs are offered first locally then regionally in successive 500-mile increments.<sup>5</sup> Since the clinical introduction of lung transplantation, the number of potential recipients has far outpaced the number of donors. This donor shortage has doubled the median time to transplant.<sup>6</sup> There are currently 3937 patients awaiting lung transplantation and recent figures demonstrate that 33% will die on the waiting list.<sup>5,6</sup> Patient characteristics that can significantly prolong time on the waiting list are blood group antigen type, small patient size, and high panel reactive antibodies. The 1992-2001 UNOS registry demonstrated that blood type O patients waited an average of 11 months longer than blood type AB patients.<sup>5</sup> In addition, small patients (those with a total lung capacity less than 4.5 L), wait an additional 60 days compared to recipients with a total lung capacity greater than 4.5 L.<sup>5</sup> Lastly, Appel et al<sup>7</sup> demonstrated that patients with high levels of panel reactive antibodies also waited significantly longer for transplantation and had higher mortality while waiting. Though no guidelines exist regarding these issues, our inclination is to refer class III and IV patients at the time of the initial evaluation. In the small group of patients with good functional status but with mitigating characteristics or history (ie, type O blood group or history of multiple previous transfusions) referral for listing is individualized and typically is reserved until some degree of disease progression has been demonstrated.

## Operation

Historically, treatment for pulmonary hypertension required transplantation of a heart-lung block.<sup>8</sup> This initial approach was consequent to the concern that right ventricular function would not improve sufficiently to prevent perioperative morbidity and mortality.<sup>9</sup> In the current era of surgical therapy for PAH, isolated lung transplantation is now used in most cases except in instances where uncorrectable structural defects or

**Table 1. Pulmonary Arterial Hypertension: Guidelines for Lung Transplantation\***

General Guidelines	Disease-Specific Guidelines
<b>Age limits</b> Single lung transplant ~65 years Bilateral lung transplant ~65 years Heart-lung transplant ~55 years	<b>Management</b> Treatment based on disease severity: Progression despite epoprostenol and standard supportive therapy <sup>‡</sup>
<b>Absolute contraindications</b> Creatinine clearance <50 mg/mL/min HIV infection Active malignancy within 2 years <sup>†</sup> Hepatitis B antigen positivity Hepatitis C with positive liver biopsy	<b>Hemodynamic predictors of poor outcome</b> Cardiac index <2 L/min/m <sub>2</sub> Mean right atrial pressure >15 mm Hg Mean pulmonary artery pressure >55 mm Hg <sup>§</sup>
<b>Relative contraindications</b> Symptomatic osteoporosis Severe musculoskeletal disease Body mass index >30 Hyperbilirubinemia >2.0 mg/dL Tobacco or substance abuse Psychosocial problems Invasive ventilator support Colonization with fungi or atypical mycobacteria	<b>Indications for transplant</b> WHO class III or IV with progression on vasodilator therapy
	<p>* Modified from international guidelines<sup>46</sup> and Pielsticker et al.<sup>11</sup></p> <p><sup>†</sup> With exception of basal cell and squamous cell carcinoma of the skin. Further, 5-year waiting period is recommended for high stage renal, breast, and colon cancers as well as advanced melanoma (level III or greater).</p> <p><sup>‡</sup> Patients often respond well to continuous intravenous epoprostenol even with severe abnormal hemodynamics as outlined here. Those not responding or with continued progression in spite of such therapy should proceed to transplant.</p> <p><sup>§</sup> In patients with congenital heart disease, mean pulmonary artery pressure is often in excess of 55 mm Hg; this measurement in and of itself does not portend same poor prognosis as in other patients with pulmonary arterial hypertension.</p> <p><sup>¶</sup>WHO=World Health Organization.</p>

left ventricular dysfunction is present in the native heart.<sup>9,10</sup> Considerable variations in practice patterns have been reported with respect to single versus bilateral lung transplantation for pulmonary hypertension.<sup>11</sup>

In a retrospective study of the University of Pittsburgh's experience, both procedures resulted in similar length of mechanical ventilation, length of intensive care unit stay, and mortality.<sup>12</sup> Registry data from the International Society for Heart and Lung Transplantation have confirmed no significant differences in survival in patients with PAH.<sup>13</sup> Despite no apparent differences in mortality, significant differences exist between those with single versus bilateral lung transplants with respect to blood flow, pulmonary artery pressure, and immediate cardiac index.

After single lung transplantation almost the entire cardiac output passes through the allograft while ventilation remains evenly distributed.<sup>14-17</sup> This is well tolerated provided that minimal allograft dysfunction is present. In the face of reperfusion injury, infection, or rejection, significant hypoxemia results from increased ventilation perfusion mismatch.<sup>16,18</sup> Single lung recipient outcomes are inextricably linked to the function of the single allograft. Unlike other recipients transplanted for other reasons, these recipients have no functional reserve from their native lung because pulmonary blood flow continues to be preferentially shunted through the allograft despite ineffectual ventilation.<sup>9</sup> Additionally, an occasional complication of single lung transplantation for pulmonary hypertension is infarction of the native lung from hypoperfusion. Though rare, such situations require emergent reexploration and pneumonectomy.

Bando and colleagues<sup>17</sup> further explored the postoperative

hemodynamic results following single lung, bilateral lung, and heart-lung transplantation in a cohort of 57 consecutive patients with pulmonary vascular disease. They demonstrated that postoperative pulmonary artery pressures remained significantly higher in those with single lung transplants than in those with heart-lung or bilateral grafts; however, despite this difference, all groups experienced a significant decrease in pulmonary artery pressures. They further noted improvement in cardiac index in only the bilateral and heart-lung transplant recipients.

The superiority of bilateral versus single lung transplantation in patients with PAH remains a matter of debate. We prefer bilateral lung transplantation because it affords a greater reduction in pulmonary artery pressure, enhanced right ventricular protection and a larger effective pulmonary reserve. In addition, recent investigations have demonstrated a significant survival advantage of bilateral lung transplantation in patients with end-stage lung disease.<sup>19-22</sup>

### Perioperative Considerations

Worsening right ventricular failure is a substantial concern in PAH. Perioperative management requires the understanding of the multiple mechanisms that can lead to progressive ventricular dysfunction, such as inadequate preload, provoked increases in pulmonary resistance, fluid overload, systemic hypotension, and hypoxemia.

Intraoperative management requires continuation of the optimized pharmacologic regimen (generally epoprostenol) through surgery because abrupt discontinuation can lead to profound pulmonary vasoconstriction, right heart failure, and

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**WARNING: Potential liver injury.** TRACLEER causes at least 2-fold (upper limit of normal, ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serious aminotransferase levels must be measured prior to initiation of treatment and then monthly (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). In a setting of close monitoring, elevations have been reversible, within a few days to 3 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae. Therefore, aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). TRACLEER should generally be avoided in patients with elevated aminotransferases ( $\geq 3 \times$  ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (nausea, vomiting, fever, abdominal pain, jaundice, or unusual fatigue or fatigue or increase in bilirubin  $> 2 \times$  ULN), treatment should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances.

**CONTRAINDICATION: Pregnancy.** TRACLEER is known to be very likely to produce major birth defects if used by pregnant women, as the effect has been seen consistently when it is administered to animals (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER and prevented thereafter by the use of a reliable method of contraception. Normal contraceptives, including oral, injectable and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving TRACLEER (see Precautions: Drug Interactions). Monthly pregnancy tests should be obtained.

Because of potential liver injury and as an effort to make the chance of fetal exposure to TRACLEER as small as possible, TRACLEER may be prescribed only through the TRACLEER Access Program by calling 1 866 381 346. Adverse events can also be reported directly to the sponsor.

**INDICATIONS AND USAGE:** TRACLEER is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class II or III symptoms, to improve exercise ability and decrease the risk of clinical deterioration.

**CONTRAINDICATIONS:** TRACLEER is contraindicated in pregnancy, with concurrent use of cyclosporins, with administration of glyburide, and in patients who are hypersensitive to bosentan or any component of the medication.

**Pregnancy Category X.** TRACLEER is expected to cause fetal harm if administered to pregnant women. The severity of malformations induced by bosentan in rodents observed in embryonic/fetal studies and in animals treated with other endothelin receptor antagonists indicate that teratogenicity is a class effect of these drugs. There are no data on the use of TRACLEER in pregnant women. TRACLEER should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription for TRACLEER should be issued by the prescriber unless the patient meets the criteria that she is not sexually active or provides negative results from a urine or serum pregnancy test performed during the first 3 days of a normal menstrual period on at least 11 days after the last completed act of sexual intercourse. Following urine or serum pregnancy tests should be obtained monthly in women of childbearing potential using TRACLEER. The patient must be advised that there is no delay in onset of menses or any other reason to suspect pregnancy, she must notify her physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk in the pregnancy and to the fetus.

**WARNINGS: Potential liver injury.** Bosentan in ALT (AST) by more than  $2 \times$  ULN were observed in 11% of bosentan-treated patients (N = 85) compared to 2% of placebo-treated patients (N = 200). The combination of hepatocellular injury (increases in aminotransferases of  $> 3 \times$  ULN) and increases in total bilirubin  $> 2 \times$  ULN) is a marker for potential serious liver injury. Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and to date have been reversible after treatment interruption or cessation. These aminotransferase elevations may reverse spontaneously while continuing treatment with TRACLEER. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual fatigue or fatigue or increase in bilirubin  $> 2 \times$  ULN), treatment should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances. Prescribing Liver Impairment: TRACLEER should generally be avoided in patients with moderate or severe liver impairment. In addition, TRACLEER should generally be avoided in patients with elevated aminotransferase  $> 2 \times$  ULN because monitoring liver injury in these patients may be more difficult.

**PRECAUTIONS: Hematology.** Change in hemoglobin concentration for bosentan-treated patients was 0.8 g/dL (range) to end of treatment. Most of this decrease in hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin values stabilized by 8-12 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained either some levels or 5% of bosentan-treated patients compared to 7% of placebo patients. The separation for the change in hemoglobin is not clear, so it does not appear to be hemolytic or hypoxic. It is recommended that hemoglobin concentrations be checked after 1 and 2 months, and every 2 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

**Information for Patients:** Patients are advised to consult the TRACLEER Medication Guide in the safe use of TRACLEER. The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases and urine or serum pregnancy testing and of avoidance of pregnancy. The physician should discuss options for effective contraception and measures to prevent pregnancy with their female patients (up to 3 years) and/or similar agent or adequate contraception should be sought as needed.

**Drug Interactions:** CYP Isoenzymes: Bosentan is metabolized by CYP2D6 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. Bosentan is an inhibitor of CYP3A4 and CYP2D6. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when TRACLEER is co-administered. Contraceptive Specific interaction studies have not been performed to evaluate the effect of co-administration of bosentan and hormonal contraceptives, including oral, injectable or implantable contraceptives. Since many of these drugs are metabolized by CYP3A4, there is a possibility of failure of contraception when TRACLEER is co-administered. Women should not rely on hormonal contraceptives alone when taking TRACLEER. Cytosine A: During the first year of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cytosine A. The concomitant administration of bosentan and cytosine A is contraindicated. Sitrus: An increased risk of elevated liver aminotransferase was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of TRACLEER and glyburide is contraindicated, and alternative hypoglycemic agents should be considered. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2D6 or CYP3A4. The possibility of increased glucose control in patients using these agents should be considered. Ketoconazole: Co-administration of bosentan (125 mg b.i.d.) and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered. Simvastatin and Other Statins: Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A4 substrate) and its active 3-hydroxy acid metabolite, by approximately 20%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that have significant metabolism by CYP3A4 such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patient using CYP3A4 metabolized statins should have cholesterol levels monitored after TRACLEER is started to see whether the statin dose needs adjustment. Warfarin: Co-administration of bosentan 300 mg b.i.d. for 14 days decreased the plasma concentrations of both S-warfarin (a CYP2D6 substrate) and R-warfarin (a CYP3A4 substrate) by 28 and 36%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline INR and other clinical studies), and the need to change the warfarin dose during the trial due to changes in INR or due to adverse events was similar among bosentan and placebo-treated patients. Diphenhydramine and Bosentan: Bosentan has been shown to have no pharmacokinetic interactions with diphenhydramine, and bosentan has no effect on plasma levels of bosentan.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses about 3 times the maximum recommended human dose (MRHD) of 125 mg b.i.d., in a 90-day study. In a 2-year study, doses greater than about 20 times the MRHD were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of lung adenocarcinoma in males at doses about 3 times the MRHD. Impairment of Fertility/Potential Fertility: Many endothelin receptor antagonists have profound effects on the morphology and function of the testes in animals. These drugs have been shown to reduce activity of the seminiferous tubules of the testes and to reduce sperm counts and male fertility in rats when administered for longer than 12 weeks. When treated, testicular tubular atrophy and decreases in male fertility observed with endothelin receptor antagonists appear reversible. In fertility studies in which male and female rats were treated with bosentan at oral doses that to 20 times the MRHD on a weight basis, no effects on sperm count, sperm quality, mating performance or fertility were observed. An increased incidence of testicular tubular atrophy was observed in rat pups born to rats mated in a study at doses as low as about 4 times the MRHD for two years by oral dose at high to about 10 times the MRHD for 6 months. An increased incidence of tubular atrophy was not observed in rats treated for 2 years at doses up to about 75 times the MRHD or in rats treated at 10 to 12 months at doses up to about 4 times the MRHD. There are no data on the effects of bosentan on other endothelin receptor antagonists or testicular function in man.

### Pregnancy, Teratogenic Effects, Category X

**SPECIAL POPULATIONS: Nursing Mothers.** It is not known whether this drug is excreted in human milk. Concomitantly drugs are excreted in human milk, breastfeeding while taking TRACLEER is not recommended. Pediatric Use: Safety and efficacy in pediatric patients have not been established. Use in Elderly Patients: Clinical experience with TRACLEER in subjects aged 65 or older has not included a sufficient number of such subjects to identify a difference in response between elderly and younger patients.

**ADVERSE REACTIONS:** Safety data on bosentan were obtained from 12 clinical studies (8 placebo-controlled and 4 open-label) in 777 patients with pulmonary arterial hypertension and other diseases. Treatment discontinuation due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent in bosentan (5%; 475 patients) than in placebo (3%; 240 patients). In this database the only cause of discontinuation  $> 1%$ , and occurring more often in bosentan was abnormal liver function. In placebo-controlled studies of bosentan in pulmonary arterial hypertension and for other diseases (primarily chronic heart failure), a total of 677 patients were treated with bosentan at oral doses ranging from 150 mg to 300 mg and 268 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 8 months, for the adverse drug reactions that occurred in  $\geq 2%$  of bosentan-treated patients the only one that occurred more frequently in bosentan than in placebo (1.7% of bosentan-treated patients) was headache (16% vs. 7%), fatigue (7% vs. 2%), abnormal hepatic function (6% vs. 2%), leg cramps (5% vs. 1%), and nausea (3% vs. 1%).

**OVERDOSE:** Bosentan has been given as a single dose of up to 300 mg in normal volunteers, or up to 300 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate severity in the pharmacokinetic interaction study, in which doses of 300 and 600 mg b.i.d. of bosentan were given concomitantly with cytosine A, though plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. All decreases in blood pressure and orthostatic hypotension in these rats were observed. There is no specific experience of overdosage with bosentan beyond the doses described above. Nausea associated with this trial in pulmonary hypertension requiring active or intravenous support.

**DOSE AND ADMINISTRATION:** TRACLEER treatment should be initiated at a dose of 62.5 mg b.i.d. for 4 weeks and then increased to the maintenance dose of 125 mg b.i.d. Doses above 125 mg b.i.d. did not appear to confer additional benefit, but patients should be monitored for liver injury. Tablets should be administered morning and evening with or without food.

### Dose Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

ALT/AST levels	Treatment and monitoring recommendations
$> 2$ and $< 5$ ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).
$> 3$ and $< 8$ ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
$> 8$ ULN	Treatment should be stopped and re-introduction of TRACLEER should not be considered. There is no experience with re-introduction of TRACLEER in these circumstances.

TRACLEER is re-introduced it should be at the starting dose, aminotransferase levels could be checked within 1 day and thereafter according to the recommendations above. If liver aminotransferase elevations are accompanied or complicated by symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual fatigue or fatigue or increase in bilirubin  $> 2 \times$  ULN), treatment should be stopped. There is no experience with the re-introduction of TRACLEER in these circumstances. Use in Women of Childbearing Potential: TRACLEER treatment should only be initiated in women of childbearing potential knowing a negative pregnancy test and only in those who practice adequate contraception that does not rely only upon hormonal contraceptives, including oral, injectable or implantable contraceptives, but also a prescription or similar agent or adequate contraception should be sought as needed. Urine or serum pregnancy tests should be obtained monthly in women of childbearing potential using TRACLEER. Dose Adjustment in Renally Impaired Patients: The effect of renal impairment on the pharmacokinetics of bosentan is oral and does not require dosage adjustment. Dose Adjustment in Geriatric Patients: Clinical studies of TRACLEER did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the use of bosentan in elderly patients due to the greater frequency of decreases hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group. Dose Adjustment in Hepatically Impaired Patients: The absence of liver impairment in the pharmacokinetics of TRACLEER has not been evaluated. Because there is in vivo and in vitro evidence that the main route of excretion of TRACLEER is biliary, liver impairment would be expected to increase exposure to bosentan. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. TRACLEER should generally be avoided in patients with moderate or severe liver impairment. Dose Adjustment in Pediatric: Safety and efficacy in pediatric patients have not been established. Dose Adjustment in Patients with Low Body Weight: In patients with a body weight below 45 kg but with at least 17 years of age the recommended oral and maintenance dose is 62.5 mg b.i.d. Discontinuation of Treatment: There is limited experience with abrupt discontinuation of TRACLEER. No evidence for acute rebound has been observed. Nevertheless, it would be prudent to monitor for clinical deterioration, gradual dose reduction (62.5 mg b.i.d. for 3 to 7 days) should be considered.

**HOW SUPPLIED:** 62.5 mg film-coated, round, bisect, imprinted with the following information: embossed with identification marking "125", NDC 60215-10-08. Tablet containing 62.5 mg film-coated, oval, bisect, orange-white tablets, embossed with identification marking "125", NDC 60215-100-08. Tablet containing 125 mg.

As only.

**STORAGE:** Store at 20°C - 25°C (68°F - 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). (See USP Controlled Room Temperature).

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**Manufactured by:** Actelion Inc., Menlo Park, CA  
**Marketed by:** Actelion Pharmaceuticals Ltd., South San Francisco, CA

Information for previous page: 1. Tracleer (bosentan) full prescribing information, Actelion Pharmaceuticals, Inc. 2001.

death.<sup>23</sup> Typically, ascitic fluid is drained to allow for greater diaphragmatic excursion (sometimes requiring a temporary peritoneal catheter for intermittent decompression of the abdomen postoperatively). Additionally, the bypass is primed with fresh frozen plasma rather than isotonic crystalloid. Careful attention must be paid to volume status and diuretics must be used with caution based on hemodynamic monitoring. The prothrombin time, fibrinogen level, and a thromboelastogram should guide replacement therapy intraoperatively. Oxygen saturation should be kept greater than 90% to avoid unnecessary hypoxic vasoconstriction.<sup>24</sup> Normally, acidosis has minimal effect on pulmonary vascular resistance; however, in the presence of alveolar hypoxia its effect is considerably augmented. Rudolph et al<sup>25</sup> have demonstrated a decrease in pulmonary vascular resistance in patients with pulmonary hypertension by reducing the arterial carbon dioxide tension and hydrogen ion concentration. In the event that inotropic support is required in the face of euolemia, dobutamine is the first agent of choice because of its pulmonary vasodilatory properties.<sup>26</sup> Milrinone can also be used, but its lack of pulmonary specificity can aggravate systemic hypotension.<sup>27</sup> If hypotension continues, norepinephrine and phenylephrine can be used to augment coronary perfusion by maintaining systemic pressures.<sup>28</sup>

Postoperative management can be quite challenging. Patients may die suddenly in the immediate postoperative period from hemodynamic perturbations. Although single and bilateral lung transplantation results in immediate afterload reduction in the operating room, right ventricular function recovers more slowly.<sup>10, 29-31</sup> Care must be taken to avoid pulmonary vasoconstriction and any therapy that decreases pulmonary vascular resistance should be weaned with caution.<sup>23</sup> Early extubation and mobilization of transplant recipients as well as negative fluid balance are the cornerstones of management. Loss of local defense mechanisms, consequent to denervation and reduction of mucociliary clearance, identifies why the allograft is more vulnerable to atelectasis and infection.<sup>32</sup> Therefore, early extubation and mobilization of recipients augment lung reexpansion and recruitment of alveoli. Fluids are restricted and diuretics administered to achieve a negative fluid balance. Passive hepatic congestion from chronic right ventricular failure will likely have resulted in impaired liver synthetic function. Patients will be prone to coagulopathy and ascites. Intermittent drainage of ascites is indicated to augment ventilatory effort. Liberal use of vitamin K and fresh frozen plasma may be needed to prevent posttransplantation coagulopathy.

## Outcomes

Reported cumulative world experience exceeds 13,000 lung transplants with 73% 1-year and 45% 5-year overall survival.<sup>33</sup> Patients with PAH, idiopathic pulmonary fibrosis, and sarcoidosis have higher early mortality rates than those with other diagnoses.<sup>33</sup> Patients with cystic fibrosis have 1-, 5-, and 10-year survival rates of 78%, 52%, and 37% while those recipients with PAH have survival rates of 64%, 44%, and 20%, respectively.<sup>33</sup> As noted, patients with PAH have the highest early hazard of all diagnoses. This can be explained by the complexity of

the operation, the requirement for cardiopulmonary bypass, and the right ventricular dysfunction common in these patients.

The two most common causes of death after the first transplant year include bronchiolitis obliterans and infection.<sup>33</sup> Long-term success of lung transplantation is limited by chronic allograft dysfunction, thought to be primarily due to chronic allograft rejection. This injury has been characterized by scar formation and fibrosis of the small airways and is defined as bronchiolitis obliterans.<sup>34</sup> The diagnosis of bronchiolitis obliterans requires a histopathologic specimen that includes the small to medium sized airways. However, transbronchial biopsy specimens are insensitive for this diagnosis, since mostly alveolar tissue is obtained and bronchioles are infrequently sampled. The International Society for Heart and Lung Transplantation developed a reproducible and reliable surrogate marker for bronchiolitis obliterans that utilizes declining FEV<sub>1</sub>.<sup>35</sup> The system has been widely adopted and validated as a useful surrogate for histological bronchiolitis obliterans.

Bronchiolitis obliterans syndrome (BOS) is the most common cause of morbidity and mortality following lung transplantation. At 5 years, 50% of transplanted patients have developed BOS and of the survivors, more than 33% continue to carry this diagnosis. Quality of life is significantly reduced once BOS develops, and the risk for death due to infection may also be increased.<sup>36-39</sup>

Kshetry and colleagues retrospectively analyzed 107 lung allograft recipients for the development of bronchiolitis obliterans to evaluate PAH as a potential risk factor. They demonstrated that patients with PAH developed bronchiolitis obliterans more often (39% vs 19%;  $P = .044$ ) and more rapidly (12 vs 15 months;  $P = .05$ ) than those with other diagnoses.<sup>40</sup> However, results from other investigators have not corroborated these findings. Sundaresan at Washington University, reported no significant tendency for development of BOS (surrogate for bronchiolitis obliterans) in patients with PAH.<sup>41, 42</sup> At present there is no consensus as to whether PAH is a risk factor for the development of bronchiolitis obliterans.

The lungs are particularly vulnerable to infection after transplantation. This is likely the consequence of multiple factors that include constant exposure to potential inhaled pathogens, impaired local defense mechanisms (cough and mucociliary transport), and immunosuppression. Bronchoscopy is an invaluable adjunct for diagnosing pulmonary infection, because clinical or physiological parameters are often unable to distinguish between the two.<sup>43</sup> Non-CMV pneumonia is most commonly caused by gram-negative bacteria and *Staphylococcus aureus* early in the postoperative period. Viruses, fungi, and protozoa compose a set of more severe late infections that are more difficult to treat if prophylaxis is unsuccessful.<sup>44</sup>

Five years after transplantation, the most common morbidities excluding bronchiolitis obliterans include hypertension, hyperlipidemia, renal dysfunction, and diabetes (**Table 2**).<sup>33</sup> Osteoporosis can be prevented to some extent. All are a consequence of immunosuppressive therapy.

Despite all of these factors, more than 80% of 1-, 3-, and 5-year survivors reported no activity limitations on follow-up. In addition, at 5 years, 40% of patients reported they were work-



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Assistant Professor in the Department of Medicine  
and in the Department of Molecular Pharmacology and  
Experimental Therapeutics at the Mayo Clinic, Rochester, MN

##### **Presentation: How Should New Treatments Be Studied?** Summary and Future Directions

Stuart Rich, MD

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## Lung Transplant Evaluation: Requirements Prior to Listing\*†

### Consultation

- Lung transplant surgeon and pulmonologist
- Physical therapy (6 minute walk, rest / exercise O<sub>2</sub> saturation, musculoskeletal evaluation)
- Nutrition service
- Transplant social work
- Medical psychology
- Cardiopulmonary anesthesia

### Diagnostic Imaging

- Chest radiogram
- Chest computed tomographic scan
- Differential ventilation-perfusion scan (relative lung perfusion)
- Mammogram (women age  $\geq 35$ , if not performed within the last year)
- Carotid ultrasound (age  $>50$ ; evaluate for stenosis / plaque)

### Cardiac / Pulmonary Studies

- Electrocardiogram
- Echocardiography with microcavitation
- Resting gated blood pool study (including right ventricular ejection fraction)
- Right heart catheterization (if age  $>40$ , left and right heart procedure)‡
- Pulmonary function testing with arterial blood gas testing

### Laboratory testing

- Complete blood count
- Electrolytes, BUN, creatinine, glucose
- Liver function tests
- Routine coagulation studies (PT / INR, aPTT)
- Serum albumin, total protein
- Uric acid
- Thyroid profile
- FANA
- Carcinoembryonic antigen
- Lipid panel
- Prostate-specific antigen
- Hepatitis B surface antigen
- Hepatitis B core antibody
- Hepatitis C virus antibody
- RPR (VDRL)
- CMV immune screen
- HIV-1 antibody
- Toxoplasma IgG antibody
- Herpes simplex IgG
- Varicella-zoster antibody
- Epstein-Barr virus antibody
- Type and screen
- HLA-AB screen
- HLA DR / DQ and HLA ABC
- Skin testing battery of 8 (PPD, fungal, etc.)

### Vaccine Administration

- Tetanus vaccine (If not administered in previous 10 years)
- Pneumovax (if not previously administered)

### Additional Testing

- Gastric pH / esophageal manometry§

\* Patients are referred to the transplant pulmonologist, who, together with the lung transplant coordinator, directs the evaluation. All consultation and diagnostic studies are thoroughly reviewed by the lung transplant team prior to listing

† Duke University Medical Center Lung Transplant Evaluation

‡ In patients with sarcoidosis, a cardiac biopsy is also performed at the time of catheterization.

§ These studies are performed if there is concern about abnormal esophageal motility or aspiration, such as in patients with collagen vascular disease. Additional diagnostic studies are often performed in transplant candidates with other underlying health problems.

**Table 2. Common Morbidities 5 Years After Lung Transplantation**

Outcome	Percentage
Hypertension	86.5
Hyperlipidemia	43.4
Renal dysfunction	38.3
Abnormal creatinine <2.5 mg/dL	20.2
Creatinine >2.5 mg/dL	13.7
Dialysis dependent	3.4
Renal transplantation	0.9
Diabetes	27.8

Adapted from Trulock.<sup>33</sup>

ing full or part time.<sup>33</sup> Further, Gross and colleagues<sup>45</sup> demonstrated significant improvement in health-related quality of life and satisfaction in about 80% of recipients interviewed.

### Comment

Prior to the availability of epoprostenol, lung transplantation for PAH was indicated when mean right atrial pressure was >15 mm Hg, mean pulmonary artery pressure was >55 mm Hg, and cardiac index was <2 L/min/m<sup>2</sup> and early survival was acceptable. Subsequent to the availability of medical therapy, the indications for transplantation have not changed but the patients are significantly more debilitated. Today, patients with pulmonary hypertension face a significant early hazard, with a 30-day survival of only 76%, while patients with CF and COPD have a survival of 91% and 93%, respectively.<sup>33</sup> Based on a conditional survival of 3 months, there is no difference between pulmonary hypertension, CF, and COPD, each with a 6-month survival of 96%.<sup>33</sup> This high early mortality seen after lung transplantation in patients with pulmonary hypertension likely reflects the ability of vasodilator therapy to prolong life despite significant pathophysiology. The advent of vasodilator therapy and the less than ideal results of lung transplantation for PAH have tempted clinicians to refer patients later when they have more advanced right ventricular failure. Despite these results, outcomes have improved since its original description and things must be kept in perspective.

With the significant medical advances in the treatment of PAH, transplantation should be reserved for those patients in whom pharmacologic therapy has failed. In this subset of patients whose condition does not respond, and which deteriorates with pulmonary vasodilator therapy, significant improvement in hemodynamics, functional class, actuarial survival, and quality of life has been demonstrated with isolated lung transplantation. Candidate selection and timing of referral to transplant centers is critical for ultimate success, particularly with current allocation protocols that do not take into account the severity of illness. Though long-term success is tempered by chronic allograft dysfunction and infection, significant improvements in outcomes have established lung transplantation for PAH as an efficacious and life-prolonging treatment.

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# Protocols in Heart and Lung Transplantation: An Essential Guide to Preoperative Assessment and Timing to Improve Outcomes



Victor Tapson, MD



Robert Frantz, MD



John Conte, MD

*This discussion was moderated by Victor Tapson, MD, Editor-in-Chief of Advances in Pulmonary Hypertension and Associate Professor, Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina. The participants included Robert Frantz, MD, Assistant Professor of Medicine, Cardiovascular Division, Mayo Clinic, Rochester, Minnesota; and John Conte, MD, Associate Professor of Surgery and Director of Heart and Lung Transplantation, Johns Hopkins University, Baltimore, MD.*

**Dr Tapson:** Let's start with a couple of general comments about transplantation and pulmonary hypertension. The first thing that comes to mind is the issue of timing and the severity of PH. When is it the right time to proceed with transplantation or listing?

**Dr Frantz:** That's a timely topic in a situation where the allocation system for donated lungs may soon be changed by the United Network for Organ Sharing (UNOS). It is sometimes difficult to know when to list patients with PH for lung transplant, especially if they are doing reasonably well with their current therapy. We tend to have to lead the curve by a long way because the waiting times for a lung transplant can be so long. If we don't think about it at least a couple of years ahead of time, the patients may be at risk of dying on the waiting list. The other thing to keep in mind is that the outcomes in general for lung transplantation for PH have been inferior to those for many other diseases, such as COPD, and results seem to vary some from center to center. There is a need to understand why it is that some patients with lung transplants don't do well if they had pulmonary hypertension as their preceding diagnosis. We would like to perform lung transplantation before advanced right heart failure develops because at that point the risk of the operation may rise. So, for us, we're always working on the questions, when is the right time for lung transplantation, is a lung transplant adequate or would a heart-lung transplant be better, and when is it too late?

**Dr Tapson:** A few years back we would list patients for lung transplantation as soon as they were diagnosed

with PH. As their illness progressed, they would end up receiving intravenous prostacyclin, and several or more years would go by. They did well enough with this drug that we'd end up inactivating them. We ultimately realized that we didn't have to list them so soon, and we'd start listing them when they began Flolan therapy, or perhaps a bit sooner. I guess to some degree it may depend on the center and the patient's blood type. If the center has a very long waiting list or a very short waiting list, the listing time may depend on those kinds of things.

**Dr Frantz:** Yes, no doubt that's true, and it may vary some from center to center. I have been impressed that young patients who have otherwise been healthy can sometimes be surprisingly well compensated until they are about to fall off the edge. And then it can be too late in the sense that sometimes patients can walk 400 or 500 meters with Flolan therapy and look remarkably well compensated, and then 2 years later they are just in disastrous trouble, where you are worried they are not going to survive to transplantation.

**Dr Tapson:** Because of its clear association with improved survival, we have been inclined to rely heavily on Flolan and sometimes, perhaps, we rely on it for too long. We need to realize that when someone taking this drug is not doing well, that we usually have little else to offer. We don't have enough data on new drugs combined with Flolan, as yet. John, when you approach transplantation and the patient is a pulmonary hypertension patient, is there anything that would particularly concern you or result in any differences with regard to your approach to surgery?

**Dr Conte:** Definitely. First and foremost, they need to have been evaluated by someone who treats patients with pulmonary vascular disease, just because of the things you've been talking about. Most people will do better in your hands than in my hands. However, oddly enough, the results of transplantation in our program with pulmonary hypertension are better than in any other patient group, but it is not because I do anything differently. I think it has to do with the fact that we have such good pulmonary vascular disease folks around. But I certainly think they should get optimal

medical therapy. Back when many of us started this, there wasn't much, other than calcium channel blockers, to treat these patients. Then the prostanoids came along and boom, we avoid transplantation. Then we kind of looked at medical therapy as a bridge to transplantation, and then as we got better and better at medical management, it became an alternative to transplantation for many patients. So I think patients need to have a thorough evaluation *and* a trial of medical therapy with vasoactive medications. Certainly, it started off with the prostanoids, but we have several other options at this point.

**Dr Tapson:** John, when patients come to you ready for transplantation, is there anything particularly that disturbs you in terms of hemodynamics? Are there values that make you feel the patient is too sick? Is there a certain cardiac index or severity of disease that concerns you about proceeding?

**Dr Conte:** We used to say that by nuclear study an ejection fraction of less than 10% was an indication for heart-lung transplantation. At every institution that number may be a little higher or a little lower than that, but I can't say there has been a patient in my experience on whom I regretted doing a lung transplant alone. I had one patient who did require inotropes for a period of time postoperatively, for about a month. But that patient was able to come off inotropes and right heart function has just continuously improved over the last 2 years. If you can get them through the operation, there is no advantage in doing a heart-lung transplant, plus getting a heart and lung is nearly impossible. With the way the UNOS allocation system is currently configured, the need for a heart-lung transplantation is a tremendous disadvantage. To get a heart-lung block you have to be in the same pool as people with just heart disease. Those with the highest priority are all in the hospital on various degrees of support. We currently have a patient who is status 1-A, the highest priority for the heart people, in the hospital sitting around waiting for a donor.

**Dr Tapson:** John, what about the old single versus bilateral lung argument? Is there a standard now, or is this still center-dependent? Are most people doing bilateral lungs?

**Dr Conte:** I think most people are doing bilateral lungs, but there are certain places where they have always done single lungs and have had fairly good results, and they are going to continue to do it. I think it boils down to your basic philosophy. Do you want to treat as many people as possible with a limited resource, or do you want to try and get the best results out of every single patient? At about 3 years there starts to be an advantage, regardless of the etiology of the end-stage lung disease, there tends to be an advantage in survival with bilateral lung transplantation. I have always believed that in younger patients I should do bilateral lung transplants. But quite hon-



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estly there are many young patients who were near death in whom we did a single lung transplant who have done very well. I think individual institutions will tailor their preferences as they see fit, and you can defend or argue against any position.

**Dr Tapson:** So timing might be a concern. If you've got someone really running out of time and you can't get a bilateral lung block, but you've got a single lung, might you proceed based on the fact that you've got something available that would be life saving?

**Dr Conte:** Absolutely.

**Dr Frantz:** John, I am very interested in your perspective about what it takes to make a pulmonary hypertension patient do well with transplantation. As you know, the UNOS database shows a 1-year posttransplant survival rate for patients with PH to be about 64% compared to about 80% for COPD. This is causing the UNOS subcommittee looking at lung allocation to consider requiring PH patients to be incredibly ill before they receive priority for lung transplantation, and I think at your center and ours that is not our experience. The PH patients are young, they often can do extremely well with transplantation, and it seems that perioperative management must be critical. What do you think explains the problem nationally with outcome in lung transplantation for PH?

**Dr Conte:** I think most people in this country who do transplantation are general thoracic surgeons. And I think lung transplantation for PH is a cardiovascular disease treatment best handled by people who are used to handling the heart-lung machine. All of these people who have significant PH have to be placed on the heart-lung machine and I think many transplant surgeons try to avoid that, not so much in patients with primary PH, but in those with secondary PH. When you do that you can see severe reperfusion injury when the first lung sees tremendous pressures during reperfusion and it gets overcirculated, pulmonary edema develops, and the spiral starts. So, I think the fact that I am used to the heart-lung machine and am not afraid of it will give me a small advantage in taking care of these patients. Anybody who has a mean pulmonary pressure greater than 40 mm Hg goes right on the heart-lung machine.

**Dr Frantz:** Well, I think those are very wise comments and it is my perception as well that this is the issue, that cardiothoracic surgeons are used to using cardiopulmonary bypass every day, and thoracic surgeons don't do that every day. They do it maybe when they have a PH patient to transplant. It has made me wonder, though, if we are potentially going to change the lung allocation system in a way that might be detrimental to PH patients because they have the worst outcome nationally. Maybe we should be talking about designating centers of excellence for lung transplant for PH and directing those patients there preferentially.

**Dr Conte:** I think you can do that at the grass roots organizational level where you can verbalize that people with PH have done very well at these centers. However, from a national and a regulatory standpoint, there is no way that anybody is going to allow that to happen. I mean, just like I may refer someone with a certain disease to a physician who is very good, I can't say every patient has to go to that physician. I don't see how we can set it up nationally that PH patients are treated only at Michigan or Kansas or wherever. Normal referral patterns will be followed. Then if the people at those centers say "We're not great with pulmonary hypertension, you ought to go to Durham, because Vic Tapson and Duane Davis are there," so be it.

**Dr Tapson:** John, we want to talk about postop management. Do you and the transplant pulmonologists manage these folks together, postoperatively? Do you keep them for a certain amount of time and then gradually turn them over to pulmonary specialists? How do you handle this at Hopkins?

**Dr Conte:** It's a team effort all the way, starting with preoperative management. As the patients begin to deteriorate a little bit we discuss them more and more frequently, so that what I might accept as a usable lung for patients when they are just being plugged into the system will be different as their condition worsens. We communicate very frequently preoperatively. Postoperatively, it is a joint management effort from as soon as they get back from the operating room until they are discharged from the hospital. It is only after they are discharged from the hospital that the medical transplant team takes over. A couple of things I've learned over the years that I think benefit these patients are maintaining higher peak airway pressures to try and reduce the amount of interalveolar fluid, interstitial fluid, and we also tend to try to keep them a bit dry. If that means they require inotropes or vasoconstrictors, so be it. I think there is probably a 72-hour period in which pulmonary interstitial fluid tends to sequester, and we try to ride patients out through that period with higher airway pressures. I think that helps shift that equation of fluid leaving the vascular space and into the interstitial spaces and alveoli in favor of keeping it in the vascular space.

**Dr Tapson:** Do you think transplant teams tend to have more rigid criteria or scrutinize PH patients a bit more carefully than other lung transplant candidates because the risk of mortality may be higher? For example, in terms of age criteria?

**Dr Conte:** From my standpoint, no. We have an age cutoff of about 60 for bilateral lung transplant patients and I really don't think we've looked at whether they would have to have normal PA pressures or not. I operated on a 61-year-old woman about 2½ weeks ago who had sacroïdosis, but severe secondary PH, and she did fine. So, I think you have patients who occasionally might not do as well, which might lead you to think you shouldn't do anybody over age 50. But I think we individualize patients no matter what their disease process is, so no, we don't have anything special for PH patients.

**Dr Tapson:** How about for scleroderma and CREST patients? At Duke we've been fairly rigid about who we will do and we very meticulously screen everyone's esophageal function, for exam-

ple, since we have felt that reflux and aspiration can be a substantial problem after transplantation, especially with the associated further reduction in gastrointestinal motility that you often see. Bob and John, how do you feel about transplantation in CREST or scleroderma patients?

**Dr Frantz:** Well, I think that's an area where we have to be extremely careful. These patients may have involvement of the kidneys, which can be an issue in terms of the toxicity of cyclosporin after transplantation. Sometimes they can have coronary involvement as well. They may be undergoing immunosuppression, including sometimes steroids and other agents, and so the ability of their wounds to heal and their tissue integrity may be impaired. Some of them also have substantial problems with ulceration in their fingers and so forth that might be a risk for infection. I think we have to be very careful and certainly more selective in terms of those types of patients than we would be for a patient with primary PH.

**Dr Conte:** I think we do screen them very thoroughly, but I don't know if we are any more restrictive. I do think cutaneous ulcers, if they are active and are not healing, would rule them out. We've performed transplantation in several patients who had healed ulcers and they had no more wound problems than anybody else.

**Dr Frantz:** I agree with that. If their ulcers have healed, they should be OK.

**Dr Tapson:** What are the criteria for esophageal dysfunction? That's what I'm always told is what precludes them from being candidates.

**Dr Frantz:** If they have a patulous esophagus with very impaired motility on barium swallow, that is a great concern. I think all of us have seen problems with patients who have recurrent aspiration, and in postlung transplantation it can just be a disaster. So we tend to look at esophageal motility and often refer to our gastroenterologist to get a feel for how well the esophagus is functioning. If there is substantial esophageal dysmotility, that would be a concern for us in terms of transplantation.

**Dr Conte:** I agree wholeheartedly, but I should not even be speaking on this. Vic, you and your colleagues at Duke have led all of us in this regard. At the Society of Thoracic Surgeons meeting a few days ago, one of the Duke residents presented a nice series of patients where postoperatively people had esophageal wraps done and had improved outcomes and decreased OB, am I correct?

**Dr Tapson:** Yes, that's right. We have seen some significant benefit in that realm and Duane and most of my colleagues here have been very aggressive in that respect. Our transplant pulmonologists scrutinize these folks very carefully, as do your centers. As Bob suggested, if there is a very abnormal esophagus, there is significant concern going into transplant. So all of our patients get a very detailed evaluation with a swallowing study and manometry to make sure there are not substantial abnormalities. I am not so sure there is a clear cutoff point of who is

too severe to be transplanted in that respect.

**Dr Frantz:** John, I'd like to come back to the issues of heart-lung versus lung transplants and deciding when it is too late to do lung transplantation in patients with PH. For example, patients with ascites developing to a substantial degree, with a low output syndrome, with creatinine levels starting to climb and we are thinking we need to add dopamine on top of Flolan to keep them alive, can patients like that still do well with a double lung transplant? Or, if the right ventricle is really in great trouble, is it too late?

**Dr Conte:** Certainly I think the postoperative course is going to be a little bit more difficult and more protracted. But I have performed transplantation in five patients who had PH and were receiving inotropes, mostly dopamine, though two actually had dopamine and dobutamine, and all five of those patients did well. Now, one patient had a very protracted postoperative course and required inotropes for about a month, but I don't think she would have received a heart-lung transplant in time, given our organ allocation system. I think if this were a perfect world and we were taking things off the shelf, a patient like that would, with no question in my mind, be better served by a heart-lung transplant. But that's not reality. So I think if somebody has two lungs that are available and they have right heart dysfunction, they can get through just about anything.

**Dr Frantz:** In your hands that is probably true, but I am trying to drive at why it is that the national outcomes are not so good. Maybe it has more to do with this issue we talked about earlier in terms of the use of cardiopulmonary bypass and being familiar with it. It would be interesting to look in more detail at the patients who didn't survive lung transplantation and see what happened. Perhaps a multicenter registry effort could help us understand what the issues really are in terms of outcomes.

**Dr Tapson:** I certainly recall 1990 and 1991 when we performed transplantation in our first PH patients. Although some patients did well, we didn't have much experience with prostacyclin back then. We really respected this disease, as we do now, but we realized the mortality was high, particularly with more severe hemodynamics. I wonder if in some cases we were simply transplanting sooner and that now we have such faith in prostacyclin that we are more reluctant to say it is time. It is clear when someone's condition is deteriorating and hemodynamics are bad in the face of prostacyclin that it is time to transplant, but it would be ideal if there were some way we could recognize a bit earlier that it is time to transplant. I am not sure there is a simple way to do that. Here we are starting to look at the BNP levels in pulmonary hypertension, but we don't really know whether these can help predict if and when someone's condition is going to deteriorate. It would be nice to know when the right ventricle is going to finally buckle and it is time to transplant rather than waiting for someone to clearly worsen with Flolan.



We have tended to list quite early because the waiting times have just been remarkably long for lungs. This may be changing though, in the sense that the one benefit of the new proposed allocation system is that fewer patients with emphysema who have relatively preserved FEV<sub>1</sub>, or whose risk of dying is relatively low may undergo transplantation.—Dr Frantz

**Dr Conte:** I don't think we have that. Unfortunately, not enough people are studying that question to have good data. Certainly, we'll never get prospective randomized data, but I think good clinical data looking at those specific markers would be helpful.

**Dr Frantz:** We do have data from the PH literature published last year by Dr Sitbon indicating that, for example, patients who despite having received IV epoprostenol (Flolan) for at least 3 months can walk less than 380 meters in 6 minutes have a worse

prognosis compared to those who could walk farther. These patients who despite several months of IV epoprostenol are still functional class 3+ are clearly ones we have to be careful to move toward transplantation much sooner than somebody who can walk 500 meters with epoprostenol therapy.

**Dr Tapson:** One thing we haven't touched on is cases, for example, of congenital heart disease, where there are extraordinarily high pressures, but reasonably good right ventricular function. It is difficult to go just by the mean PA pressure, and in terms of timing for transplantation, the same sort of things apply for walk distance, RV function by echocardiography, and clinical right heart failure. We have had a few cases of transplantation based on significant hemoptysis that has developed and been relatively refractory. Any thoughts on congenital heart disease patients and the approach to transplant or timing?

**Dr Conte:** The teaching I grew up with was that patients with congenital heart disease will live forever and you don't have to rush as much as you would with those in whom disease develops later in life. I don't think I'd do anything markedly different in their evaluation, with one exception. For patients with congenital heart disease, I very frequently get an MRI or an angiogram or an aortogram looking for aortopulmonary collaterals. It's the thing that when you least expect it you're going to get into this friable little vessel that's going to bleed and cause problems, and that's the only thing I do from an evaluation standpoint.

**Dr Frantz:** Patients with congenital heart disease tend to have more gradual deterioration than primary PH patients in general. Some of it I think is if they have a residual right to left shunt it may offload the right ventricle and allow them to avoid problems with right heart failure for a longer period. So it can make it more difficult to know when to move to transplantation. For some of them the operative risk of transplantation is also substantial if they have had multiple prior operations and, as Dr Conte mentions, have collaterals in the chest so they bleed a lot at operation. They may have received multiple transfusions, so they have high positive panel reactive antibody titers that make it harder to identify suitable organs. It's a complex group that has to be treated in a very individual way, given the complexity and variety of congenital heart disease.

**Dr Tapson:** I'm sure that it is further complicated by the fact that

some of these patients cannot get by with a bilateral lung transplant and VSD repair, for example. Some require heart-lung transplantation, which makes timing more of a concern as well.

**Dr Conte:** The data as to which patients require heart-lung transplants and which can receive bilateral or single lung transplants with intracardiac repair are pretty sketchy. I've tended to look at supraventricular problems as repairable (ie, ASV, PDA), those types of things. Patients who have anything other than a very simple membranous VSD are those who need a heart-lung transplant. Those with tetralogy, single ventricles, or even more complex muscular VSDs require heart-lung transplantation.

**Dr Tapson:** Anything, John, along the lines of right ventricular mechanical assist devices in the surgical realm that might buy time or help postoperatively in these patients?

**Dr Conte:** We have been looking at a percutaneous right ventricular support system from a company called A-Med that has recently been bought out by Guidant and it's something we certainly will consider, not just for this patient population but for those who undergo regular cardiac surgery and have right ventricular dysfunction.

**Dr Tapson:** So that is on the horizon?

**Dr Conte:** Right.

**Dr Tapson:** Great. I don't think we need to talk about postoperative issues in any detail since eventually these folks tend to be similar in terms of management of immunosuppressive therapy and the like. Any other issues we want to talk about? Anything else about the UNOS allocation or anything else that may be worth mentioning in more detail?

**Dr Frantz:** I think it's important that we talk a little bit about that because the new guidelines for lung allocation are in flux. I am trying to have some impact on that discussion by bringing to the attention of the UNOS committee that the data they are using looking at outcomes do not reflect outcomes at some centers such as ours and Hopkins. Essentially the UNOS subcommittee has been suggesting that we give priority to patients with PH who can walk less than 150 feet, not meters but feet. That's less than 50 meters. Those patients are moribund. If we went in that direction, we might well cause more harm than good by transplanting in those who are extremely end stage. I am hoping we will be able to work out a recommendation that allocation be made for patients with PH who can walk less than some other distance. We might pick something like 380 meters based on Dr Sitbon's data or 300 meters, or something like that. It concerns me that the current system appears to make it difficult for patients with PH unless they are extremely impaired. I shouldn't say the current system. I should say the current *proposed* system. I don't think it will turn out that way because I think we will be able to modulate the recommendations before they become working recommendations.

**Dr Tapson:** Are you folks seeing the use of septostomy very often in these PH patients?

**Dr Frantz:** It is a situation where, if patients are doing poorly, with right heart failure despite epoprostenol, then it is worth thinking about. The issue is that if they have systemic desaturation on a regular basis, then you are going to aggravate that with septostomy. Many patients for whom I have considered it have already had systemic stats that are low, and I worry that I am just going to aggravate their hypoxemia. On the other hand, if the systemic stats are adequate, it can be considered, but in the very patients where we think about it where the right atrial pressure is quite high, the cardiac index is low, it is a higher risk group for not doing well with it. So, honestly, we've not performed it here in any of these patients receiving epoprostenol.

**Dr Tapson:** Any strong feelings about exactly when to list? I should mention that we usually used to list people when they were initially diagnosed with PH and learned that that is too soon in most cases. We generally list now if someone has to have prostacyclin therapy and sometimes sooner than that.

**Dr Frantz:** We have tended to list quite early because the waiting times have just been remarkably long for lungs. This may be changing though, in the sense that the one benefit of the new proposed allocation system is that fewer patients with emphysema who have relatively preserved FEV<sub>1</sub> or whose risk of dying is relatively low may undergo transplantation. This might free up some donor lungs to help patients in even greater need. A very large number of patients with emphysema receive transplants at variable times in their disease course, so we have felt the need to list our PH patients very early.

**Dr Tapson:** Is there any penalty for that? Is there some reason centers might not want to list people and then inactivate and have a large number of patients on their list inactive?

**Dr Frantz:** Well, it is a bit cumbersome because you have this list that has people on it who aren't really ready to proceed with transplantation. It also makes your waiting times look really long if you are listing people and then deliberately not doing transplants because they are too well. Under the proposed new system there may be listing criteria at the time of listing where those numbers influence priority, so if you list people early who have relatively preserved walk distances, they are going to be low priority for transplant anyway, and you may be better off waiting until they meet higher priority scores. But we need to see how the rules are going to work.

**Dr Tapson:** Bob, you gave an example of a patient regarding whether you should do a heart-lung transplant or just lungs, someone with advanced right ventricular failure and a lot of ascites. How much does that ascites bother you? Do you worry that at some point it is more than just fluid overload, that it is turning into cardiac cirrhosis and you are transplanting in someone who may now have substantial liver dysfunction, too?

**Dr Frantz:** This issue does come up sometimes. It probably comes up even more in patients who do not have primary PH. Sometimes other patients who have restrictive cardiomyopathy or are waiting for heart transplantation have ascites for a couple of years and their LFTs are off a bit. In some of those

patients we have done a liver biopsy to make sure it is essentially a noncirrhotic liver, in order to be confident that we weren't going to have a problem in that way. For most PH patients we have found that if we treat them with enough inotropes and really treat them vigorously, we can usually control the ascites. If we couldn't control it, I would be quite worried and might consider liver biopsy in some situations. I have

actually not encountered that yet, where I couldn't control the ascites with inotropes and diuretics in a primary PH patient.

**Dr Tapson:** Bob and John, I'd like to thank you both for taking the time to discuss these issues for *Advances in Pulmonary Hypertension*. I look forward to our future interactions.

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## Profiles

(continued from page 3)

strain. We did it by gradually constricting the pulmonary artery with a band, tightening it every week or two until the right heart failed just as it does in the clinical situation. Then we released the band, dropping the pressure to more normal in these dogs and we studied how quickly the right ventricle recovers if you take the load off of it. This was a prelude to considering lung transplant rather than heart-lung transplant and we found that in these dogs there could be very rapid recovery of function in the right ventricle."

This led Dr Cooper and colleagues to rethink their strategy, namely, that they did not need to perform both a heart and a lung transplant. This meant that many more organs would be available for additional patients. "You could do a lung transplant and the heart would recover. We found that the heart undergoes remodeling, the thickened right ventricle returns to a more normal shape and thickness." Dr Cooper recalls that a

single lung transplant for PH was performed on November 21, 1989, in a woman who survived and lived for a number of years. "We do have good results for single lung transplant for PH even though a bilateral is done most of the time now. Fortunately, medical management of these patients has greatly improved, so the number of patients coming to transplant has diminished somewhat," he added.

"I've always felt that lung transplantation for PH is the most critical, most demanding surgery—not so much from a technical standpoint, although it does involve the use of cardiopulmonary bypass, but in terms of postoperative care of the patient. Therefore, the best results will be obtained by centers that are very experienced. The problem is, if you have too few centers of excellence, you are not accessible to the patient."

The program at Barnes Hospital, however, is exceptional in that the hospital assumes the responsibility for the patient while he or she is on the waiting list. "In the long term, successful outcomes for lung transplantation, particularly for PH, require an experienced team," said Dr Cooper.

## *In the Next Issue*

### Portopulmonary Hypertension

- Understanding the natural history and pathophysiology
- Screening and current diagnostic criteria
- Therapeutic options
- Liver transplant considerations and outcomes

# 2004 Program Announcement: June 1, 2004, Deadline



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