References


Referral for Lung Transplantation

A Moving Target

Successful human lung transplantation has evolved significantly since 1963, when the first lung transplant recipients lived only a few days after transplantation. Changes in surgical techniques and advances in immunosuppressive therapy have been credited with the advancing lung transplantation, making it an invaluable tool for the management of advanced respiratory diseases. This is apparent by the growing number of transplants performed each year and by the increase in the number of patients listed for transplantation. A gross disparity exists, however, between the number of potential recipients and the number of donor organs available, resulting in many patients dying while on the waiting list.2,3 Due to long wait times, transplant physicians are no longer just faced with trying to improve survival after transplantation, but are now facing the challenge of improving a patient’s chances of survival while on the waiting list for transplantation. As a further challenge, the natural history of various advanced lung diseases vary and are somewhat unpredictable. This is especially true of diseases for which we do not have adequate prognostic scales, unlike cystic fibrosis or idiopathic pulmonary fibrosis.4,5 As a result, predicting survival in specific advanced pulmonary diseases is one of the major issues confounding referral for transplantation. As waiting list times appear to be increasing from 24 months to a median of 46 months, questions are now being raised regarding the appropriate disease-specific time for referral to ensure maximum survival before and after transplantation.3

Much attention has been given to better defining lung transplant candidacy guidelines in order to...
allow more efficient and equitable distribution of organs and to improve survival. Recent strides toward a "lung allocation score" are laudable efforts in this direction. However, much less attention has been given to the timing of referral of these patients to a lung transplant center for initial lung transplant evaluation. In this issue of CHEST (see page 1006), Nathan examines this issue in light of the 1998 lung transplantation candidacy guidelines set forth by the American Thoracic Society in conjunction with the European Respiratory Society and the International Society for Heart and Lung Transplantation. The author advocates earlier referral to a lung transplant center in the best interest of patients with advanced respiratory diseases. All physicians who evaluate patients for lung transplantation have seen patients cannot be placed on the waiting list because they are referred too late in the course of their illness and are too sick and out of the "lung transplant window" by the time they are seen. In addition, such referral places the patient with an advanced lung disease in the care of a physician who has experience dealing with such patients, has the resources of a large tertiary care center at his/her disposal, and may be aware of potential therapeutic options from which the patient may benefit. Early referral also allows for appropriate processing and management of issues prior to listing, may improve survival during the waiting period, and may alleviate the patient’s and family’s anxiety and distress as they deal with their illness.

Early referral poses challenges and creates potential inequities. For example, some patients are listed early in the course of their disease in order to accrue waiting time. Early referrals may also pose an unnecessary burden for the transplant center utilizing resources (including physician and coordinator time) in evaluating patients who may not be appropriate for transplantation and diverting these away from appropriate patients, which could delay their evaluation. Another sometimes overlooked factor is the tremendous regional variation in wait times from a few months at some centers to years at others. In addition to priority on the list, waiting time on the lung transplant list is the end result of a number of local and regional factors that may be very difficult to modify but which need to be addressed. Such factors include the number of centers performing the procedure in a given geographic area, available organs in a given population base, and the rate of consent to donate. Other center-specific factors include how aggressive the center is in pursuing "marginal" donors, listing candidates considered high risk by other centers, and the level of expertise and comfort with combined procedures, such as transplant with bypass surgery or valve replacement, or transplanting more than one organ.

Yet another challenge to optimizing referral for lung transplantation is that survival prediction modules based on spirometry alone are inadequate. Indeed, fuller prediction requires more comprehensive modules that include a variety of parameters including subjective breathlessness, weight loss, exercise tolerance, hospitalizations, and lung morphology in reviewing diseases such as COPD and idiopathic pulmonary fibrosis. The role of newer therapies such as lung volume reduction in COPD and the use of prostanoids and endothelin antagonists in pulmonary arterial hypertension should be included in such a model. There is a clear need for more studies to develop accurate, disease-specific predictors of progression. For example, measures such as the 6-min walk test and the brain natriuretic peptide in assessing pulmonary arterial hypertension severity could be used in combination with other prognostic parameters to determine response to therapy and timing for referral. Articles such as this one by Nathan will encourage studies that shed new light on the rates of progression and expected survival for various advanced respiratory diseases and find better surrogate markers of disease progression. Another benefit may be increased dialogue in the lung transplant community to better define guidelines for referring physicians in the context of emerging developments, e.g., new data regarding the natural history of advanced diseases such as idiopathic pulmonary fibrosis, new disease-specific survival analysis, and possible alternative therapies that may delay the option for transplantation in certain disease states such as COPD and pulmonary arterial hypertension. The new lung allocation strategy may, over the years, help improve our understanding of this and other related issues. Successful lung transplant centers usually have a close working relationship and partnership with their referring physicians to promote better care for their patients and appropriate, timely referrals. Education of physicians and other health-care providers caring for these patients is integral to this process.

Overall, we feel that the current general recommendation that evaluation for lung transplantation should be sought when activities of daily living are significantly impaired may be one that unintentionally causes patients to be referred too late in the course of their disease, thus impacting survival on the waiting list and after transplantation. Timely referral based on more comprehensive and accurate prediction models would help optimize patient out-

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comes and resource utilization and allow patients to make a more informed choice about their options.

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Etomidate for Endotracheal Intubation in Sepsis

Acknowledging the Good While Accepting the Bad

We would like to commend Dr. Jackson (see page 1031) on both his historical review and critical appraisal of the use of etomidate as an anesthetic induction agent. This appraisal is a good summary of the debate that has occurred over the past quarter century in regard to the safety of etomidate as an anesthetic induction agent. The observations of Led-ingham and Watt in the early 1980s indicated that etomidate should not be used for long-term sedation in the ICU due to the mortality cost incurred from long-term adrenal suppression. The effect of etomidate on adrenal function is both dose-dependent and cumulative. A single dose of etomidate will blunt the adrenocortical axis for up to 24 h. The effect of short-term suppression of adrenal synthesis on patient outcome is, however, less clear. This clinical question, although seemingly simple, is quite complex. The net effect of etomidate as an anesthetic induction agent is the sum of several factors. Etomi-date has several properties, which makes it, at least in theory, a good first-line anesthetic induction agent. The dose required to achieve unconsciousness is relatively predictable. This hypnotic effect is much more predictable than that with benzodiazepines. The onset of action is fast, essentially in one arm to brain circulation. In addition, etomidate has a short duration of action. Etomidate does not cause histamine release, which is a factor contributing to its relative hemodynamic stability (the reader is referred to an in-depth clinical review of the pharmacology of etomidate). One would expect that these factors would result in a mortality benefit; however, the magnitude of this benefit is unknown. The major concern regarding the use of etomidate is transient adrenal suppression. The unpublished subgroup analysis data presented in the study by Annane et al may provide us with a glimpse of the cost resulting from the adrenal suppression by etomidate. The fact that 68 of the 72 patients (94%) who received etomidate for the induction of anesthesia did not respond to a high-dose cosyntropin stimulation test, is consistent with other published reports of adrenal insufficiency 12 to 24 h after the administration of etomidate. The data from the study by Annane et al seems to indicate a significant mortality cost for etomidate anesthetic induction in septic patients. The mortality rate in the placebo-treated group was 75.7% vs 54.8% for the corticosteroid-treated group. These data indicate that the adrenal insufficiency of sepsis should be treated with the administration of stress doses of corticosteroids. The continued use of etomidate for anesthesia induction would be a clinical conundrum if this mortality effect persisted despite corticosteroid administration. From the available data, we have a presumed, but have not yet measured, mortality benefit incurred from the beneficial effects of etomidate as an anesthetic induction agent. The mortality cost of adrenal suppression by etomidate anesthesia induction seems to be completely offset by corticosteroid administration in those patients who show evidence of adrenal insuf-