that examining cost effectiveness was planned for the future.

What happens in medicine is quite predictable. Once a good and useful idea comes to light and is accepted, it is often accepted with religious fervor. The pendulum swings to the extreme. It is not until a lot of effort, time, and money is spent that people come to realize the inappropriateness of the extreme position taken. The same is true of asthma education. It is now 5 years since the initial NHLBI workshop on asthma education and it is time to reevaluate. A full program of asthma education to all individuals with asthma is not a likely cost-effective avenue, and is not necessary for a large population of people with asthma. Simple brief information along with instructions on how to use inhaled medication is possibly all that is necessary in many people with asthma. The few individuals with moderate-to-severe or labile asthma should be targeted for a more extensive program. The most significant problem relates to trying to reach the “difficult-to-reach” individual who is unlikely to participate in present programs and who is likely to belong to a lower socioeconomic group. What is required is needs assessments of such individuals, novel methods of disseminating information that should incorporate a behavioral component, and access to medications without inducing financial hardship. The allocation of resources needs to be re-evaluated, duplication needs to be reduced, and populations need to be targeted.

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Bronchiolitis Obliterans In Lung Transplant Recipients

The “Thorn in the Side” of Lung Transplantation

There are several clinical conditions associated with bronchiolitis including inhalational injury, infection (particularly viral), and drug or chemical exposure. In addition, bronchiolitis can be idiopathic and develop without a clear preceding cause. Clinical associations with idiopathic bronchiolitis include bronchiolitis with connective tissue disease, bronchiolitis obliterans with organizing pneumonia (BOOP), and bronchiolitis associated with bone marrow, heart-lung, and lung transplantation.

In the early era of heart-lung transplantation (HLT), up to 50% of recipients developed bronchiolitis obliterans, a major cause of morbidity and mortality.1 With the use of increased immunosuppression, including corticosteroids, cyclosporin A, and particularly with the addition of azathioprine, the incidence of bronchiolitis decreased to approximately 20%,2 and disease progression was slowed.3 In

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the mid-1980s, it was thought that single lung and double lung transplant (SLT and DLT) recipients would experience a lower incidence of bronchiolitis than HLT recipients due to the smaller amount of immunologic material transplanted. However, as more SLT and DLT procedures were performed and survival extended, it became apparent that the occurrence of bronchiolitis in lung transplant recipients was not reduced. A 20 to 50% incidence of bronchiolitis has been reported by the majority of large lung transplant centers.4,7

The pathogenesis of bronchiolitis following lung transplantation remains unknown. The majority of available data suggest that this process is immunologically mediated against the epithelial cells of the pulmonary airways6 and is most likely a manifestation of chronic graft rejection. Supportive evidence for an immunologic etiology of bronchiolitis comes from several sources. The Pittsburgh group has shown a relationship between donor-specific alloreactivity (as assessed by primed lymphocyte testing of cells from bronchoalveolar lavage fluid or transbronchial biopsy lymphocyte culture), and the eventual development of bronchiolitis.8 Several groups have documented increased expression of class II HLA antigens in the donor airway epithelium of those patients with bronchiolitis.1,9 The Papworth transplant group and others have shown that those patients who developed more frequent, more histologically severe, and more persistent acute rejection were at an increased risk for eventual development of bronchiolitis.4,10 Previous studies support an immunologic relationship to the development of chronic graft rejection or bronchiolitis in bone marrow transplant and other solid organ transplant recipients. These studies have led investigators to support a similar etiology in those patients receiving lung transplants.

Other proposed pathogenic etiologies of bronchiolitis following lung transplantation have included infectious agents such as viruses (particularly cytomegalovirus [CMV]) and ischemic airway injury postoperatively. The association of CMV with bronchiolitis is a well-described occurrence in nontransplant patients.11 Regardless of the specific etiology, it appears that inflammation of some type is a key predisposing factor to the development of lung transplant-related bronchiolitis.

Bronchiolitis following lung transplantation has been defined clinically by an obstructive pulmonary function defect and histologically by obliteration of terminal bronchioles. Therefore, many investigators in the field of lung transplantation refer to this process as obliterative bronchiolitis (OB) as opposed to the more common proliferative bronchiolitis seen in other bronchiolitic clinical syndromes that present with restrictive physiology and peribronchial fibrosis histologically.

Clinically, OB has been reported anytime after the second month posttransplantation, but the typical onset is 8 to 12 months following surgery.5 The onset of OB may be heralded by an upper respiratory tract infection and can be mistakenly treated as such. Sometimes patients may present asymptotically but with gradual obstructive dysfunction on pulmonary function testing. Chest radiographs are usually unchanged from baseline and are not helpful in the diagnosis of OB. Transbronchial lung biopsy can be used to confirm the diagnosis of OB, however, the sensitivity for detection of OB by transbronchial biopsy in various studies has ranged from 5 to 100%.12 Our bias is the more severe the OB, the less likely the chance of retrieving many bronchioles in the transbronchial biopsy specimen.

Because of the difficulties in the histologic diagnosis of bronchiolitis in lung transplant recipients, clinical criteria are often used. In 1993, a committee from the International Society for Heart and Lung Transplantation defined and standardized a clinical staging of chronic graft dysfunction secondary to progressive airways disease for which there is no other identifiable cause, referred to as the bronchiolitis obliterans syndrome (BOS).13 In the BOS system, stage 0 or no OB is defined by an FEV1 of 80% or greater of baseline value; stage 1 or mild OB is defined by an FEV1 of 66 to 80% of baseline; stage 2 or moderate OB is defined by an FEV1 of 51 to 65% of baseline and stage 3 or severe OB is defined by an FEV1 less than 50% of baseline value. Each stage listed above can be subcategorized “a” or “b” reflecting pathologic or no pathologic evidence of obliterated bronchioles, respectively.

The article in this issue of Chest by Nathan and coworkers (see page 967) describes three distinct clinical subgroups of OB based on rates and patterns of progression. In addition, the authors report on yet an earlier way to detect clinically, or at least suspect, the diagnosis of OB by a drop in FEF25-75%. In the first group, OB was characterized by a rapid onset of obstructive dysfunction (mean decrement in FEV1 of 44% over a mean 7-month period) followed by a rapid progressive course. The second group had an initial rapid decline in lung function comparable to the group above, followed by stabilization (a mean FEV1 decline of 35% over a mean 9-month period). The third group had an insidious onset of OB (as defined by a mean decline in lung function of 20% FEV1 over a mean period of 11 months) followed by a relatively stable course over a mean of 10 months. Although the number of patients in Nathan’s study is small, and the data retrospective, we and investigators at other transplant centers have observed similar clinical patterns of OB.
Abernathy and others have described two histologically distinct patterns of OB in HLT recipients, one with acellular concentric fibrosis of the terminal bronchioles and a second with focal, cellularity extending into the distal alveolar spaces. The report by Nathan, and colleagues would have given us additional insight into the nature of this disease had they attempted to correlate the rates of progression they observed with the histologic subsets reported by Abernathy et al. 

Similarly, in the Nathan report we are told that all patients were treated with triple drug maintenance immunosuppression consisting of cyclosporin A, azathioprine, and prednisone. Considerable variation can occur in individual doses of each of these drugs. In fact, it is our practice as well as the practice of other transplant programs to increase these maintenance drugs to their maximally tolerated levels when BOS is diagnosed. We have been shown that lympholytic therapy does not account for the differences in OB progression among Nathan’s groups. Could individual differences in maintenance immunosuppressants account for the differences in these patterns of progression? As discussed previously, episodes of acute rejection and CMV infection have been identified as risk factors for the development of OB. Could differences in the frequency or severity of acute rejection or CMV or both account for the differences that Nathan and coworkers observed? 

The investigators in this issue of Chest noted some transient improvement following administration of solumedrol or lympholytic agents. Unfortunately, it is becoming apparent that neither corticosteroid nor lympholytic treatment of this disorder is beneficial. Although an initial remission may occur, relapse is nearly universal. Regardless of the presentation and subsequent clinical course of BOS, the eventual outcome is almost always disability or death due to either respiratory failure or infection (related to augmentation of immunosuppression). Clearly the only hope for elimination of this problem is to definitively determine the cause or causes of OB and then to practice preventive therapy. An alternative approach would be to improve treatment of OB once it manifests either with currently available immunosuppressive agents or more likely with alternative immunosuppressive therapy. It would be interesting to see whether the three patterns of OB described in this issue of Chest could have different etiologies, different prevention strategies, and different treatment responses.

A final issue to consider is retransplantation for debilitating OB. Early data on retransplantation for debilitating OB have reported rapid recurrence of OB in the new lung graft. A recent multicenter study of retransplant procedures for OB has documented a 1-year survival of approximately 35%. Survival did not differ depending on original diagnosis, indication for retransplantation, or the type of retransplantation procedure performed. Retransplantation raises several questions: (1) Should a patient who has already received a donor lung be entitled to receive a second lung graft when there are over 1,000 patients in the United States currently awaiting a donor lung? (2) In today’s society of limited health care expenditures, is this costly procedure with a relatively low 1-year survival rate justified?

In summary, the last decade has seen an explosion in the number of lung transplant procedures performed worldwide. Several of the early problems with these procedures such as anastomotic complications, poor immunosuppression, and inadequate prophylaxis and treatment of infection, have been ironed out. The major conundrum in lung transplantation is the development of obliterative bronchiolitis. Hopefully, the near future will bring a solution to the “thorn in the side” of lung transplantation.

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