0272-5231/97 $0.00 + .20

PROPHYLAXIS POST-TRANSPLANT

The Role of Monitoring Surveillance Bronchoscopy and Antimicrobials

Paul A. Corris, MB, FRCP

Success in pulmonary transplantation depends upon careful monitoring of both graft and patient in order to identify problems at an early stage, when treatment can influence outcome. Many strategies have been developed including the use of prophylactic therapy, in particular, antibacterial and antiviral agents and, more recently, antifungal agents, to help prevent infections in patients identified as susceptible. The strategies adopted to monitor both patient and graft function vary according to institutional practices because prospective studies to evaluate the efficacy of specific strategies are lacking in most cases. Strategies employed often differ according to the time elapsed after surgery, so this discussion considers surveillance and prophylaxis under immediate, early, and late periods after transplantation.

IMMEDIATELY POSTOPERATIVE

The immediate postoperative period is defined as the first 24 to 48 hours after surgery.

Monitoring

When a lung transplant recipient is first transferred from the operating room to the intensive care unit (ICU), continuous hemodynamic monitoring via arterial, central venous, and Swan-Ganz catheters is usually employed. Early graft dysfunction may occur in about 20% of patients because of reperfusion injury, which leads to endothelial dysfunction.[15, 32] Continuous monitoring of the mixed venous oxygen saturation and arterial oxygen saturation, together with regular estimates of arterial blood gases, provide early markers of graft dysfunction. Chest radiographs are performed at least daily in the initial postoperative period. Reperfusion injury may be suggested by diffuse infiltrates. Nitric oxide recently was shown to be of benefit in the early management of reperfusion injury in transplanted lungs.[7] One special complication of single lung transplantation in recipients with emphysema involves overinflation of the native lung, leading to mediastinal shift and compression of the transplanted lung. That often appears in early postoperative radiographs and is accompanied by a reduction in oxygen saturation and, sometimes, rising hypercarbia on blood gas analysis. The early use of a double-lumen endotracheal tube with sequential lung ventilation may be required.[9] Alternatively, some centers recently reported volume reduction of the native lung as another approach to the problem.

From the Department of Medicine, University of Newcastle upon Tyne, Freeman Hospital, United Kingdom

A perfusion lung scan within the first week or so post-transplant is a useful tool in assessing function of single lung grafts. The graft should have immediate preferential perfusion compared with the native lung; evidence of hypoperfusion of the new lung should alert one to the probability of a vascular anastomotic stricture or thrombosis.

Infections and Their Prophylaxis

Bacteria and Fungi

Lung secretions may be obtained by gentle suction or lavage from the donor lung or lungs prior to implantation to provide specimens for Gram stain and culture.[23] Bronchial tissue trimmed from the donor bronchus also may be sent for culture. That practice allows for the identification of colonizing bacteria or fungi in the donor lungs, permitting rational changes to routine antimicrobial prophylaxis.[20] Routine immediate prophylaxis with antimicrobial agents—until donor data are available—is practiced almost universally and varies according to each unit and the underlying lung disease of the recipient.

It is our policy, for example, to use flucloxacillin and metronidazole antibiotic prophylaxis in recipients with nonsuppurative lung disease because the potential for occult aspiration is high in the donor. The flucloxacillin is continued for 48 hours and the metronidazole until the bronchial anastomosis has been inspected at 7 days.

Patients with cystic fibrosis or bronchiectasis who are colonized with pseudomonads require antipseudomonal prophylaxis. The rational choice is determined by the sensitivity of the colonizing organism identified immediately preoperatively, as well as the patient's previous history of response to various antibiotic agents.

Recipients with airways colonized by *Aspergillus* are generally given prophylactic antifungal treatment to reduce the incidence of disseminated fungal infections as well as infections at the anastomotic site. As noted subsequently, the risk of dissemination is of particular concern in patients with a complicated postoperative course. Nebulized amphotericin, 20 mg twice a day, can be used. Other options include low-dose intravenous amphotericin, liposomal amphotericin, or itraconazole. Itraconazole has some drawbacks in the early postoperative period because its absorption is difficult to predict with an unpredictable stomach pH, and it may have a significant impact on cyclosporine levels. Some donor lung lavages show evidence of *Candida* and prophylactic use of fluconazole is often used in that case. The risk of serious systemic disease, however, appears to be less with *Candida* spp. than with *Aspergillus* spp.

If early complications necessitate continued mechanical ventilation beyond 48 hours, nebulized antibiotic agents—e.g., colistimethate sodium or tobramycin—may help prevent colonization of the lungs with gram-negative organisms.[30] In the immediate postoperative period, bacterial and fungal infections predominate and are the most important infectious complications.

Other Forms of Prophylaxis

Pain control is extremely important in the immediate postoperative period because the aim is to extubate the patient as quickly as possible. In this period, physiotherapy and early rehabilitation are important to reduce pooling of secretions in the lower respiratory tract, thereby reducing the risk of pneumonia. Many patients benefit from effective analgesia via an epidural catheter to prevent chest pain associated with physiotherapy and coughing. The importance of adequate pain control to prevent early infectious complications cannot be overstressed.

EARLY

The early postoperative period is defined as the first three months following transplantation.

Monitoring

Imaging

After extubation, patients may be transferred from the ICU to a step-down ward. Central venous and arterial catheters are no longer necessary and oxygen saturation can be monitored via an oximeter. Daily chest radiographs during the first week can be monitored for ill-defined perihilar infiltrates and septal lines, which suggest acute rejection. Pleural effusions may occur in addition to parenchymal changes. If clinical dete-

rioration is seen, additional chest radiographs should be performed, as indicated, during the first week. After the second week, the frequency of radiographic and other studies can be adjusted according to the patient's clinical status. It should be remembered that the chest radiograph shows normal appearances in 26% of cases of acute rejection during the first month.

Lung Function

Spirometry should be performed as soon as practicable after surgery, often before discharge from hospital. Formal testing in the laboratory, including vital capacity, forced expiratory volume in 1 second (FEV_1), total lung capacity, and diffusing capacity using the single-breath method, should be performed. Some groups make use of a hand-held, battery-operated spirometer and teach patients how to monitor and record their own lung function.[5] That enables patients to self-monitor their lung function on discharge from hospital. Most groups using this method of self-monitoring have patients report any 5% to 10% drop in FEV_1 that is sustained for at least 2 days on the assumption that a sustained drop in FEV_1 may indicate the onset of a complication—either infection or rejection. The Papworth group[27] has reported that a 5% reduction in FEV_1 or vital capacity is a sensitive and specific marker of lung rejection or infection. In the author's experience, however, there is often considerable variability in measuring and recording home-based pocket spirometry, despite clinical stability, and that impairs its effectiveness as a potential monitor of graft function. Although there is no doubt that a sustained drop of 5% to 10% in any spirometric parameter on formal lung function tests is a sensitive and specific mark of graft dysfunction that warrants further investigation, even in the absence of clinical symptoms or chest radiographic abnormalities,[17, 27, 28] it is not clear that daily home spirometry is the most effective or efficient monitoring system.

Over the first 3 months, the use of formal surveillance lung function testing has certainly aided the early diagnosis of pulmonary infection or rejection in this patient population, and it is the most effective early indicator of graft dysfunction apart from patient symptoms. It should be appreciated that over the first 2 to 3 months following transplantation, the FEV_1, vital capacity, and diffusing capacity should rise progressively as the lung and chest wall recover from the effects of reperfusion injury and surgical trauma. That explains why relatively small but sustained drops in lung function during the early period are important. The resolution of dysfunction on treatment can also be monitored and confirmed by repeated lung function testing.

Bronchoscopy

Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB) has a central role in surveillance of the lung allograft. In the first 3 months after lung transplantation, bronchoscopy should be carried out in response to a deterioration in clinical condition, a new infiltrate on chest radiograph, or a drop in lung function detected spirometrically. Although TBB may have a 15% to 28% false-negative rate for rejection,[29, 35] it remains the gold standard, in practical terms, for diagnosing acute lung rejection.[13] It is generally believed that at least six biopsies should be taken and serial sections should be reported by a pathologist familiar with lung transplant pathology, and graded using the guidelines established by the International Society of Heart and Lung Transplantation.[37] Drops in lung function in the first 3 months, of course, may be caused by lung infection. A number of studies[16, 34] have shown that infection and rejection are seen commonly (and sometimes concurrently) in the first 3 months after transplantation. For those reasons, it is important to perform BAL at the same time as TBB to provide samples for microbiologic examination. Studies should include cytology and culture for bacteria, fungi, and viruses.

The diagnosis of cytomegalovirus (CMV) infection may be facilitated by a combination of different methods. Excretion of virus in BAL fluid can be detected by immunofluorescence, by direct early antigen fluorescence on inoculated cell lines, and by culture. Serology is largely unhelpful, although the appearance of immunoglobulin in previous antibody-negative recipients is helpful. Detection of antigenemia by immunohistochemical demonstration of CMV_{pp65} antigen in leukocytes from peripheral blood recently was described and may become increasingly useful in detecting significant infection.[8] Cytology may demonstrate the pathognomonic CMV-infected cells. The gold standard for diagnosis of CMV pneumonitis remains biopsy, in

which characteristic inclusion bodies may be seen and the level of associated inflammation can be gauged. That reminds us that TBB specimens as well as BAL fluid should always be examined for the presence of infection, with particular emphasis on excluding diagnoses of either *Aspergillus* or *Pneumocystis carinii*. Sections of TBB should always be kept for groccolt, methenamine silver, and methyl green pyramine stains, together with Ziehl-Neelsen and rhodamine auramine fluorescence studies when indicated clinically or morphologically. Finally, BAL fluid should be examined for *P. carinii*, when indicated, using a specific monoclonal antibody.

The Role of Surveillance Bronchoscopy

Although there is little controversy over the role of bronchoscopy with TBB in the investigation of a drop in lung function or deterioration in clinical state, the role of bronchoscopy with TBB in patients without pulmonary symptoms and with satisfactory lung function—i.e., true surveillance bronchoscopy— has not been established. Large hospital centers have differing policies with respect to surveillance bronchoscopy.[3, 10, 13, 29, 31, 39] Moreover, the timing of surveillance studies varies from center to center. Communications from St. Louis, Stanford, and Pittsburgh reported the results of 90, 133, and 255 surveillance procedures, respectively. All three reports detected a high incidence of positive findings (31%–57%) in the procedures. Interestingly, in the report from Pittsburgh, the majority (68%) of positive results occurred in the first 6 months of a surveillance program that continued over 2 years from transplantation. Our unit has demonstrated an incidence of 20% or greater unexpected A2 rejection on routine surveillance biopsies taken at 1 week and 1, 3, and 6 months after transplantation. It is our policy (as it is at most institutions doing surveillance studies) to treat such episodes with augmented immunosuppression, as one would for an acute symptomatic rejection episode.

It is not clear, however, from any of the reported studies whether treating positive results impacts patient outcomes. Centers that interpret the literature as being nonsupportive of performing surveillance TBB note that the literature does not show this practice has reduced the subsequent risk of developing bronchiolitis obliterans (OB) at a later stage. Although that is true, it must be noted that an effective surveillance program requires that effective treatment be available in addition to the ability to identify and detect the occult rejection in the first place. The introduction of newer potentially more effective immunosuppressive agents in lung transplantation, such as tacrolimus,[18] mycophenolate mofetil,[33] rapamycin,[25] and leflunomide[25] may eventually confirm the value of surveillance in reducing the incidence of OB. At the moment, however, the role of surveillance biopsy remains uncertain in terms of value, frequency, and how long one ought to continue the practice after transplantation.

Infection Prophylaxis

Infections, including bacteria, fungi, viruses, and protozoa, remain common causes of morbidity and mortality in the first 3 months after lung transplantation.[4]

Viruses

CMV is the most common viral pathogen. A recipient negative for CMV antibody who receives an organ from an antibody-positive donor has the potential for most severe disease.[36] Antibody-positive patients receiving lungs from either antibody-positive or negative donors also may develop CMV disease, but the risk is not as great as in the former category. Antibody-negative patients receiving lungs from antibody-negative donors have a negligible risk, providing they receive seronegative blood products. There is much literature concerning the prophylaxis and management of CMV disease in lung transplant recipients. The high incidence of CMV disease in antibody-negative recipients of lungs from positive donors has led to a number of strategies for prophylaxis and, because no good prospective studies have been done comparing prophylactic regimens in large groups of patients, current practice varies widely. The following are a few examples of reported regimens. First, some groups, including our own, use intravenous high-titer anti-CMV immunoglobulin given weekly (or at other intervals) for 6 to 8 weeks post-transplantation until the patient's serum converts.[12]

Second, ganciclovir is often given at varying doses for varying periods from 14 days to 6 weeks or more post-transplantation.

Each of these regimes has its advantages and disadvantages. Hyperimmune globulin allows seroconversion to occur, making troublesome recurrence of infection unlikely. But it is expensive and patients may develop a flu-like illness around the time of seroconversion. Ganciclovir is an effective agent but has significant toxicity to bone marrow and reproductive organs, particularly in males. It is viristatic rather than viricidal, so infection may recur when prophylaxis is discontinued. One advantage of delaying the onset of CMV disease is that immunosuppression is usually less at the later date, so the host may be more capable of dealing with the pathogen. Nevertheless, prophylactic ganciclovir may fail to prevent CMV disease.[1] In some centers, combination prophylaxis with hyperimmune globulin and ganciclovir is used.

A third approach is to use pre-emptive therapy with ganciclovir based on weekly testing for antigenemia in at-risk patients. It is conceptually more scientific but, by nature, relies on repeated blood sampling and the availability of a reliable antigenemia testing service. That may not be practical after patients have been discharged from hospital. There is still debate about the sensitivity and positive predictive value of antigenemia testing in the prediction of CMV disease in CMV-antibody-negative recipients receiving lungs from antibody-positive donors. The role of prophylaxis in antibody-positive recipients is also debated. With an incidence of disease in that group ranging from 15% to 30%, the potential gains of prophylaxis need to be weighed carefully against cost and toxicity of available agents. Most recently, an oral form of ganciclovir has become available and the results of clinical trials are eagerly awaited.

Herpes virus pneumonia was reported as a common problem in early heart–lung transplant recipients and, for that reason, acyclovir prophylaxis is usually given for 6 to 12 weeks after transplantation in patients not receiving ganciclovir prophylaxis. Either of the drugs virtually eliminates the threat of serious herpes simplex disease.

Bacteria

Prophylactic antibiotic therapy commenced in the immediate postoperative period usually is continued up to 2 weeks after transplantation if the recipients' lungs were colonized by chronic bronchial sepsis. Antibiotic therapy has to be justified carefully to ensure balance between efficacy against colonizing bacteria and selection of pan-resistant organisms. Inappropriate use of broad-spectrum antibiotic agents may predispose to colonization with more resistant bacteria or fungi at a time when the patient is most vulnerable to infections. In general, once the initial antibacterial prophylaxis is stopped, prophylactic antibiotic treatment is stopped. The exceptions are (1) the use of nebulized antibiotic agents—e.g., colistimethate sodium or tobramycin—in patients who have pseudomonal colonization of their upper respiratory tract and who have evidence that organisms are contaminating the lower respiratory tract, and (2) trimethoprim-sulfamethoxazole combination (discussed subsequently), which probably is effective in reducing the numbers of community-acquired and some opportunistic bacterial infections.

Patients at risk for pseudomonal problems can be identified by retrieving low numbers of organisms at BAL. There is a high risk that such patients will develop pseudomonal pneumonia and nebulized antibiotic administration should be strongly considered.

Occasionally, hospital water systems become colonized by strains of *Legionella* spp. and it may be sensible to give in-patient prophylaxis against those organisms during outbreaks.

Fungi

Patients identified as needing prophylactic antifungal therapy in the immediate postoperative period because *Aspergillus* or *Candida* is identified in donor or recipient lungs usually receive continued therapy for at least the first month. Studies have not been done to assess whether prolonged prophylaxis is of any benefit. After the initial course of prophylaxis, antifungal therapy is generally given only if fungi are repeatedly grown on BAL. Nebulized amphotericin (20 mg twice a day) may be the best choice to protect the bronchial anastomosis. The risk of developing serious *Aspergillus* infection in the first 3 months is increased during building work at transplant hospital sites when respirable *Aspergillus* spores are increased in number. One could consider the use of prophylactic itraconazole or amphotericin, as previously described, in such circumstances.

P. carinii is one of the opportunistic infections following lung transplantation that has virtually been eliminated by the widespread

use of prophylaxis. Without it, the incidence of infection has been reported in up to 88% of heart–lung transplantations.[14] It is rare before 6 months post-transplantation but prophylaxis is usually started within the first month. Prophylactic treatment taken twice daily for 3 days each week (or some similar regimen) using trimethoprim, 160 mg, and sulfamethoxazole, 800 mg, in combination (co-trimoxazole) is very effective.[21] It is unclear how long prophylaxis needs to be continued and no prospective studies have evaluated that need. Because the transplanted lung is exquisitely sensitive to infection, co-trimoxazole probably has a much broader impact than simply *P. carinii* prophylaxis, and the drug is generally well-tolerated; it has been our policy to continue it indefinitely. At the very least, if the prophylaxis is stopped, it should be restarted during periods of augmented immunosuppression. Patients unable to tolerate trimethoprim and sulfamethoxazole prophylaxis can be give alternative treatments, including Fansidar (Roche Laboratories, Nutley, NJ) and trimethoprim, dapsone, or aerosolized pentamidine.

LATE

The late period is defined as the period beyond three months after transplantation.

Monitoring

Chronic Rejection

Chronic rejection after lung transplantation is characterized by OB, defined as an inflammatory disorder of the small airways leading to severe airflow obstruction.[2] Although it can occur within 2 months of transplantation, most cases appear between 6 and 18 months after transplantation.[19] The prevalence of the condition varies from 25% to 62% of long-term survivors. The diagnosis of OB is based on physiologic and pathologic aspects. Detection of a sustained drop in FEV_1 caused by airflow obstruction should be followed by fiberoptic bronchoscopy and TBB. The bronchoscopy helps rule out potential pitfalls in the diagnosis, including, for example, anastomotic narrowing leading to obstruction. TBB may show pathologic evidence of OB, but the sensitivity of TBB for detecting OB is highly variable and, moreover, the specificity of the pathologic diagnosis is low.[22, 38] When clinical symptoms and lung function are compatible with OB and other causes are eliminated, therefore, OB should be the diagnosis even though histologic confirmation is absent.

To that end, bronchiolitis obliterans syndrome (BOS) has been adopted as a functional assessment to describe lung dysfunction after lung transplantation, recognizing that there may or may not be pathologic evidence.[6] Surveillance of the lung graft using spirometry allows the BOS staging system to classify the degree of impairment of lung function after lung transplantation. BOS is a major problem for medium- to long-term survivors after lung transplantation, and the persistence of acute rejection within the first 6 months after transplantation is a sensitive prognostic indicator of subsequent functional decline.[11] It is potentially possible to identify different risk groups in patients developing BOS. In particular, the early development of BOS, with rapid progression from BOS 1 to BOS 2, suggests a poor long-term prognosis. Based on available data, it seems likely that primary prevention of BOS would be best achieved by the control of acute rejection in the first 6 months.

Although the FEV_1, by definition, is used to classify OB from a functional viewpoint, it has been recognized that OB is associated with a progressive decline in the midexpiratory flow between 75% and 25% of the vital capacity, and the development of a tail in the final part of the maximal expiratory flow. Moreover, the latter physiologic measures have been proposed as more sensitive for the development of OB, leading to its identification at an earlier stage. The ability to identify OB at an early stage is important because it confers the potential for making a diagnosis during the inflammatory phase—as opposed to the fibrotic stage—of the condition when augmented immunosuppression may arrest the loss of lung function.[37] Accordingly, it is advisable to perform expiratory flow volume curves at all times when performing formal lung function tests.

Infection Prophylaxis

Some centers withdraw *Pneumocystis* prophylaxis after 12 months, as the level of immunosuppression is reduced. Others continue indefinitely. There are no controlled studies to advise us which policy is best. Our

own policy is to continue with prophylaxis and we have had no episodes of *Pneumocystis* pneumonia in 200 consecutive lung transplantations.

The development of OB is commonly associated with proximal dilatation of larger airways and bronchiectasis. Removal of secretions is impaired, and it is common for such patients to colonize their airways with gram-negative organisms, particularly *Pseudomonas*. It is often advisable to start nebulized Colymycin or tobramycin as a prophylactic measure in such patients to reduce the frequency of gram-negative pneumonia, which may speed the loss of lung function.

DRUG MONITORING AND SURVEILLANCE

The dose of immunosuppressives such as cyclosporine or tacrolimus has to be decided by monitoring the trough blood level. Such drugs have many toxicities. Cyclosporine, for example, impairs renal function to some degree in almost all patients and the effect is dose-related.[26] Careful monitoring of blood, urea, and serum creatinine therefore is essential. Azathioprine is myelotoxic and may be hepatotoxic, so the full blood count and liver function tests must be monitored. The majority of centers perform blood tests as just indicated on a regular basis, and it is our policy to carry out routine monitoring at 6-week intervals. A number of drugs have important interactions with the immunosuppressives, making it necessary to monitor more frequently whenever one of those drugs is added to a transplant recipient's drug regimen. Complications of immunosuppressive agents and drug interactions are discussed in more detail elsewhere in this issue.

EDUCATION OF PATIENTS

An important part of monitoring is successful education of the patient so he or she is aware of the symptoms and signs of rejection, infection, and the side effects of medication. In that way, complications can be identified at an early stage.

SUMMARY

One of the key areas of successful organ transplantation is the prompt recognition and treatment of problems that otherwise can progress rapidly, leading to morbidity and mortality. Surveillance and prophylaxis are essential in the field of transplant medicine.

References

1. Bailey TC, Trulock EP, Ettinger NA, et al: Failure of prophylactic ganciclovir to prevent CMV disease in lung transplant recipients. J Infect Dis 165:548–552, 1992
2. Burke CM, Theodore J, Baldwin J, et al: Twenty-eight cases of human heart lung transplantation. Lancet 1:517–519, 1986
3. Chan CC, Abi-Saleh WJ, Arroliga AC, et al: Diagnostic yield and therapeutic impact of flexible bronchoscopy in lung transplant recipients. J Heart Lung Transplant 15:196–205, 1996
4. Chapparo C, Maurer JR, Chamberlain D, et al: Causes of death in lung transplant and recipients. J Heart Lung Transplant 13:758–766, 1994
5. Chowienczyk PJ, Lawson CP: Pocket size device for measuring forced expiratory volume in 1 second and forced vital capacity. Br Med J Clin Res Ed 285:15–17, 1982
6. Cooper JD, Billingham M, Egin T, et al: A working formulation for the standardization of nomenclature for clinical surgery of chronic dysfunction in lung allografts. J Heart Lung Transplant 12:713–716, 1993
7. Date H, Triantafillou AN, Trulock EP, et al: Inhaled nitric oxide reduces human lung allograft dysfunction. J Thorac Cardiovasc Surg 57:715–722, 1994
8. Degre M, Bukholm G, Holter E, et al: Rapid detection of CMV infection in immunocompromised patients. Eur J Clin Microbiol Infect Dis 13:668–670, 1994
9. Gavazzeni V, Iapichino G, Maschernoni D, et al: Prolonged independent lung respiratory treatment after single lung transplantation in pulmonary emphysema. Chest 103:96–100, 1993
10. Girgis RE, Reichenspurner H, Robbins RC, et al: The utility of annual surveillance bronchoscopy in lung transplant recipients. Transplantation 60:1458–1461, 1995
11. Glanville AR, Baldwin J, Burke C, et al: Obliterative bronchiolitis after heart–lung transplantation: Apparent arrest by augmented immunosuppression. Ann Intern Med 107:300–304, 1987
12. Gould FK, Freeman R, Taylor CE, et al: Prophylaxis and management of CMV pneumonitis following pulmonary transplantation. A review of experience in one center. J Heart Lung Transplant 12:695–699, 1993
13. Guilinger RA, Paradis IC, Dauber JH, et al: The importance of bronchoscopy with transbronchial biopsy and bronchoalveolar lavage in the management of lung transplant recipients. Am J Respir Crit Care Med 152:2037–2043, 1995
14. Gryzan S, Panctis IC, Zeen A, et al: Unexpectedly high incidence of *P. carinii* infection after lung–heart transplantation. Implications for lung defense and allograft survival. Am Rev Respir Dis 137:1268–1274, 1988
15. Haydock DA, Trulock EP, Kaiser LR, et al: Lung transplantation. Analysis of 36 consecutive procedures performed over a 12-month period. J Thorac Cardiovasc Surg 103:324–340, 1992
16. Higenbottam TW, Stewart S, Pethets A, et al: Transbronchial biopsy for the diagnosis of infection in

heart–lung transplantation. Transplantation 46:532–539, 1988
17. Hoeper MM, Stamm M, Schaefers HJ, et al: Evaluation of lung function during pulmonary rejection and infection in heart–lung transplant patients. Chest 102:864–870, 1992
18. Keenan RJ, Knoshi H, Kaussi A, et al: Clinical trial of tacrolimus versus cyclosporine in lung transplantation. Ann Thorac Surg 60:580–585, 1995
19. Kramer MR: Bronchiolitis obliterans following heart–lung and lung transplantation. Respir Med 88:9–15, 1994
20. Kramer MR, Marshall SE, Starnes VA, et al: Infectious complications in heart–lung transplantation. Analysis of 200 episodes. Arch Intern Med 153:2010–2016, 1993
21. Kramer MR, Stoer C, Leniston NJ, et al: Trimethoprim sulfamethoxazole in heart–lung and lung transplantations—how effective and for how long? Transplantation 53:586–589, 1992
22. Kramer MR, Stoer C, Uthang JL, et al: The diagnosis of obliterative bronchiolitis after heart–lung and lung transplantation. Low yield of transbronchial lung biopsy. J Heart Lung Transplant 12:675–681, 1993
23. Low DE, Kaiser LR, Haydock DA, et al: The donor lung: Infections and pathological factors affecting outcome in lung transplantations. J Thorac Cardiovasc Surg 106:614–621, 1993
24. Milne DS, Gascoigne ADK, Ashcroft TA, et al: Organizing pneumonia following pulmonary transplantation and the development of obliterative bronchiolitis. Transplantation 57:1757–1762, 1994
25. Morris RE, Huang X, Gregory CR, et al: Studies in experimental models of chronic rejection: Use of rapamycin (sivolimus) and isoxazole derivatives (leflunomide and its analogue) for the suppression of graft vascular disease and obliterative bronchiolitis. Transplant Proc 27:2068–2069, 1995
26. Myers BD, Ross J, Newton L, et al: Cyclosporine-associated chronic nephropathy. N Engl J Med 322:699–705, 1984
27. Otulana BA, Higenbottam TW, Scott JP, et al: Pulmonary function monitoring allows diagnosis of rejection in heart–lung transplant recipients. Transplant Proc 21:2583–2584, 1989
28. Otulana BA, Higenbottam TW, Scott JP, et al: Lung function associated with histologically diagnosed acute rejection and pulmonary infection in heart–lung transplant patients. Am Rev Respir Dis 142:329–332, 1990
29. Pomerance A, Madden B, Burke MM, et al: Transbronchial biopsy in heart and lung transplantation: Clinicopathological correlations. J Heart Lung Transplant 14:761–773, 1995
30. Ramsey BW, Dorkin HL, Eisenberg JD, et al: Efficacy of aerosol tobramycin in patients with cystic fibrosis. N Engl J Med 328:1740–1746, 1993
31. Sibley RK, Berry GJ, Tazelaar HD, et al: The role of transbronchial biopsies in the management of lung transplant recipients. J Heart Lung Transplant 12:308–324, 1993
32. Sleiman C, Mal H, Fournier M, et al: Pulmonary reimplantation response in single lung transplantation. Eur Respir J 8:5–9, 1995
33. Sollinger HW, Deierhvi MH, Belzer FO, et al: RS-61443—a phase 1 clinical trial and pilot rescue study. Transplantation 53:428–432, 1992
34. Starnes VA, Theodore J, Oyer PE, et al: Pulmonary infiltrates after heart–lung transplantation. Evaluation by transbronchial biopsies. J Thorac Cardiovasc Surg 98:945–950, 1989
35. Trulock EP, Ettringer NA, Brunt EM, et al: The role of transbronchial lung biopsy in the treatment of lung transplant recipients. An analysis of 200 consecutive procedures. Chest 102:1049–1054, 1992
36. Wreghitt TG, Hakim M, Gray JJ, et al: Cytomegalovirus infections in heart and heart–lung transplant recipients. J Clin Pathol 41:660–667, 1988
37. Yousem SA, Berry GJ, Cagle PT, et al: Revision of the 1990 working formulation for the classification of pulmonary allograft rejection. J Heart Lung Transplant 15:1–15, 1996
38. Yousem SA, Paradis IL, Daubert JH, et al: Efficacy of transbronchial lung biopsy in the diagnosis of bronchiolitis obliterans in heart–lung transplant recipients. Transplantation 47:893–895, 1989

Address reprint requests to

Paul A. Corris, MB, FRCP
Department of Medicine
University of Newcastle upon Tyne
Freeman Hospital
United Kingdom NE7 7DN