Analysis of time-dependent risks for infection, rejection, and death after pulmonary transplantation

Infection and rejection remain the greatest threats to the survival of pulmonary allograft recipients. Furthermore, a relationship may exist between these events, because the occurrence of one may predispose to the other. By using multivariate analysis for repeated events, we analyzed the risk factors for bacterial, fungal, and viral infection, grade II or greater acute rejection, and death among 239 lung transplant recipients who received 250 allografts between January 1988 and September 1993. A total of 90 deaths, 491 episodes of acute rejection, and 542 infectious episodes occurred during a follow-up of 6 to 71 months. The hazard or risk patterns of death, infection, and rejection each followed an extremely high risk during the first 100 days after transplantation, a second modest risk period at 800 to 1200 days, and a lower constant risk. Infection and graft failure manifested by diffuse alveolar damage were the major causes of early death (<100 days), whereas infection and chronic rejection were primary causes of later death after pulmonary transplantation. By multivariate analysis, cytomegalovirus mismatching risk for primary infection was the most significant risk factor for death, rejection, and infection. Absence of cytomegalovirus prophylaxis was also a risk factor for early and late death and late infection. Survival of recipients who received cytomegalovirus prophylaxis was significantly improved. Immunosuppression based on cyclosporine versus FK 506 was a risk factor for late death and late infection. Graft failure manifested by diffuse alveolar damage/adult respiratory distress syndrome was a significant risk for death late after transplantation. These data suggest the following: (1) The hazard for death, infection, and rejection after pulmonary transplantation appears biphasic; (2) lower survival is associated with ischemia-reperfusion lung injury represented by diffuse alveolar damage/adult respiratory distress syndrome; (3) cytomegalovirus mismatch, absence of cytomegalovirus prophylaxis, and development of cytomegalovirus disease are significant threats for death, rejection, and infection after pulmonary transplantation; (4) prevention of cytomegalovirus disease should improve survival by decreasing the prevalence of infection and rejection. (J THORAC CARDIOVASC SURG 1995;109:49-59)

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Lung and heart-lung transplantation have become acceptable therapeutic alternatives for patients with end-stage pulmonary parenchymal or vascular diseases.¹ Nevertheless, survival at 1 and 2 years after lung or heart-lung transplantation remains lower compared with kidney, liver, or heart transplantation (UNOS Update, January 1994). As a step toward improving survival, we retrospectively analyzed donor and recipient characteristics, as well as events after pulmonary transplantation that influenced survival and the risk of infection or rejection.

Patients and methods

Recipient population. This study examined the experience of all 250 lung (99 single lung, 102 bilateral lung, and 49 heart-lung) recipients who received their allografts at the University of Pittsburgh between January 1, 1988, and September 30, 1993, and were observed through January 31, 1994 (Table I). The mean duration of follow-up was 16 months (range 6 to 71 months). The recipients included 114 male patients (46%) and 136 female patients (54%) whose ages ranged from 1 to 66 years (mean 37 years, median 39 years). The diseases that necessitated transplantation are given in Table I. All but 11 donor and recipient pairs were ABO blood type identical (Appendix 1) but half of the donors and recipients were cytomegalovirus (CMV) mismatched and 56 recipients (22%) were at risk of primary CMV infection (donor+/recipient – [D+/R–]) (Appendix 2).

Donor selection. Donor selection criteria included a clear chest radiograph, an arterial oxygen tension greater than 300 mm Hg at an inspired oxygen fraction of 1.0 with a positive end-expiratory pressure of 5 cm H₂O, no evidence of a significant pulmonary contusion, negative human immunodeficiency virus antibody and hepatitis antigen titers, minimal sputum, and no evidence of aspiration as detected with a bronchoscope. The causes of brain death and other characteristics of the donors are listed in Appendix 3. Sixty-eight percent of the donors were male and 32 percent were female. Their ages ranged from 1 to 55 years (mean 28 years, median 26 years). Specimens of blood, urine, and sputum were obtained from the donor for smears and cultures. Antibiotic therapy was started during the transplantation procedure on the basis of the results from the sputum Gram stain.¹

Immunosuppression. For recipients without pretransplantation septic lung disease, the immunosuppressive therapy consisted of cyclosporine or FK 506 as the primary immunosuppressant combined with azathioprine and low-dose corticosteroids (10 to 15 mg/day). Immediately before transplantation, doses of azathioprine (4 mg/kg) and methylprednisolone (500 mg) were administered intravenously. Cyclosporine or FK 506 was begun by continuous infusion as soon as the recipient was in hemodynamically stable condition, which was usually 6 to 8 hours after transplantation. The cyclosporine dose was titrated to maintain a whole blood level of 800 to 1000 ng/ml by the Abbott TDx method and FK 506 was titrated to maintain a plasma level of 1.0 to 1.5 ng/ml. Prophylactic

Table I. Indications for pulmonary transplantation

	No.	Transplant procedure		
		SLT	BLT	HLT
Pulmonary vascular disease				
PPH	37	6	12	19
Eisenmenger's syndrome	41	5	16	20
PH due to other disease	12	6	0	6
Nonseptic obstructive lung disease				
COPD	52	43	7	2
α_1 -Antitrypsin deficiency	20	16	4	0
Septic obstructive lung disease				
Cystic fibrosis	40	0	40	0
Bronchiectasis	7	0	7	0
Restrictive lung disease				
Idiopathic pulmonary fibrosis	3	3	0	0
Sarcoidosis	8	7	0	1
Others	19	8	10	1
Retransplantation	11	5	6	0
Total	250	99	102	49

PPH, Primary pulmonary hypertension; PH, pulmonary hypertension; COPD, chronic obstructive pulmonary disease; SLT, single lung transplantation; BLT, bilateral lung transplantation; HLT, heart-lung transplantation.

rabbit antithymocyte globulin (1.5 mg/kg per day) for 5 days was administered only if the recipient remained hemodynamically unstable, and cyclosporine or FK 506 was avoided for 3 to 5 days. The dose of azathioprine was titrated to maintain a white blood cell count of about 5000 mm³. For recipients with pretransplantation septic lung disease, posttransplantation immunosuppression consisted only of cyclosporine or FK 506, and their doses were titrated to maintain a lower level of immunosuppression (cyclosporine 500 to 700 ng/ml, FK 506 0.8 to 1.0 ng/ml). Azathioprine and corticosteroids were added to the regimen when a favorable outcome seemed certain or multiple episodes of grade II acute rejection or greater had occurred.

Antibiotic prophylaxis. The choice of antibiotics and duration of treatment were titrated according to the results of microbiologic cultures obtained from the donor and recipient airways at the time of transplantation and periodically thereafter.² For recipients without pretransplantation septic lung disease, clindamycin and ceftazidime were begun immediately after transplantation. If the recipient and donor airway cultures contained no organisms, these antibiotics were stopped at 48 to 72 hours. If cultures contained oral flora organisms, clindamycin was continued for 10 days. If these cultures contained *Staphylococcus* organisms, clindamycin was continued and vancomycin was added to complete a 10-day course. If these cultures contained gram-negative organisms, ceftazidime was continued, and another culture-specific antibiotic was added to the regimen if *Pseudomonas* was the gram-negative organism isolated. For recipients with pretransplantation septic lung disease, three or four antibiotics active against *Pseudomonas aeruginosa* or *Pseudomonas cepacia* were begun during the operation and continued for 2 full weeks or until the clinical outcome was certain. The choice of antibiotics was determined by the antibiotic

sensitivities of the organism present in airways of the recipient before transplantation. A single-strength tablet of trimethoprim methoxazole was prescribed every other day just before the initial hospital discharge.

Antiviral prophylaxis. Three different regimens of ganciclovir with or without acyclovir were used in seropositive recipients and donors to try to determine the optimal regimen that would prevent CMV infection.³ Although these regimens varied in terms of dose and duration of treatment, ganciclovir at a dosage of 5 mg/kg twice a day from postoperative days 7 to 21 and 5 mg/kg per day from postoperative days 22 to 28 was common to all regimens. Seronegative recipients and donors received only CMV negative blood and blood products. Recipients at primary risk of herpes simplex infection (D+/R-) received acyclovir 400 mg four times a day from postoperative days 7 to 90.

Definition and treatment

Infection. In this analysis, multiple consecutive positive microbial cultures from the same body site were considered part of the same infectious episode. Clinically important infections at different sites were considered separate infectious episodes even if they involved the same organism. CMV illness was analyzed separately from other bacterial, fungal, and viral infections for risk factor analysis.

CMV illness. CMV infection was defined by the presence of CMV in a culture obtained from any body site in the absence of symptoms of CMV infection, histologic evidence of CMV disease, rejection, or the isolation of any other infectious pathogen. CMV disease was defined by a positive culture for CMV plus the presence of intracellular inclusions typical of CMV in cells or tissue obtained from any body site. CMV syndrome was defined by the presence of CMV in a culture from any body site plus symptoms typical for CMV infection that were not related to rejection or isolation of any other infectious pathogens. The few ($n = 5$) episodes of CMV syndrome have been included in the group with CMV infection for the purpose of this analysis. CMV infection in D+/R- recipients and CMV disease were managed with ganciclovir 5 mg/kg twice a day for 2 weeks followed by 5 mg/kg per day for an additional week.

Acute rejection. Acute rejection was defined by histologic criteria, and only histologically proved episodes of acute rejection were tabulated in this analysis. A rejection episode was considered resolved when the biopsy specimens indicated less than grade II acute rejection. Thus several consecutive positive biopsy specimens with grade II rejection or more were considered only a single episode of acute rejection.

Acute rejection was treated with intravenous methylprednisolone (1 gm/day) for 3 days for the first and usually the second episode. Refractory rejection episodes were treated with cytolytic therapy of rabbit antithymocyte globulin (1.5 mg/kg per day for 5 days) or equine antithymocyte globulin (10 to 20 mg/kg per day) for 14 days.

Obliterative bronchiolitis. Obliterative bronchiolitis was defined according to histologic⁴ or clinical criteria.⁵ Clinical criteria included symptoms or cough with or without sputum or a decrease in the forced expiratory volume in 1 second of 20% or more from baseline that

Table II. Possible risk factors for morbidity and mortality after transplantation

A: Donor related
Age
Gender
Cause of brain death
Arterial blood gases before harvest
History of smoking
Culture (blood, urine, sputum)
Preservation technique
History of cardiac arrest
History of respiratory arrest
History of cardiopulmonary resuscitation
Requirement for inotropic support
B: Donor/recipient matches
ABO blood type
CMV status
HLA status
Gender
C: Recipient preop. related
Age
Gender
Underlying disease
Panel reactive antibody
Year of transplantation
D: Intraop. related
Ischemic time
Type of transplant
Requirement for cardiopulmonary bypass
E: Postop. related
Early and late
Airway ischemia
ARDS/DAD
Rabbit antithymocyte globulin in first week postop.
CMV prophylaxis
CMV infection
CMV disease
Frequency of acute rejection ($\geq$ grade II)
Frequency of infection other than CMV
Posttransplantation lymphoproliferative disease
Late
Obliterative bronchiolitis

could not be explained by the presence of bronchomalacia, stenosis of the anastomosis, or infection in the allograft. Obliterative bronchiolitis was treated with the same agents as for acute rejection or with Minnesota antithymocyte globulin 10 to 15 mg/kg per day for 14 days or OKT3 5 mg/day for 10 days.

Statistical analysis. Data were collected prospectively in an ongoing transplant recipient database and were analyzed by SAS 6.08.⁶ The cumulative survival function was estimated by the actuarial (life-table) method and its standard error was determined by the Greenwood formula.⁶ Log-rank tests were used to evaluate the differences between the survival curves. The Cox proportional hazard model was used to identify the independent contribution of potential risk factors for infection, acute rejection, and death after transplantation. Potential risk factors were examined in both the early (postoperative days 0 to 100)

Fig. 1. Overall survival after pulmonary transplantation at the University of Pittsburgh (January 1988 to September 1993).

Table III. Causes of early and late death after pulmonary transplantation

Cause	No.
A. Early death (≤ 100 days)	
Intraoperative bleeding	6
Technical failure	5
ARDS/DAD	13
Infection	25
Posttransplantation lymphoproliferative disease	1
Others	3
Total	53
B. Late death (>100 days)	
Infection	20
Obliterative bronchiolitis	8
ARDS/DAD	2
Acute rejection	1
Posttransplantation lymphoproliferative disease	1
Others	5
Total	37

and late phases (postoperative days >100) after pulmonary transplantation. The variables entered in the risk factor analysis for infection, rejection, and death included donor-related factors, donor/recipient matching, recipient preoperative and intraoperative related factors, and postoperative related factors (Table II: A, B, C, D, and E—early and late). The selection of independent variables in the models was a forward stepwise method with a critical value for variable inclusion and exclusion of 0.15. A p value of 0.05 or less was used to determine the significance of variables.

Results

Survival. For the overall group of recipients, calculated survival was 68% at 12 months and 54%

at 36 months (Fig. 1). Infection, adult respiratory distress syndrome (ARDS)/diffuse alveolar damage (DAD), and intraoperative complications (bleeding and technical failure) were the major causes of death early (0 to 100 days) after transplantation (Table III). Infection and obliterative bronchiolitis were primary causes of late deaths (>100 days) after pulmonary transplantation (Table III). A hazard function analysis for risk of death revealed an extremely high risk phase within 100 days after transplantation followed by a period of more moderate risk around 820 days after transplantation (Fig. 2). By multivariate analysis, time of transplantation (before 1992), CMV mismatch for risk of primary infection (D+/R-), absence of CMV prophylaxis, and infection other than CMV were significant risk factors for early death after transplantation (Table IV). Risk factors associated with later death included a panel reactive antibody greater than 10%, CMV mismatch (D+, R-), human leukocyte antigen (HLA-DR) mismatch, absence of CMV prophylaxis, CMV disease, DAD/ARDS, and cyclosporine-based immunosuppression. Survival of the recipients with or without CMV prophylaxis (Fig. 3), and FK 506-based versus cyclosporine-based immunosuppression (Fig. 4) indicated that these factors had independent significant risk for death after pulmonary transplantation.

Acute rejection. Analysis of the risk of acute rejection revealed an extremely high risk within the first 100 days after transplantation followed by a period of intermediate risk around 830 days after

Fig. 2. Hazard rate of death after pulmonary transplantation.

Fig. 3. Impact of CMV prophylaxis on survival after pulmonary transplantation. $p < 0.05$ between the two groups by generalized Wilcoxon test.

transplantation (Fig. 5). By multivariate analysis, older donor age (>40 years), CMV mismatch (D+/R-), CMV disease, single lung transplant procedure, and pulmonary hypertension were significant risk factors for early acute rejection (Table V). Risk factors for late acute rejection included previous episodes of acute rejection and prior CMV disease (Table V).

Infection. A hazard function analysis for the risk of bacterial, fungal, and viral infection including CMV revealed an extremely high risk period during

the first 100 days after transplantation, followed by a peak of intermediate risk between 700 and 1300 days after transplantation (Fig. 6). By multivariate analysis, risk factors for infection other than CMV early after transplantation included longer donor ischemic time (>6 hours), lower donor arterial oxygen tension (<350 mm Hg) before harvest, positive donor sputum culture, older recipient age (>40 years), and CMV mismatch (D+/R-) (Table VI). Risk factors for late infection other than CMV included older recipient age, CMV mismatch, ab-

Fig. 4. Impact of immunosuppression on survival after pulmonary transplantation. CyA, Cyclosporine; FK, FK 506. $p < 0.05$ between the two groups by generalized Wilcoxon test.

Fig. 5. Hazard rate of acute rejection after pulmonary transplantation.

sence of CMV prophylaxis, CMV disease, cyclosporine-based immunosuppression, and previous episodes of infection (Table VI).

Discussion

This study confirms several important clinical impressions that those of us involved in pulmonary transplantation have "known" for a long time.^{1,7} First, the risk of infection, rejection, and death is greatest in the first 100 days after transplantation (see Figs. 2, 5, and 6). Second, death in the first 100 days is usually due to infection and/or DAD/ARDS in the allograft, whereas death more than 100 days after transplantation is primarily due to infection and obliterative bronchiolitis (see Table III). Fi-

nally, acute rejection rarely is a cause of death at any time after transplantation (see Table III).

What is new and exciting about this study is the analysis of the risk factors for infection, rejection, and death. Although some of the risk factors make sense (i.e., agree with our clinical impressions), some should more strongly reinforce our clinical impressions, some do not agree with our clinical impressions, and some are conspicuous by their absence.

Not surprisingly, infection other than CMV was a significant risk for early death (see Table IV). This agrees with our clinical impressions and observations (see Table III). Also, not surprisingly, a longer ischemic time, lower arterial oxygen tension in the

Fig. 6. Hazard rate of infection after pulmonary transplantation.

donor, positive donor sputum culture, and older recipient were significant risk factors for early infection. It was distressing to find that a positive donor culture, as previously reported^{2,8} and now reconfirmed, was still a risk factor for early infection (see Table VI). Although our current antibiotic prophylaxis regimen, which is based on Gram stain results and modified on the basis of cultures obtained from the donor and recipient lungs, has reduced our prevalence of early bacterial pneumonia.⁹ This is apparently not enough because we have not yet succeeded in eliminating this risk of infection.

CMV mismatching (D+/R-) for risk of primary infection, absence of CMV prophylaxis, and the development of CMV disease were the most significant risk factors for death, rejection, or infection both early and late after pulmonary transplantation (see Tables IV, V, and VI). Actuarial survival of recipients without CMV prophylaxis was significantly lower than that of recipients who received prophylaxis (see Fig. 3). This suggests that prophylaxis for CMV can favorably influence the outcome of lung transplantation.³ On the other hand, these results suggest that matching by donor and recipient CMV status might be advisable if we cannot develop a regimen that can prevent this infection in this high-risk group of recipients.

Currently, despite our prophylaxis regimen, CMV disease develops in 52% (25/48) of our D+/R- recipients, but in the vast majority (22/25, 80%) this disease has occurred after completion of CMV prophylaxis (unpublished data). Thus our current

Table IV. Risk factors for death after pulmonary transplantation

Risk factors	p Value	Risk ratio
A. Early death		
Demographic		
Year of transplantation	0.01	0.68
Matching		
CMV mismatch	0.01	1.27
Clinical		
No CMV prophylaxis	0.0001	0.40
Infection episode	0.01	270.70
B. Late death		
Matching		
PRA >10%	0.05	2.37
CMV mismatch	0.01	1.38
HLA-DR mismatch	0.01	2.06
Clinical		
No CMV prophylaxis	0.02	0.64
CMV disease	0.03	0.82
DAD/ARDS	0.01	2.37
Cyclosporine immunosuppression	0.02	0.34

PRA, Panel reactive antibody.

CMV prophylaxis appears only to delay the emergence of CMV disease. The optimum regimen of prophylaxis for D+/R- recipients remains to be determined.

With experience and refinement of operative technique,² the number of intraoperative complications was significantly reduced (January 1988 to December 1991, 17%; January 1992 to September 1993, 4%, $p < 0.05$) and survival was significantly improved.² This result is well correlated with the fact that year of transplantation was a significant risk

Table V. Risk factors for acute rejection after pulmonary transplantation

Risk factors	p Value	Risk ratio
A. Early rejection		
Donor		
Older donor	0.03	1.01
Demographic		
SLT	0.03	0.55
PH	0.02	0.45
Matching		
CMV mismatch	0.001	0.54
Clinical		
CMV disease	0.0001	0.32
B. Late rejection		
Clinical		
Prior rejection episodes	0.0002	1.33
CMV disease	0.0001	0.43

SLT, Single lung transplantation; PH, pulmonary hypertension.

factor for early death after pulmonary transplantation.

Obliterative bronchiolitis was the second most frequent cause of late death and was frequently associated with pulmonary graft infection.^{10, 11} A recent analysis of risk factors for the development of obliterative bronchiolitis at our institution indicated that CMV disease and frequent, severe acute rejection episodes were the primary risk factors for the subsequent development of obliterative bronchiolitis.¹¹

The results from this study further supported the early results of our ongoing randomized study comparing FK 506 versus cyclosporine in pulmonary transplantation.¹² Even with year of transplantation accounted for, this multivariate analysis showed that FK 506-based immunosuppression resulted in better survival (see Fig. 4) and less risk for late infection (see Table VI). However, the duration of follow-up is still limited to a mean of 13 months in the FK 506 group and 19 months in the cyclosporine group. Also the two groups in this analysis were not randomized.

A panel reactive antibody greater than 10% and HLA-DR mismatching were also associated with an adverse outcome. The higher panel reactive antibody is probably associated with more aggressive acute rejection, which histologically and clinically might look like DAD/ARDS. HLA-DR mismatching may affect outcome via its permissive effect on CMV disease, which is most probably why it surfaced as a risk factor for infection other than CMV (see Table VI). Development of graft failure manifested by DAD/ARDS was also associated with an

Table VI. Risk factors for infection after pulmonary transplantation

Risk factors	p Value	Risk ratio
A. Early infection		
Donor		
Long ischemic time	0.0006	1.46
Lower arterial oxygen tension	0.01	1.95
Sputum culture (+)	0.004	0.71
Demographic		
Older recipient	0.01	1.02
Matching		
CMV mismatch	0.006	1.33
B. Late infection		
Demographic		
Older recipient	0.02	1.02
Matching		
CMV mismatch	0.05	1.20
Clinical		
No CMV prophylaxis	0.0001	0.66
CMV disease	0.03	1.25
Cyclosporine immunosuppression	0.02	0.60
Prior infection episodes	0.007	1.31

adverse outcome. The reason that DAD/ARDS is a significant risk factor for late but not early death is unexplained, because the majority of the episodes of DAD/ARDS were related to poor graft preservation and usually occurred early after transplantation.⁹ The most probable explanation for this observation is that most of the recipients with DAD/ARDS survived more than 100 days (mean 121 days). The majority of the recipients with DAD/ARDS died of late infection, which was most likely related to prolonged intubation and long stay in the intensive care unit.

Several risk factors identified in this study remain unexplained. For example, why should older donors (>40 years old), candidates with pulmonary hypertension, and recipients of single lung transplants have a greater risk of acute rejection? In addition, several risk factors that should have been present were not recognized in this study. For instance, acute rejection and prevalence of obliterative bronchiolitis should be risk factors for infection, but these factors were risks for late infection only by univariate analysis and they failed to reach statistical significance by multivariate analysis. Longer cohort^{13, 14} and a larger number of recipients including a multicenter study¹⁵ may be necessary to definitively answer these important questions.

In summary, the risks for death, infection, and rejection after pulmonary transplantation appear to be biphasic. Lower survival is associated with ischemia-reperfusion lung injury represented by DAD/

ARDS. CMV mismatch, absent CMV prophylaxis, and the development of CMV disease were the most significant threats for death, rejection, and infection after pulmonary transplantation. Thus adequate prevention of CMV disease should improve survival.

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Discussion

Dr. Craig R. Smith (New York, N.Y.). This is an exhaustive review of a large number of variables and is further evidence of Pittsburgh's leadership in this area. I agree with most of the conclusions, but I do have a few comments.

I noticed that only 6% of your patients had restrictive lung disease, which is a far smaller proportion than one would expect from the registries. Does this reflect a bias on your part against that diagnosis? If so, which patients with restrictive lung disease should receive a transplant?

Your experience seems to favor double lung transplantation for pulmonary hypertension. I assume, then, that you would list patients with pulmonary hypertension for double lung and not single lung transplantation.

There has been a controversy running through the United Network for Organ Sharing (UNOS) about whether or not blood group O recipients are disadvantaged by current policy allowing ABO-compatible matching. It was curious in your experience that only five ABO donors of the entire 250 were placed in A or B recipients. If there is a disadvantage, it is not obvious in Pittsburgh. Is the size of your waiting list the reason for that?

Finally, what emerges from this series and many others is that CMV infection and disease is a persistent and serious problem. I am particularly aware of this at the moment, as I defend myself in a lawsuit brought against me because of a decision to put a CMV-positive heart-lung block in a CMV-negative recipient. I think the waiting list in the United States is long enough that it would always be possible to find a CMV-negative recipient for any CMV-negative donor. The "problem" is that it may not be my recipient or your recipient. With more than 70 centers in the United States claiming expertise in lung transplantation and competing for 750 donors, magnanimous gestures are not going to be very frequent, and strict CMV matching would probably have to be mandated. Do your data support such a mandate, or has prophylaxis made this question moot? If you do not think your data support a mandate, what level of evidence would it take? Would you have to see a clear difference in survival, or would a difference in morbidity and cost be enough?

Dr. Bando. Thank you very much for your comments, Dr. Smith. Let me answer your question regarding candidates with restrictive lung disease. Patients with idiopathic pulmonary fibrosis (IPF) constitute the largest group of candidates with restrictive lung disease. These patients

constitute 13% of our referrals, but only 2% of our recipients. This is because this group of candidates is much more likely to die waiting compared with patients with other types of lung disease. In our most recent analysis of the patients accepted as candidates between 1990 and 1993, 47% of the candidates with IPF have already died waiting compared with only 7% of the candidates with emphysema.

The second question regarding single versus bilateral lung transplantation for pulmonary hypertension is controversial. Our preference and our results suggest that bilateral lung transplantation for pulmonary hypertension is the better procedure because single lung transplant recipients have a significant ventilation/perfusion mismatch between the allograft and native lung. As a result, they appear to have less oxygenation reserve compared with bilateral lung transplant recipients when complications develop in the allograft. However, because of the shortage of donor organs and the results of significant (20% in Pittsburgh) risk of death while waiting, we still do single lung transplant, because we do not know how long that particular candidate needs to wait until we would get a good bilateral lung donor. Thus we list candidates with pulmonary hypertension for either single or bilateral lung transplant, and we perform a transplant with whatever donor first becomes available.

Your third question regards the transplantation of organs from blood group O donors into A or B recipients. As you pointed out, the small number of such transplants in our experience ($5/250 = 2\%$) is probably because of our large candidate list. With more than 200 candidates on our waiting list all the time, we rarely encounter a situation in which we do not have a suitable ABO identical recipient for every donor.

Your fourth question relates to the risk and consequences of CMV infection/disease in recipients at risk for primary CMV illness (R-/D+). CMV disease is a significant risk factor for acute rejection, other infections, chronic rejection, and increased mortality. CMV matching would eliminate this problem, but CMV seronegative recipients would undoubtedly have to wait longer for a seronegative donor to become available and hence have a higher risk of death while waiting for a suitable donor. Thus we would rather try to find a good prophylactic regimen for CMV infection than go with CMV matching.

Dr. Alec Patterson (St. Louis, Mo.). Dr. Bando has once again demonstrated why the Graham Committee made such a wise choice several years ago in selecting him as a Graham Fellow. He continues to produce a prolific amount of work. I would also point out that Dr. Bahnson is here in the audience. It must be a proud moment for you to see two of your young colleagues presenting two great papers in this forum. It is a real tribute to your whole program.

I am a statistical neophyte. However, when an enormous number of data points are put into a computer and 30 or 40 risk factors are evaluated, it seems to me that chance alone is going to make a couple of them significant. I am particularly interested in the CMV because it is a big problem for us. You notice an identification of CMV disease like true infection, biopsy-proved infection, as a

risk factor. We know also from your own data that CMV disease is going to occur whenever the prophylaxis is stopped. The onset can be delayed, but the disease is going to occur anyway. Does it matter when that CMV disease occurs? In other words, is there any difference between CMV disease early on versus CMV disease that occurs many months after transplantation?

Dr. Bando. Thank you for your kind comments, Dr. Patterson. In this analysis, we did not separately analyze the effect of early versus late onset of CMV as risk factors for subsequent events. As you mentioned, CMV disease still develops in 65% of recipients at risk for primary infection despite up to 90 days of prophylaxis with ganciclovir. Most (96%) of these recipients do develop CMV after ganciclovir prophylaxis has been completed. Thus our current regimen of CMV prophylaxis for recipients at risk of primary illness is not adequate. We have started another randomized trial of two different CMV prophylactic protocols for this CMV R-/D+ group. Dr. Paradis, a coauthor of this study, is in charge of this project. He will eventually let us know whether early or late onset CMV infection make any difference in outcome and whether we are able to find more efficacious prophylactic regimen particularly for R-/D+ recipients.

Dr. Thomas M. Egan (Chapel Hill, N.C.). Dr. Bando, how many patients in your analysis had their transplant operation before ganciclovir was readily available? Is it possible that the impact of CMV disease is less problematic now than it was in the days before ganciclovir? How much has that changed your analysis?

Dr. Bando. Only 12 recipients in the first 6 months of 1988 had transplantation without receiving CMV prophylaxis and we did not remove this small number from the rest of our group for the purpose of this analysis. Thus we do not know whether this might have significant impact on our results. Because the number of recipients not receiving prophylaxis is so small, however, we doubt that this significantly affected our results.

Dr. Joel D. Cooper (St. Louis, Mo.). I want to address an issue of CMV which I think is important. And I would love to defend Dr. Craig. We do keep an international registry. It is voluntary. We have about 2700 patients in it. One of the analyses that we have done is to study the influence of CMV. We have looked at the two extreme groups: the negative recipient who gets the negative donor, and rarely gets CMV infection, and the negative recipient who gets a positive donor, and always gets CMV disease. In fact, half the world's transplants are not a mismatch. A quarter are negative/negative and a quarter are positive donor/negative recipient. By analyzing the two extreme groups, both in our own series and in the world series as reported to us, we find absolutely no difference whatsoever in the 1- or 2-year survival between the matched and mismatched groups. In our own series there is no difference in pulmonary function studies at 1 and 2 years. Yes, it is costly to use prophylaxis. Yes, the CMV disease occurs in the one case and not at all in the other. However, we have been unable to detect any difference whatsoever in 1- and 2-year survivals between the negative recipient groups who get either a positive or negative donor. I think one need not absolutely restrict negative recipients to negative donors.

Appendix 1. Matching of donor and recipient ABO blood type

Blood type		Patients	
Donor	Recipient	No.	%
A	A	88	35
O	A	4	2
B	B	35	14
O	B	1	<1
AB	AB	6	2
A	AB	4	1
B	AB	2	<1
O	O	110	44
		250	100

Appendix 2. Matching of donor and recipient CMV status before transplantation

CMV status		Patients	
Donor	Recipient	No.	%
–	–	65	26
–	+	77	31
+	–	56	22
+	+	52	21
		250	100

Appendix 3. Donor characteristics

	Donor	
	No.	%
Sex		
Male	169	68
Female	81	32
Cause of death		
Gunshot wound	50	20
Intracranial bleeding	77	31
Motor vehicle accident	65	26
Head trauma	34	14
Others	24	10
Smoking history	76	30
Cardiac arrest	27	11
Respiratory arrest	28	11
Cardiopulmonary resuscitation	27	11
Sputum Gram stain positive for gram-negative rods	27	11
Inotropic support >10 mg/kg per minute	31	12