



FEATURE ISSUE:

ORGAN TRANSPLANTATION AT ST VINCENT'S CAMPUS TODAY

- HEART TRANSPLANTATION
- LUNG TRANSPLANTATION
- BLOOD STEM CELL TRANSPLANTATION
- RENAL TRANSPLANTATION
- OCULAR COMPLICATIONS OF ORGAN TRANSPLANTATION



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EDITOR, PROCEEDINGS

St Vincents and Organ Transplantation



IN 1993 Dr John Roarty published the first issue of the journal *Proceedings*, of St Vincent's Clinic, as a material reflection of the commitment of its doctors to education and research. Seven issues of the Journal have since been printed under John's supervision. As the Journal's new editor I would like to thank John for his pioneering efforts. I will endeavour to maintain the high standard which he established.

This issue is devoted to the theme of 'Transplantation' and, in particular, to the major organ transplants which are now possible on St Vincent's Campus.

St Vincents has always been at the forefront of development of organ transplantation in Australia. The nationally funded Heart Transplantation Programme was established at St Vincent's Hospital in 1984 and the first heart-lung and lung only transplants took place in 1986 and 1990. Drs Macdonald and Glanville have provided comprehensive reviews of the medical aspects of heart and lung transplantation, respectively. The first bone marrow transplantation (for a patient with acute leukemia) was performed at St Vincents in 1975. Major advances in cellular biology have transformed this specialty so that it is

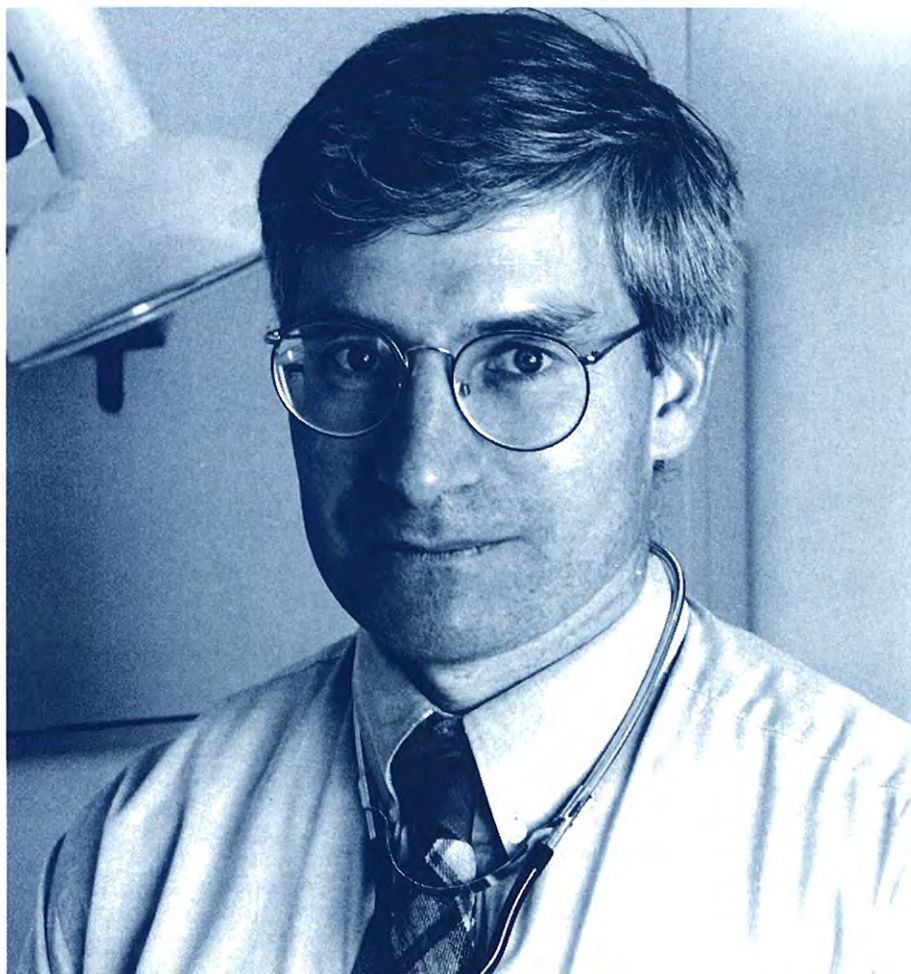
now more appropriate to speak in terms of blood stem cell transplantation as outlined in the article by Drs Dodds, Concannon and Milliken. It has recently become possible to extend its application to non-haematological disorders including advanced breast cancer and certain chronic, debilitating immunological conditions. Essential to the success of any type of major organ transplantation is the use of pharmacological immunosuppressive agents to prevent rejection. The new immunosuppressive drugs have been comprehensively reviewed by Drs Savdie and Hayes as part of their review of renal transplantation since this procedure was first performed at St Vincents in 1969. As acknowledged by all authors, major organ transplantation involves risks and this is well illustrated by Dr McCluskey's

article which focuses on the ocular complications of transplantation.

Regardless of type, a transplantation procedure for any individual is a major undertaking and all authors wish to acknowledge that they are part of a large team comprising dedicated medical colleagues, nurses and vital ancillary medical and administrative personnel.

Issues of *Proceedings* were initially jointly funded by the doctors of St Vincent's Clinic and St Vincents Private Hospital. They are now funded by St Vincent's Clinic Foundation, a fundraising body for selected research projects on St Vincent's Campus. The Foundation is very pleased to announce a recent donation of \$12,500 by FAI for sponsorship of *Proceedings*.

Heart Transplantation



INTRODUCTION

More than 500 heart transplants have been performed at St Vincent's Hospital since the establishment of the nationally-funded Heart Transplant Program in 1984. The success of this pioneering program has stimulated the establishment of heart transplant programs in Victoria, Queensland, Western Australia and New Zealand. Collectively, these programs have also performed more than 500 transplants. Approximately two-thirds of Australian heart transplant recipients are still alive and well 10 years after their transplant operation, with the majority returning to active employment in the community. These outcomes are significantly better than those reported by the international registry of the International Society for Heart & Lung Transplantation. Recent refinements in immunosuppressive therapy have resulted in more selective targeting of the alloimmune response, resulting in further improvements in

survival and less immunosuppression-related morbidity. Cardiac allograft vascular disease, also known as chronic rejection, is emerging as the major cause of late graft failure and mortality. Intense research into this insidious complication has led to the development of promising novel therapies that are likely to produce further improvements in long-term outcome. In spite of the dramatic success of heart transplantation as a treatment for end-stage heart disease, its application is limited to only a small percentage of patients who might benefit due to the severe limitation of donor organ availability. Two potential solutions to this problem are the xenotransplantation of organs from genetically modified pigs specially bred for this purpose or the development of artificial hearts capable of providing long-term support. While there are still formidable hurdles to be overcome, it appears likely that both approaches will reach clinical application within the next decade.

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Contra-indications to Heart Transplantation

	1984	1998
Age (years)	<6 yrs >50 yrs	>65 yrs
Pulmonary Vascular Resistance	PVR.6 Units	PVR.4 (on inhaled NO) TPG.15 mmHg*
Severe Primary Lung Disease	Absolute	Heart-Lung Transplant
Chronic Renal Failure	Absolute	Combined heart-kidney transplant
Chronic Liver Failure	Absolute	Combined heart-liver transplant
Malignancy	Absolute	Relative, cured cases accepted
Peripheral Vascular Disease	Absolute	Accept if surgically correctable
Diabetes Mellitus	Absolute	Accept provided no microangiopathic complication
Alcoholism, Drug Dependency	Absolute	Reformed cases considered
Severe Psychiatric Disorder	Absolute	Absolute
Morbid Obesity	Absolute	Absolute

* Transpulmonary gradient (TPG) = mean pulmonary artery pressure – mean pulmonary artery wedge pressure. Patients with an elevated TPG may be suitable for heterotopic (piggy-back) heart transplant or heart-lung transplant.

Table 1

REASON FOR TRANSPLANT

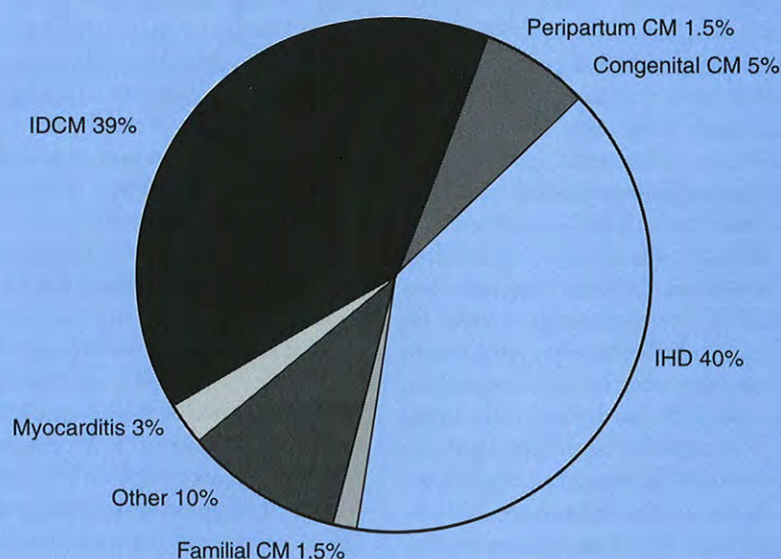


Figure 3. Indications for heart transplantation (Data from the Australian & New Zealand Cardiothoracic Transplant Registry).

HISTORICAL PERSPECTIVE

The first human heart transplant was performed by Christiaan Barnard more than 30 years ago in late 1967. Within a few months, multiple other centres around the world including St Vincents in Sydney had followed his lead. However it rapidly became apparent that the immunosuppressive therapy that was available at that time (prednisolone and azathioprine) was unable to prevent overwhelming and rapidly fatal rejection in the large majority of patients. Only a small percentage of these early heart transplant recipients achieved long-term survival. With the exception of a few transplant programs such as those at Stanford in California and La Pitie-Salpatriere in Paris, the procedure was largely abandoned until the discovery of the powerful immunosuppressive properties of cyclosporin by Jean Borel in the late 1970s. The success of cyclosporin-based immunosuppressive protocols in renal transplantation as demonstrated by Calne and colleagues from Cambridge in the early 1980s led to renewed interest in heart transplantation and the re-opening of the nationally funded heart transplant program at St Vincent's Hospital in February 1984. Fourteen heart transplants were performed in the first year of the program. This annual number increased steadily throughout the 1980s reaching a peak of 49 heart transplants in 1989. Since then the annual number has declined to between 35 and 40 as new transplant programs have become established in other states. At present, approximately 100 heart transplants are performed annually throughout Australia (Figure 1).

PATIENT SELECTION

A Indications

The primary indication for heart transplantation has been endstage heart disease with an expected survival of less than two years with conventional medical and/or surgical therapy. The vast majority of patients (more than 95%) suffer from severe symptomatic heart failure with symptoms of fatigue or

breathlessness on minimal exertion (so called New York Heart Association Class 3) or at rest (NYHA Class 4). About ten percent of those waiting for transplant are dependent for their survival on the administration of continuously administered intravenous inotropic agents or some form of mechanical circulatory support, either an intra-aortic balloon pump or left ventricular assist device (LVAD, Figure 2).

A small subset of patients are referred because of intractable angina which is unresponsive to medical therapy and is unsuitable for any form of surgical or catheter-based revascularisation. Until recently, heart transplantation was the only option available to these patients but a new experimental technique known as transmyocardial laser revascularisation (TMLR) may provide an alternative for these patients. TMLR is a surgical technique that involves the creation of up to 50 small laser channels through the myocardium. A number of laser devices have been developed including a Holmium-Yag device that is currently being evaluated in the Cardiothoracic Surgical Unit at St Vincent's Hospital.

Occasionally, patients with intractable and debilitating cardiac arrhythmias are also considered for heart transplantation. The efficacy of automatic implantable cardioverter-defibrillators (AICDs) has made this a rare indication for transplantation, however occasional patients with incessant or repeated firing of the defibrillator may be cured by transplantation.

The types of cardiac disease for which patients undergo heart transplantation are summarised in Figure 3. Approximately 80% of adult patients have either ischaemic heart disease or dilated cardiomyopathy with roughly equal proportions of these two diagnoses. Of the remaining 20%, the majority have end-stage valvular heart disease. Congenital heart disease is the indication for heart transplantation in only 1-2% of adult patients. In paediatric patients the proportions of patients with underlying congenital heart disease and ischaemic heart disease are reversed.

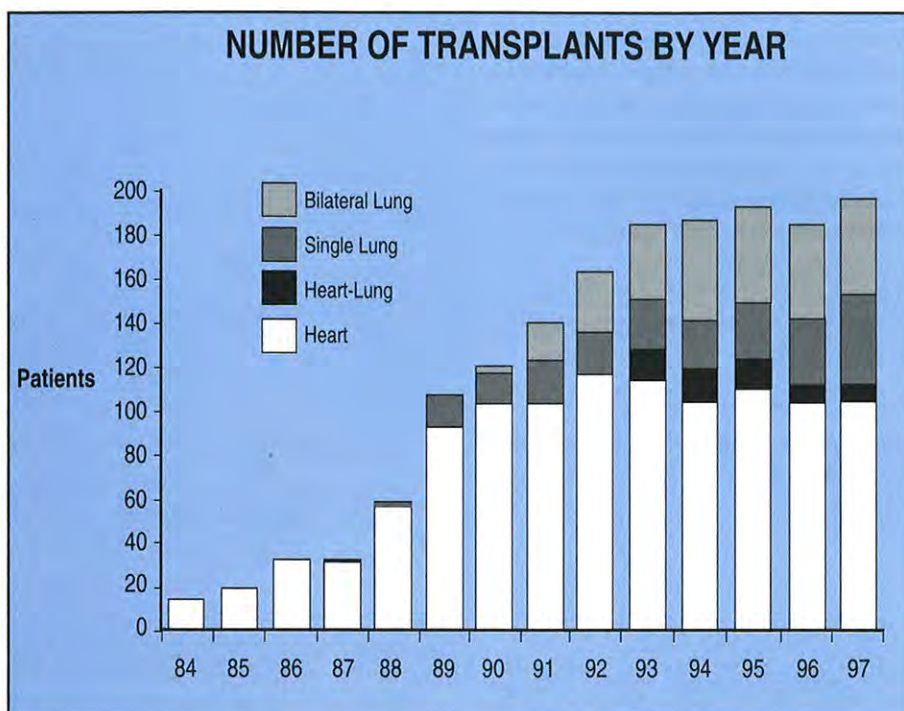


Figure 1. Annual cardiothoracic transplantation rate in Australia, 1984-97 (Data from the Australian & New Zealand Cardiothoracic Transplant Registry).

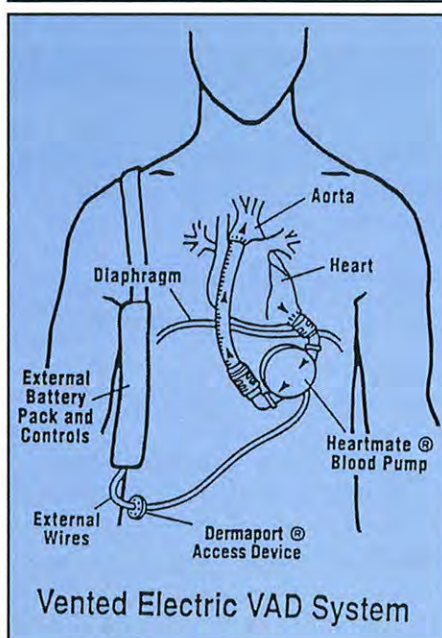


Figure 2. Electrically driven left ventricular assist device currently used to provide long-term circulatory support for patients with terminal heart failure awaiting heart transplantation at St Vincent's Hospital. Rechargeable batteries worn on a holster or belt allow the patient to mobilise freely for up to 6 hours. Once patients are trained in the technique of recharging and changing batteries, they can be managed as outpatients.

B Contraindications

The current contraindications to heart transplantation, as distinct from those that applied at the commencement of the heart transplant program in 1984, are shown in Table 1. As shown in the table there has been an easing of the contraindications particularly with regard to age. Because of the vast excess of patients with end-stage heart disease in relation to the number of donors (current estimates put this ratio at more than 10:1), strict selection criteria have been established for the acceptance of patients onto the heart transplant waiting list. The major criterion is that the individual undergoing transplantation should have

a high probability of full rehabilitation and return to an active life-style after transplantation. For this reason the patients with concurrent major comorbidities such as severe chronic air-flow limitation, surgically uncorrectable peripheral vascular disease or malignancy are generally considered unsuitable for transplantation. Furthermore, patients with conditions that are likely to be exacerbated by immunosuppression such as morbid obesity or advanced osteoporosis or individuals who are unable to comply with the complex medical therapy and monitoring post transplant (eg alcoholics, drug-dependents, intellectually disabled individuals) are also unsuitable.

Patient Assessment

The majority of patients referred for heart transplantation are able to be assessed as outpatients, however about 15% require inpatient evaluation and management. Investigations are aimed at establishing the following:

1. Conclusive evidence that there is no alternative medical or surgical options for management of heart failure
2. The pulmonary vascular resistance – this can only be established reliably by right heart catheterisation
3. Exclusion of comorbidities – investigations depend on history and examination findings eg spirometry for individuals with signs suggestive of severe airways disease, vascular studies for those with clinical evidence of cerebral or peripheral vascular disease
4. Concurrent or previous exposure to infections that may be activated by immunosuppression – Serology for CMV, Hepatitis B and C, HIV, Toxoplasmosis, Swabs for MRSA
5. Blood Group, HLA Antigen Status, Lymphocyte Panel Reactive Antibodies – the latter are usually IgG antibodies directed against non-self HLA Antigens
6. Biochemical assessment of renal, hepatic and thyroid function

Donor Selection and Donor-Recipient Matching

With the exception of “domino” donors (recipients of heart-lung transplants who are able to donate their heart), all cardiac donors are brain dead. It is now recognised that brain death results in acute injury to the donor heart which may result in severe early graft dysfunction and also predispose to “chronic rejection”. Further injury to the donor heart may occur during its preservation between excision and implantation. Hypothermic storage of the donor heart up to 6 hours is generally considered safe with current preservation solutions, but more prolonged storage times are associated with increased risk of early graft failure. In addition, there is evidence that hearts from donors older than 55 years are also associated with higher rates of early and late graft failure.

Recipients need to be ABO blood group compatible with (but not identical to) the donor, have no preformed antibodies directed against donor HLA antigens (negative direct-crossmatch) and usually be within 20% of the donor body-weight. Recipients with an elevated pulmonary resistance may require a donor with a weight advantage.

Immediate Post-Operative Management

Patients are uniformly treated with intravenous isoprenaline and the majority require temporary cardiac pacing for the first 3 days. Preoperative amiodarone therapy has been shown to increase the duration of temporary pacing required. Rarely, heart transplant recipients require permanent pacing probably as a result of ischaemic injury to the sino-atrial node at the time of transplantation. Most patients establish a resting heart rate between 90 and 110 beats per minute within one to two weeks of transplantation, the higher resting heart rate reflecting the denervated state of the heart.

Immunosuppression

A major goal of post-transplant management is to provide sufficient immunosuppression to prevent acute rejection without subjecting the patient to an unacceptable risk of infection or neoplasia. Currently, all heart transplant recipients are maintained on “triple immunosuppressive therapy” consisting of cyclosporin, azathioprine and prednisolone. The doses of all three agents are highest during the first three months post-transplant when the risk of acute rejection is highest. Most patients are weaned to chronic maintenance doses by about 6 months post-transplant. Cyclosporin is administered as a twice daily oral medication with the dose tailored according to 12 hour trough blood levels of the drug. Most patients are maintained on a chronic dose of 3-5 mg/kg/day. We and others have previously shown that approximately 50% of heart transplant recipients will develop acute rejection during or after weaning from corticosteroids, therefore our current policy is to wean all patients to a daily prednisolone dose of 0.1 mg/kg/day. Complete weaning from prednisolone is only attempted in patients with serious steroid-related side-

effects. Most patients are maintained on an azathioprine dose of 1-1.5 mg/kg/day.

Newer Immunosuppressive Agents

A number of promising new immunosuppressive agents have emerged in the last 5 years. These include tacrolimus (FK506), mycophenolate mofetil, sirolimus (rapamycin) and humanised monoclonal antibodies directed against the α chain of the IL2 receptor. Trials of these agents in heart transplantation are still ongoing, but preliminary experience suggests that their use will result in a lower incidence of acute rejection, fewer severe rejection episodes and a higher rate of steroid-free maintenance immunosuppression.

Rejection Surveillance

Heart transplant recipients are constantly at risk of acute rejection and for this reason require life-long immunosuppression. The risk varies with time, being highest during the first 3 months post-transplant then declining to a fairly constant low level by approximately 9 months post-transplant. Acute rejection beyond this period is unusual in the absence of any deliberate or accidental non-compliance with immunosuppressive therapy.

In spite of the advances in immunosuppressive therapy, 90% of patients will experience at least one “acute rejection episode”, defined as the presence of lymphocytic infiltration plus myocyte necrosis on endomyocardial biopsy. Surveillance endomyocardial biopsies are performed weekly for the first month post-transplant, fortnightly for the next two months, then less frequently until 9 months after transplantation. Approximately two thirds of acute rejection episodes identified in this way are asymptomatic. Such episodes are treated by “pulsed” corticosteroid therapy administered intravenously within the first month of transplantation or orally with later rejection episodes. Less than 10% of rejection episodes are associated with severe graft dysfunction in which case “rescue” therapy with T cell cytolytic agents such as OKT3 or antithymocyte globulin may be required to reverse the rejection episode and graft dysfunction. Some of the newer agents such as tacrolimus or mycophenolate may also be used to “rescue” patients. Some

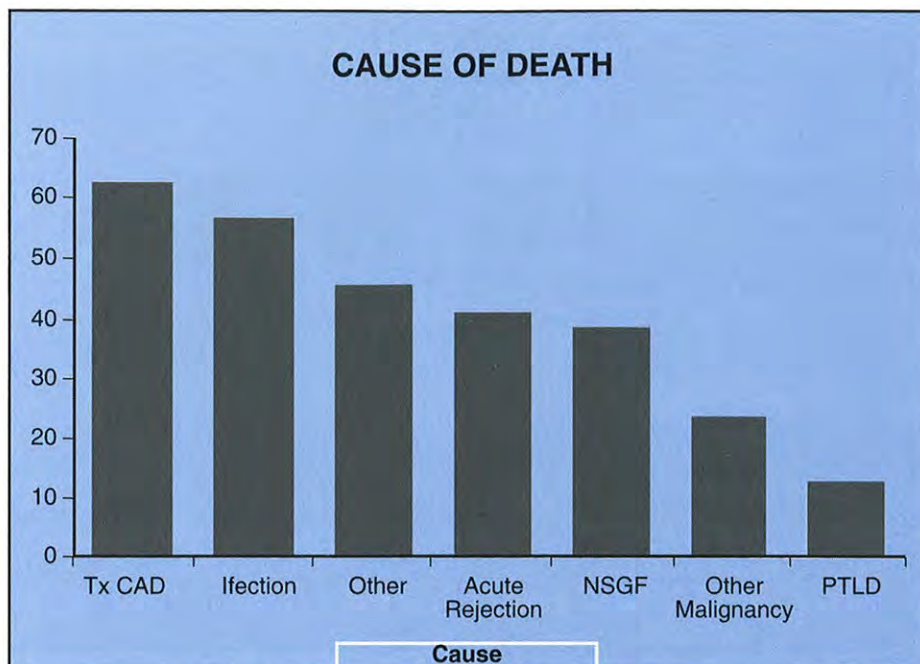


Figure 4. Causes of death after heart transplantation (Data from the Australian & New Zealand Cardiothoracic Transplant Registry).

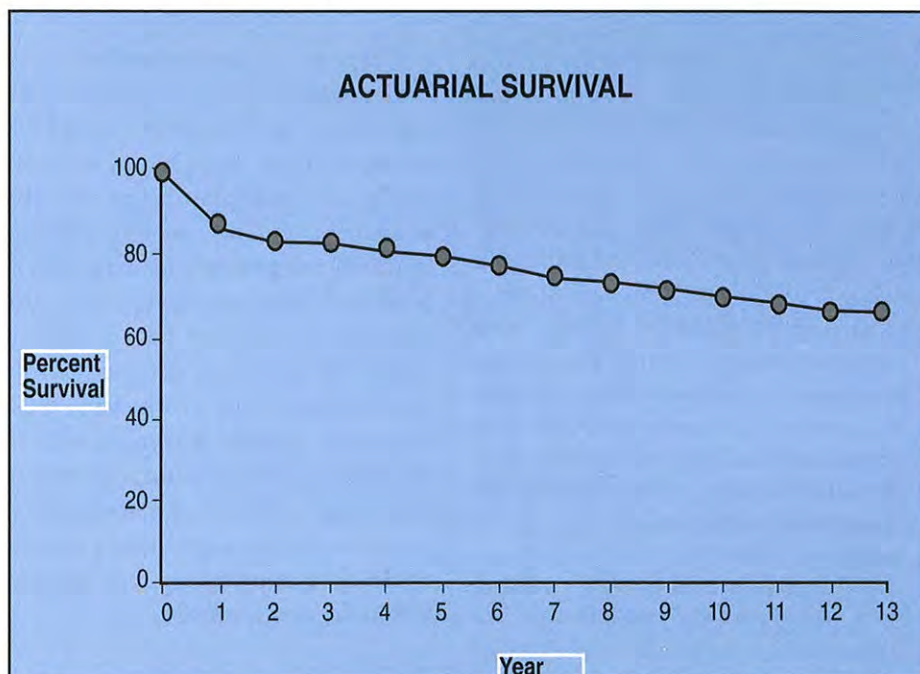


Figure 5. Actuarial survival after heart transplantation (Data from the Australian & New Zealand Cardiothoracic Transplant Registry).

individuals experience multiple recurrences of acute rejection. Most of these patients respond to tacrolimus or mycophenolate. Alternatively, we have found that low dose total lymphoid irradiation will prevent further recurrences in the majority of such patients.

Infections after heart transplantation

The major complication of immunosuppression is infection. Infection may occur at any time post-transplant, but is most common in the

first 3 months post-transplant when patients are receiving the highest doses of immunosuppressive therapy and often superadded "pulsed" steroid therapy. The type of infection varies according to time post-transplant. In the immediate post-operative period, bacterial infections due to multi-resistant hospital-acquired organisms are the most common serious infection. Oropharyngeal herpes simplex and candidiasis are also common but not life-threatening. Between one and four months, cytomegalovirus, fungal and protozoal infections due to pneumocystis

or toxoplasmosis may occur, however the frequency and severity of these infections has been blunted by the use of prophylactic antimicrobial agents including ganciclovir, itraconazole and cotrimoxazole. The emergence of resistant strains of these organisms is an ongoing concern but has not yet become apparent in the Australian heart transplant population.

Other post-transplant morbidities

Currently used immunosuppressive agents are associated with a variety of serious sequelae apart from infection. It is now recognised that post-transplant patients are at increased risk of malignancy. Overall, 8% of heart transplant patients develop some form of malignancy within 3 years of transplant. Skin cancer and post-transplant lymphoproliferative disease (PTLD) are the most common neoplastic conditions, but it is now recognised that all forms of cancer are more common in transplant recipients. Post-transplant malignancies tend to be more aggressive than corresponding malignancies in non-immunosuppressed individuals and are generally associated with poorer survival rates. Some malignancies, particularly PTLD, respond to reduction in immunosuppressive therapy.

Hypertension, hyperlipidaemia, diabetes, osteoporosis, obesity

Hypertension occurs in more than 80% of heart transplant recipients maintained on cyclosporin. It often appears within the first week post-transplant and may progress rapidly to hypertensive encephalopathy if not recognised and treated early. Often multiple anti-hypertensive agents are required to achieve acceptable blood pressure control. An angiotensin converting enzyme inhibitor together with diltiazem is currently our preferred combination. Diltiazem has also been found to reduce the rate of development of transplant coronary artery disease (see below).

Hyperlipidaemia, both hypercholesterolaemia and hypertriglyceridaemia, are very common after transplantation. Both cyclosporin and prednisolone have been implicated in the pathogenesis of these hyperlipidaemias but the exact mechanism remains unclear. There is now clinical trial data

linking both forms of hyperlipidaemia to transplant coronary artery disease and the prophylactic use of pravastatin has been shown recently to reduce the incidence of this dreaded complication.

New onset diabetes mellitus requiring drug therapy occurs in 15-20% of heart transplant recipients. Even higher rates have been reported in tacrolimus-treated patients. Obesity and osteoporosis are also common complications of immunosuppressive therapy. Although not life threatening, they may cause major morbidity and markedly impair patient's quality of life. Osteoporosis may be ameliorated by prophylactic administration of calcitriol or biphosphonates.

Transplant coronary artery disease

Transplant coronary artery disease is the major cause of death beyond the first year after heart transplantation (Figure 4). Pathologically it resembles an accelerated form of atherosclerosis and is characterised by a diffuse intimal thickening involving both small and large coronary arteries. Ultimately, the lesion progresses to complete luminal occlusion resulting in ischaemic necrosis of the myocardium. Both small and large myocardial infarcts may occur, often without chest pain due to the denervated state of the heart. Multiple aetiological factors have been implicated in the pathogenesis of transplant coronary artery disease including ischaemic injury to the graft at the time of implantation, chronic rejection and conventional atherogenic risk factors. Common to all these aetiological factors is coronary endothelial injury. Clinically apparent transplant coronary artery disease is evident in about 50% of heart transplant recipients by 5 years post-transplant. Common clinical presentations include abrupt onset of heart failure or sudden death. Transplant coronary artery disease is often not amenable to conventional revascularisation due to the diffuse nature of the lesion. As mentioned previously, clinical trials with pravastatin and diltiazem have shown that these agents reduce the rate of development of clinical events attributable to transplant coronary artery disease.

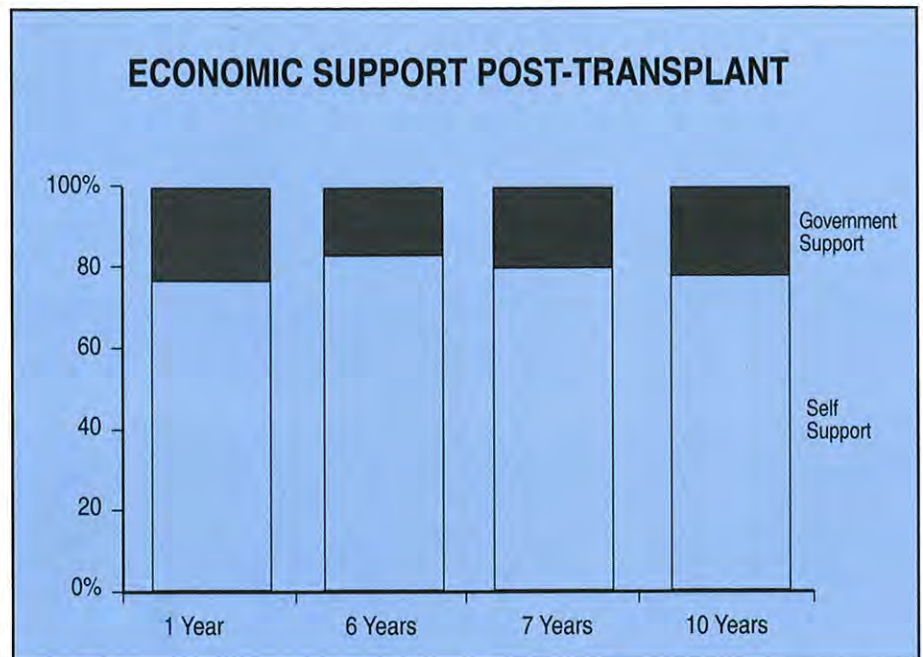


Figure 6. Rehabilitation after heart transplantation (Data from the Australian & New Zealand Cardiothoracic Transplant Registry).

Survival after heart transplantation (Figure 5)

Overall, 87% of heart transplant recipients survive the first year after heart transplantation. Actuarial survival rates at 5 and 10 years are 79% and 68% respectively. The primary cause of death varies according to time post-transplant. Within the first month, non-specific graft failure (NSGF) is the most common cause of death. Thereafter, acute rejection and infection are the two major causes of death up to one year post-transplant. Beyond the first year, transplant coronary artery disease and malignancy account for the majority of deaths.

Rehabilitation

Individuals undergoing heart transplantation are usually markedly debilitated by intractable chronic heart failure. In spite of this and the considerable immunosuppression-related morbidity, the vast majority are able to return to an active life-style (Figure 6). Approximately 70% of heart transplant recipients return to some form of employment (full-time, part-time, home duties or study) and are able to pursue a range of sports and other leisure activities. Most eventually require only annual check-ups through the transplant clinic.

Future developments

Despite improvements in immunosuppressive agents, patients are still subject to considerable morbidity related to their use. One of the holy grails of transplantation is the attainment of donor-specific tolerance in which the patient's immune system remains unresponsive to the transplanted organ but fully competent against other foreign antigens. While this is relatively easy to achieve in small laboratory animals, it is rarely seen in the clinic. Nonetheless, tolerance remains an active area of transplantation research and it is hoped that clinically applicable approaches will emerge within the next few years.

In spite of the dramatic success of heart transplantation as a treatment for end-stage heart disease, its application is limited to only a small percentage of patients who might benefit due to the severe limitation of donor organ availability. Two potential solutions to this problem are the xenotransplantation of organs from genetically modified pigs specially bred for this purpose or the development of artificial hearts capable of providing long-term support. While there are still formidable hurdles to be overcome, it appears likely that both approaches will reach clinical application within the next decade.

Lung Transplantation



HISTORICAL DEVELOPMENT

The first successful lung transplant was performed in 1981 at Stanford University Medical Centre, on a 45 year old woman with primary pulmonary hypertension, who received an en bloc bilateral lung and heart transplant, a procedure which became known as a heart lung transplant (HLT).

The impetus for developing this novel form of surgery was based on the inability of heart transplantation alone to treat patients with irreversible pulmonary hypertension and the failure up until that time of single lung transplantation to provide enduring survival due to limitations with ischaemic breakdown of anastomoses, uncontrolled rejection and uncontrolled infection.

Two developments were critical to allow the success of this endeavour, namely, the development of cyclosporin

to allow the utilisation of a lower dose of corticosteroid and the demonstration of prolonged survival of sub-human primates who had received heart lung transplants in the Stanford Animal Laboratory.

Hitherto, it had been thought that the Hering-Breuer inflation inhibition reflex would prevent adequate ventilation in primate species. That this reflex showed considerable intra-species variability was confirmed and paved the way for human experimentation. An additional feature of the en bloc procedure was the provision of oxygenated blood to the tracheal anastomosis by a previously unrecognised collateral circulation from the right coronary artery. The viability of this critical anastomosis was thereby ensured.

Four years later, Joel Cooper, working in the Toronto program, reported successful use of a technique of omental wrapping of the bronchial anastomosis to provide adequate circulation and

ACKNOWLEDGEMENT

The author acknowledges the efforts of every member of the lung transplant team who has contributed to the results described herein.

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thereby prevent ischaemic breakdown for single lung transplant (SLT) recipients. By the end of the decade, this procedure was employed widely for both single and bilateral sequential lung transplant (BSLT) recipients and, with the pressure to share vital organ resources amongst lung only and heart lung transplant recipients, the frequency of performance of the combined heart lung transplant procedure began to reduce.

Other milestones in the development of lung transplantation included:

1. the recognition that obliterative bronchiolitis, a fibrosing condition of small airways, was perhaps the major limiting factor for quality of life and survival following otherwise successful lung transplantation.
2. the importance of pulmonary allograft rejection which was recognised following the development of the technique of transbronchial lung biopsy which has allowed a comprehensive assessment of graft pathology without recourse to open-lung biopsy.
3. the advent of effective preventive therapy for cytomegalovirus (CMV) in 1988 which has virtually eliminated this pathogen as a cause of early mortality following transplant.

TRANSPLANTATION AT ST VINCENTS

Heart lung transplantation commenced at St Vincents in 1986, but it was not until 1989 (Figure 1) that procedures were performed in any number. Activity has remained fairly static over the last five years, with approximately 35 procedures per year. Activity is limited by donor availability. During the last decade, the Lung Transplant Unit at St Vincents has become one of the ten largest lung

Key to Table 2

PPH	primary pulmonary hypertension
CHD	congenital heart disease
CF	cystic fibrosis
AAT	alpha-1 antitrypsin deficiency
COAD	chronic obstructive airway disease
CFA	cryptogenic fibrosing alveolitis
TEPH	thromboembolic pulmonary hypertension
PLAM	pulmonary lymphangioleiomyomatosis

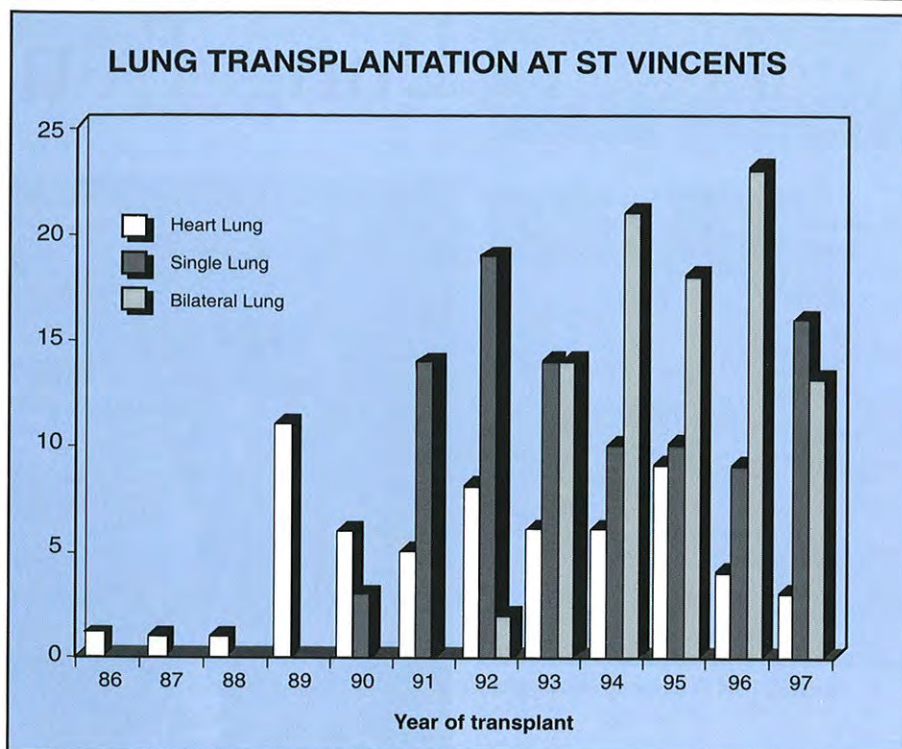


Figure 1. Lung Transplantation by Mode and Year of Transplant at St Vincents.

	HLT	SLT	BSLT
NUMBER	63	98	100
AGE RANGE (mean)	14-52 (35)	26-57 (49)	21-57 (36)
GENDER (f:m)	34:29	46:52	43:57
OUTCOME			
Patients alive	31 (50%)	65 (68%)	77 (77%)
Early deaths (<30 days)	6 (10%)	7 (7%)	6 (6%)
Late deaths	26 (40%)	26 (25%)	17 (17%)

Table 1. Demography and Outcome by Mode of Lung Transplant at St Vincents.

DIAGNOSIS	HLT	SLT	BSLT
PPH	21		1
Eisenmenger's	14		
CHD	8		
CF	5		46
AAT	5	30	16
COAD	2	51	18
CFA	1	12	5
Bronchiectasis	2		13
TEPH	1		
Sarcoidosis	1	1	
Asbestosis	1		
Silicosis	1		1
Alveolar cell ca		1	
PLAM		2	
Histiocytosis X	1	1	
TOTAL	63	98	100

Table 2. Specific Indications for Lung Transplantation at St Vincents.

MEDIAN LENGTH OF PATIENT STAY AFTER LUNG TRANSPLANTATION AT ST VINCENTS

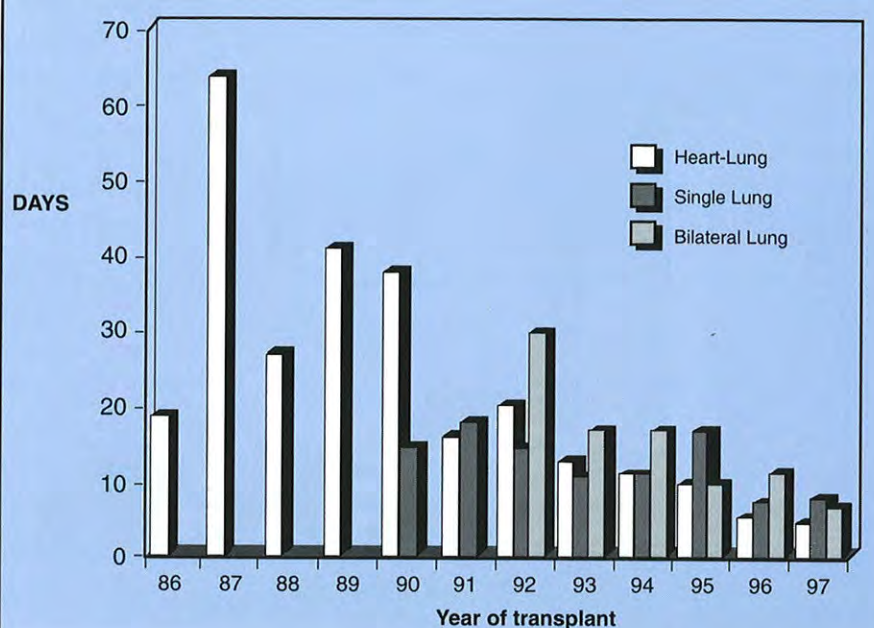


Figure 2. Median length of Inpatient Stay After Lung Transplantation at St Vincent's by Mode of Transplant.

	Range	Mean	Total Days
HLT	0 - 3871	1104	67,361
SLT	1 - 2595	1009	95,818
BSLT	2 - 1938	755	69,499
TOTALS	0 - 3871	934	232,678

Table 3. Survival After Lung Transplantation at St Vincent's Measured in Postoperative Days as of 30.06.1998.

INDICATIONS*

- Cystic fibrosis
- Emphysema and other forms of primary lung disease
- Interstitial fibrosis
- Primary pulmonary hypertension
- Congenital heart disease with Eisenmenger complex

INCLUSION CRITERIA

- Informed consent
- Under 45 years of age (HLT) or 55 years of age (SLT & BSLT)
- End-stage symptoms

EXCLUSION CRITERIA

- Mediastinal irradiation
- Severe psychiatric disturbance
- Substance abuse
- Morbid obesity or cachexia
- Malignancy
- Current high-dose corticosteroid therapy
- Coagulopathy
- Active bronchopulmonary infection with fungi or mycobacteria
- Severe hepatic or renal dysfunction
- Diabetes mellitus with end organ disease
- Collagen vascular disease, eg. SLE, PSS
- Immunodeficiency states, eg. AIDS, hypogammaglobulinaemia
- Multiresistant bacteria, eg. MR Staphylococcus aureus, MR Klebsiella pneumoniae, MR Burkholderia cepacia/gladiolus

Table 4. General Indications, Inclusion and Exclusion Criteria for Lung and heart-Lung Transplantation at St Vincents. *Type of transplant as appropriate to individual case.

transplant units in the world with an activity level per annum in the top six and a survival rate second to none. St Vincents has been active in training physicians and surgeons throughout Australia to provide a national strategy for lung transplant services and, importantly, to guarantee a mantle of safety for patients who are geographically isolated from St Vincents.

To date, 424 lungs and 63 hearts have been transplanted into a total of 261 recipients, ranging from 14 to 57 years (Table 1) with an overall perioperative (30 day) mortality of 7%. Specific indications for transplantation at St Vincents are outlined in Table 2 and to date, the patient group has experienced over 600 years survival post-transplant (Table 3). Improvements in recipient selection, donor selection, surgical technique and perioperative management have led to a remarkable reduction in inpatient stay following transplantation (Figure 2), so that median stays for all transplants performed over the last two years have been less than 10 days. An active exercise physiotherapy rehabilitation program has been a key feature in achieving these remarkable results.

PATIENT SELECTION

Since the commencement of lung transplantation at St Vincents in 1986, the overall philosophy regarding listing for transplantation has changed from a highly selective process, where many patients were denied the opportunity of transplantation due to perceived high risks at that time of development of the program, to one where, with the maturation of the program and increased experience with a multitude of indications, the philosophy is now how best to effect a successful result for that individual patient, irrespective of their underlying condition and co-morbidities. However, a number of patients have major exclusion criteria (Table 4) which would lead to their having an unacceptable risk-benefit ratio and, hence, not all patients who are referred for transplantation are indeed suited to these modalities.

DONOR SELECTION AND MATCHING

Unlike heart transplantation where weight is the major determining

criterion, given blood group and crossmatch suitability, in lung transplantation the lung size is determined predominantly by height and gender. The intention is to match the recipient with a donor whose predicted total lung capacity is within 20% of the measured total lung capacity of the recipient. Ideally, donor and recipient should be matched for CMV status and Epstein-Barr virus status but this is not always practical and, providing prophylactic therapy for these viruses is employed, the long-term survival for miss-matched patients is at least as good as those who are matched. Gender miss-matching of donor and recipient does not appear to be associated with deleterious side effects long-term.

PERIOPERATIVE MANAGEMENT

The perioperative management phase is a critical period for success or failure of an individual transplant. Ischaemia reperfusion injury of the graft is a major complication which may prolong the need for ventilatory support and promote graft injury, pulmonary fibrosis and secondary infection. Profound ischaemia is also associated with increased risk of anastomotic necrosis, dehiscence and late stricture formation. The availability of inhaled nitric oxide has allowed the salvage of a number of patients in recent years who may have had prolonged ventilation following transplant. Nitric oxide is a selective inhaled pulmonary vasodilator with minimal systemic effects due to local pulmonary metabolism. The effect is to promote and maximise ventilation perfusion matching, thereby reducing dead space ventilation and allowing a reduction in inspired oxygen concentration (FiO_2). The use of a lower FiO_2 has beneficial effects in the reduction of oxygen free radical damage to the lungs, which results in hyaline membrane formation and secondary fibrosis.

IMMUNOSUPPRESSION

The St Vincents program has swung away from using cytolytic induction chemotherapy in view of the increased risk of life-threatening infection associated with these modalities. Our current maintenance immuno-

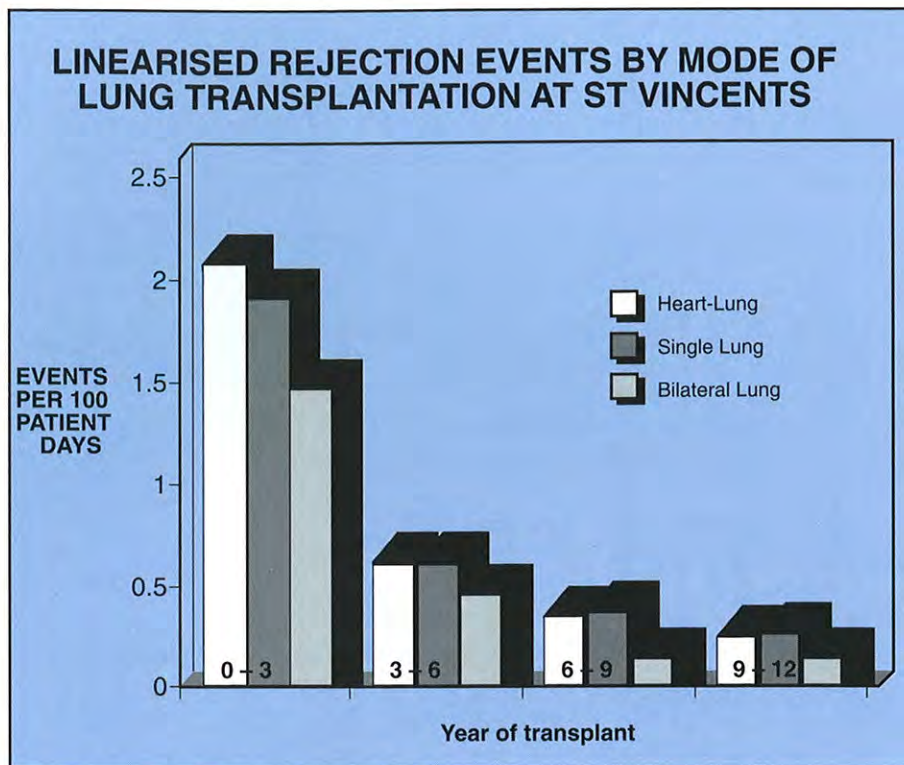


Figure 3. Linearised Rejection Events by Mode of Lung Transplant at St Vincents.

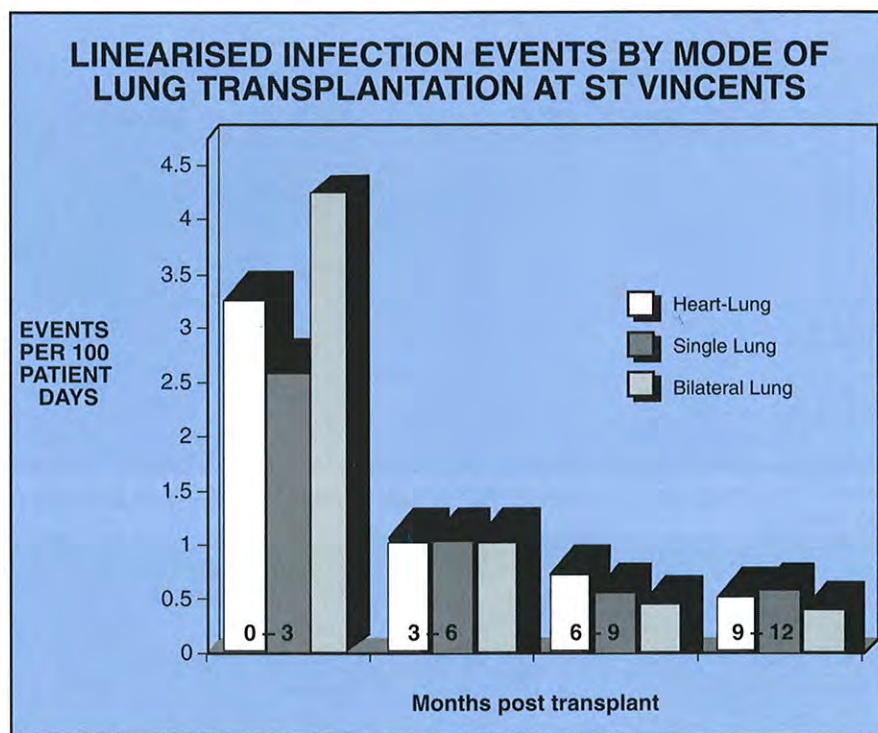


Figure 4. Linearised Infection Events by Mode of Lung Transplant at St Vincents.

suppressive therapy comprises cyclosporin (targeting a reducing blood level according to time post-transplant), azathioprine (monitoring white cell count and liver function) and prednisolone (aiming to reduce the maintenance dose to 0.1mg/kg or less in patients who have not demonstrated significant rejection). We have utilised tacrolimus (FK506) successfully in patients who have had lung rejection refractory to corticosteroid therapy,

substituting FK506 for cyclosporin. However, increased renal, neurological and diabetic sequelae have been noticed. Mycophenolate Mofetil is currently on trial as an alternative to azathioprine as part of an international study where St Vincents has been accorded Special Investigator status. St Vincents has also commenced an international trial with an agent previously not utilised in lung transplant recipients, SDZ-RAD, a rapamycin derivative which, in

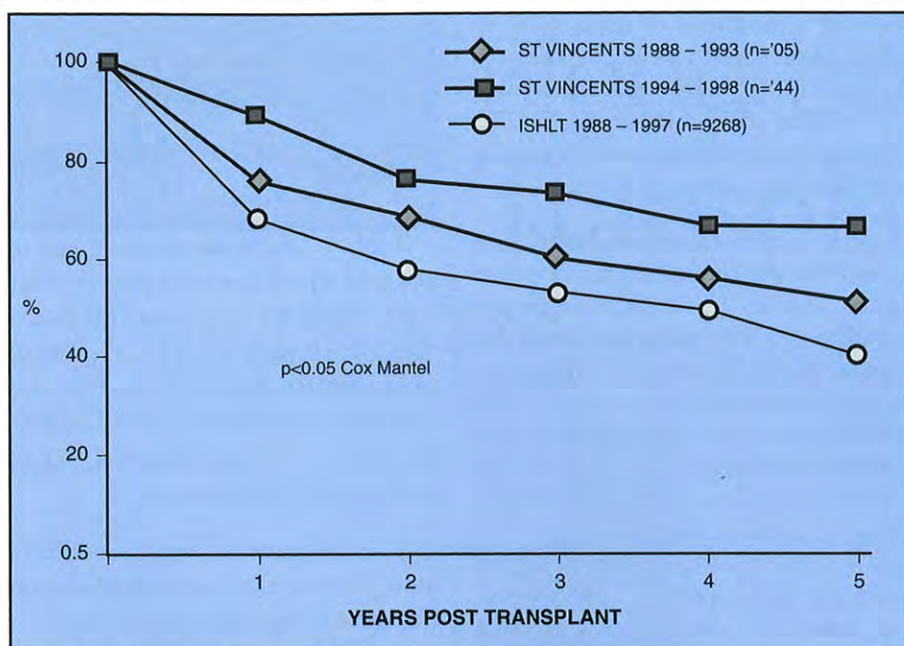


Figure 5. Actuarial Survival After Lung Transplantation at St Vincents.

	HLT	SLT	BSLT
Infection	9	15	7
Obliterative Bronchiolitis	5	8	7
Lymphoid Malignancy	6		1
Cerebrovascular Disease	2	1	1
Graft Failure	1	3	1
Haemorrhage		2	1
Rejection	1	1	
Graft Atherosclerosis	3		
Lung Ca			1
Pancreatitis	3		
Bronchial Dehiscence		1	2
Tracheal Dehiscence	1		
ABO Incompatibility	1		
Reperfusion Injury		1	
Dissecting Aortic Aneurysm		1	
Chondromalacia			1
Unknown			1
TOTAL	32	33	23

Table 5. Cause of Death After Lung Transplantation at St Vincents.

experimental work, shows great promise in preventing the development or progression of obliterative airway lesions by reducing proliferative and fibrogenic responses. Other novel immunosuppressive agents include Interleukin 2 receptor blockers, which may be particularly useful to reduce airway damage.

REJECTION

Acute pulmonary allograft rejection is most common in the first three months after lung transplantation. However, whilst the frequency falls, patients are always at risk of rejection and hence

immunosuppression is continued for life. There is no significant difference in rejection events between modalities of transplant (Figure 3).

Lung rejection is diagnosed histopathologically by performing bronchoscopy with transbronchial lung biopsy, where 6 - 12 samples are taken from one lung to give a 95% confidence of excluding significant pulmonary allograft rejection. Allograft rejection is the most significant association for the development of subsequent obliterative bronchiolitis. In the first year post-transplant, patients average 6.6 transbronchial lung biopsies, with a range of 2 - 12.

	(n)	(%)
Transplanted	105	55
Died Waiting	31	16
Delisted	11	6
Still Waiting	44	23
TOTAL	191	100

Table 6. Outcome of Patients Listed For Lung Transplantation 1995-1998.

The treatment of rejection depends on histopathological severity as graded by the International Society of Heart and Lung Transplantation (ISHLT) criteria, the antecedent rejection history, the time post-transplant and the clinical sequelae of the rejection event. The majority of first rejection episodes are treated with intravenous pulse Solu-Medrol therapy (methylprednisolone 12.5mg/kg bodyweight x 3 doses) + oral corticosteroid pulse (1mg/kg reducing by 5mg/day back to maintenance) with a repeat biopsy to prove that the rejection has been successfully treated. Rejection events that are refractory to this treatment are managed with cytolytic therapy (ATG or OKT3) or increasingly, conversion to FK506.

Rejection, per se, is an uncommon cause of death following transplant (Table 5). However, the effects of augmented immune suppression are an increased risk of both infection and malignancy, including post-transplant lymphoproliferative disease (PTLD), which is a significant cause of mortality in our group.

INFECTION

Bilateral lung transplant recipients appear to have more infection events in the first three months post-transplant (Figure 4). This is related to the indication for transplant, namely cystic fibrosis or bronchiectasis. The majority of such patients continue to be colonised by gram negative bacilli, eg pseudomonas. The practice of routine use of prophylactic antibiotics after surgery has reduced perioperative pulmonary infection, need for prolonged assisted ventilation and reduced inpatient stays.

Prophylactic anti-fungal therapy with nebulised amphotericin has reduced significant infections with aspergillus and candida in the perioperative period. However, these organisms, particularly aspergillus, remain significant causes of graft deterioration and loss in long-term patients.

Lifelong prophylactic therapy with sulfamethoxazole/trimethoprim is employed to reduce the risk of infection with *Pneumocystis carinii* pneumonia, *Nocardia* and *Toxoplasma*.

Prophylactic ganciclovir therapy (5mg/kg bodyweight 3 times per week) is used for 10 weeks post-transplant in sero-negative CMV recipients who receive a sero-positive graft. Based on evidence that up to 50% of Epstein-Barr virus naive recipients who receive a positive EBV graft will develop post-transplant lymphoproliferative disease, long-term prophylactic therapy with acyclovir is used in this group.

Approximately 9% of patients post-transplant have been diagnosed with mycobacterial infection, the majority of whom have had either pulmonary or cutaneous infection with atypical organisms. Our experience is the largest in the world with this particular type of infection after solid organ transplant and we have demonstrated that the majority of infections can be treated without recourse to surgery such as amputation. A number of patients with graft dysfunction due to mycobacterial infection have shown improvement to normal following treatment. However, the risks of multi-drug interactions and the effect of rifampicin in particular, causing an accelerated metabolism of cyclosporin via the cytochrome P450 system, are not to be understated.

CHRONIC REJECTION

In heart lung transplant patients, chronic coronary allograft vascular disease has been responsible for a number of deaths following transplant. The mechanism and management is identical to that in heart only transplants.

Obliterative bronchiolitis is perhaps the pulmonary equivalent of graft coronary disease. Obliterative bronchiolitis represents an ineffective

healing mechanism of small airways which have received a mucosal and sub-mucosal injury and responded with a proliferative and fibrogenic response to form granulation tissue and ultimately scar tissue with neovascularisation.

Small airways in a transplanted lung reflect the pre-transplant status of the lungs and all those factors which comprise the antecedent history of the donor, including previous infection, occupational and smoking exposure. The mode of death of the donor is relevant, particularly as to whether there has been pulmonary aspiration at the time, in addition to which there are specific effects on the lung due to brain death per se, the method of preservation and handling of the lungs, the duration and severity of ischaemia reperfusion injury, the presence or absence of pulmonary infection and the resultant history of acute rejection of the graft. Acute pulmonary allograft rejection in the first 45 days post-transplant does not impact negatively on the development of obliterative bronchiolitis. Recurrent and higher grade rejection thereafter do and about 50 per cent of lung transplant patients are thought to develop chronic rejection.

MORBIDITY

The majority of morbid events occurring after lung transplantation are similar to those occurring after heart transplantation. Many are drug-related, specifically the effects of oncogenesis related to immunosuppression (eg the development of PTLD and cutaneous malignancy). Side effects of chronic steroid and cyclosporin treatment are common. Bronchial stricture is unique to lung only transplantation and occurs in approximately 11% of bronchial anastomoses. It generally reflects ischaemic injury $\pm$ local infection and providing frank dehiscence does not occur, can be managed effectively with balloon dilatation $\pm$ insertion of either a flexible endoxane (Dumon) stent or a flexible, non-covered wallstent. The advantage of the endoxane stent is that it is easy to remove subsequently, leaving a patent airway. The wallstent tends to become epithelialised and thereby incorporated into the airway, hence it is more difficult to remove and is usually left in situ. Both stents are prone to lamination with secretions and patients

may need to utilise inhaled mucolytics to prevent this complication.

SURVIVAL AND QUALITY OF LIFE

Table 6 illustrates the outcome of patients who have been accepted for active listing for lung transplant over a three year period. Whilst 55% of patients listed during this period received a transplant, 31, (16%) died on the waiting list, reflecting the lack of availability of donor resources.

The pattern of post-operative mortality has changed somewhat over the last ten years with a slight reduction in early infectious deaths and a slight increase in long-term deaths due to chronic graft failure due to obliterative bronchiolitis (Table 5). Sporadic deaths due to non-transplant related events including cerebral aneurysm, aortic aneurysm and pre-existing malignancy, are an inescapable feature of the patient population despite a comprehensive evaluation prior to transplantation.

Actuarial survival is improving (Figure 5) with a significant increase in five year survival since our early experience. Indeed, St Vincent's results are significantly better than those reported by the ISHLT. The current expectation for all modes of lung transplant is for a 90% 1 year survival with a slow attrition rate thereafter. Analysis of actuarial survival by mode of transplant shows that bilateral lung transplant, the most recent form of transplant performed at St Vincents (since 1992), has the best results. This in part reflects the learning curve from the early heart lung and single lung transplant experience.

The majority of lung transplant recipients are independent in activities of daily living, no longer dependent on oxygen therapy, capable of gainful employment and many are able to enjoy vigorous physical pursuits such as horseriding, swimming and even running triathlons. Moreover, approximately 80% of recipients remain independent of government financial assistance.

**Drs Tony Dodds,
Alan Concannon
and Sam Milliken**

Blood Stem Cell Transplantation

INTRODUCTION

Clinical bone marrow transplantation began over 30 years ago and it is now 23 years since the first Australian adult transplant was performed at St Vincent's Hospital in Sydney. From uncertain beginnings with a high mortality, the therapy has now progressed to be a standard means of treatment of forms of leukaemia, lymphoma, myeloma, solid tumours and some non-malignant disorders such as thalassaemia major and severe aplastic anaemia (Table 1). Large bodies of data accumulated on the International Bone Marrow Transplant Registry and The Autologous Blood and Bone Marrow Transplant Registry have provided evidence for the effectiveness of transplantation. In addition, an increasing number of randomised studies have shown transplantation to be superior to standard treatment in acute myeloid leukaemia, poor prognosis lymphoma and metastatic breast cancer. Advances over the last 5-10 years have made this therapy progressively safer and more effective (Table 2).

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ADVANCES

In the last 30 years better understanding of stem cell biology has enabled a change in the source of blood stem cells from the bone marrow to peripheral blood. We now refer to this therapy as **blood stem cell transplantation** rather than bone marrow transplantation. Blood stem cells can be collected from the peripheral blood by a process called **mobilisation**. This involves giving a haemopoietic cytokine with or without chemotherapy to the donor. Mobilisation releases large numbers of stem cells into the blood from where they can be collected using an apheresis machine. Initially all transplants were from allogeneic donors but use of the patient's own stem cells (autologous blood stem cell transplantation) has increased and now constitutes the most common form of blood stem cell transplantation. There has also been a growth in the use of

SOME INDICATIONS FOR BLOOD STEM CELL TRANSPLANTATION

Acute leukaemia
Chronic Myeloid Leukaemia
Malignant Lymphoma
Multiple Myeloma
Severe Aplastic Anaemia
Thalassaemia major
Breast Cancer

Table 1

matched unrelated donors from large donor registries (both national and international) and a more recent use of cord blood stem cells. The use of cord blood stem cells has mainly been confined to children but methods to expand their number may widen their applicability.

Supportive care has improved to the extent that autologous transplantation has become an extremely safe procedure with **mortality of <1%** in our hands. This has been achieved by the use of haemopoietic growth factors, antimicrobial prophylaxis and prevention of veno-occlusive disease and haemorrhagic cystitis. Haemopoietic growth factors such as G-CSF are used both to mobilise blood stem cells and to speed engraftment of these stem cells after transplant. Antimicrobial prophylaxis with norfloxacin, fluconazole and trimethoprim-sulfamethoxazole has been applied to reduce serious infections post-transplant. Ganciclovir is also used in allogeneic transplants to eliminate CMV infections. Heparin in low dose is effective in reducing the risk of veno-occlusive disease of the liver. Hyperhydration with forced diuresis is used to reduce haemorrhagic cystitis.

Newer techniques to concentrate and purify blood stem cells have been developed. These techniques mainly use monoclonal antibodies directed against the CD34 antigen which identifies a population of cells containing the stem cells. Positive or negative selection can then be used to concentrate the stem cells thus removing contaminating tumour cells in autologous transplants or immunoreactive T-cells in allogeneic transplants. Such techniques will also be used in **gene therapy** when it becomes available.

RESULTS AT ST VINCENTS

St Vincents has remained a leader in blood stem cell transplantation. Almost 800 transplants have been carried out on the Campus since 1975 (Figure 1). The transplant unit carries out 50-60 transplants per year with referrals from throughout NSW and a number of patients from Asia. A complete data base of all the transplants is kept within the Unit and an annual report of all transplant outcomes is produced which provides a vital quality measure enabling us to improve the success of the procedure. For example a recent review of our matched unrelated transplants in poor risk otherwise terminal patients has revealed a survival probability of 23% (Fig 2). We now plan to extend this

RECENT ADVANCES IN BLOOD STEM CELL TRANSPLANTATION

- Use of alternate sources of stem cells
- Better patient selection
- Stem cell selection and purging of tumour cells
- Improvements in supportive therapy
 - Use of haemopoietic cytokines
 - Antimicrobial prophylaxis
 - Prevention of veno-occlusive disease
 - Prevention of haemorrhagic cystitis

Table 2

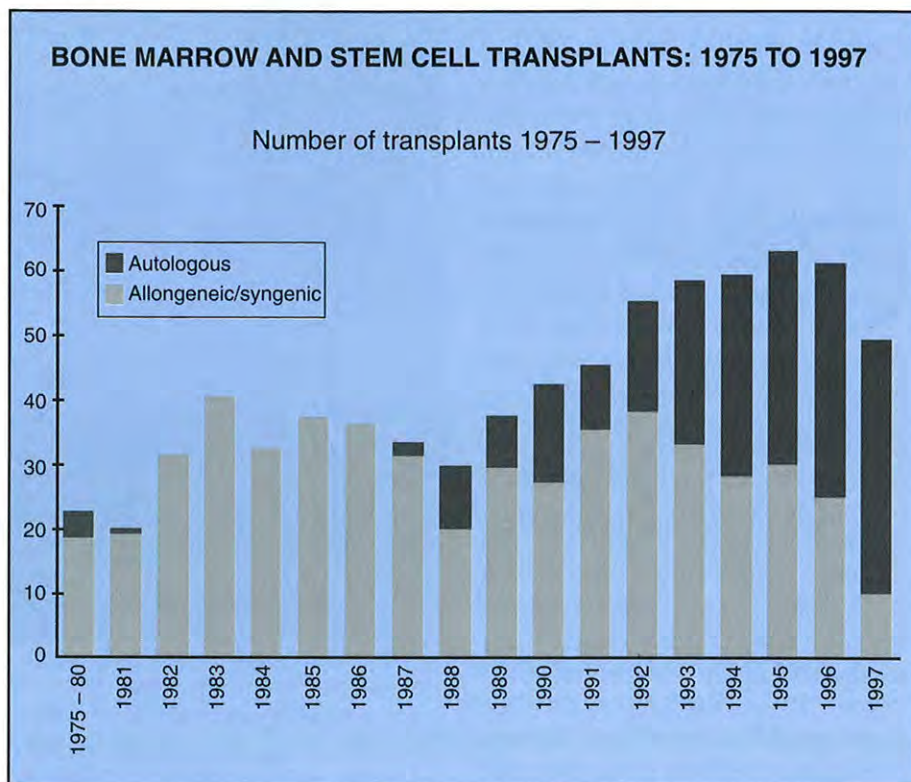


Figure 1: Number of bone marrow and blood stem cell transplants at St Vincents from 1975 – 1997.

program to better risk patients. This should improve the overall survival as most deaths are related to the transplant itself rather than relapse.

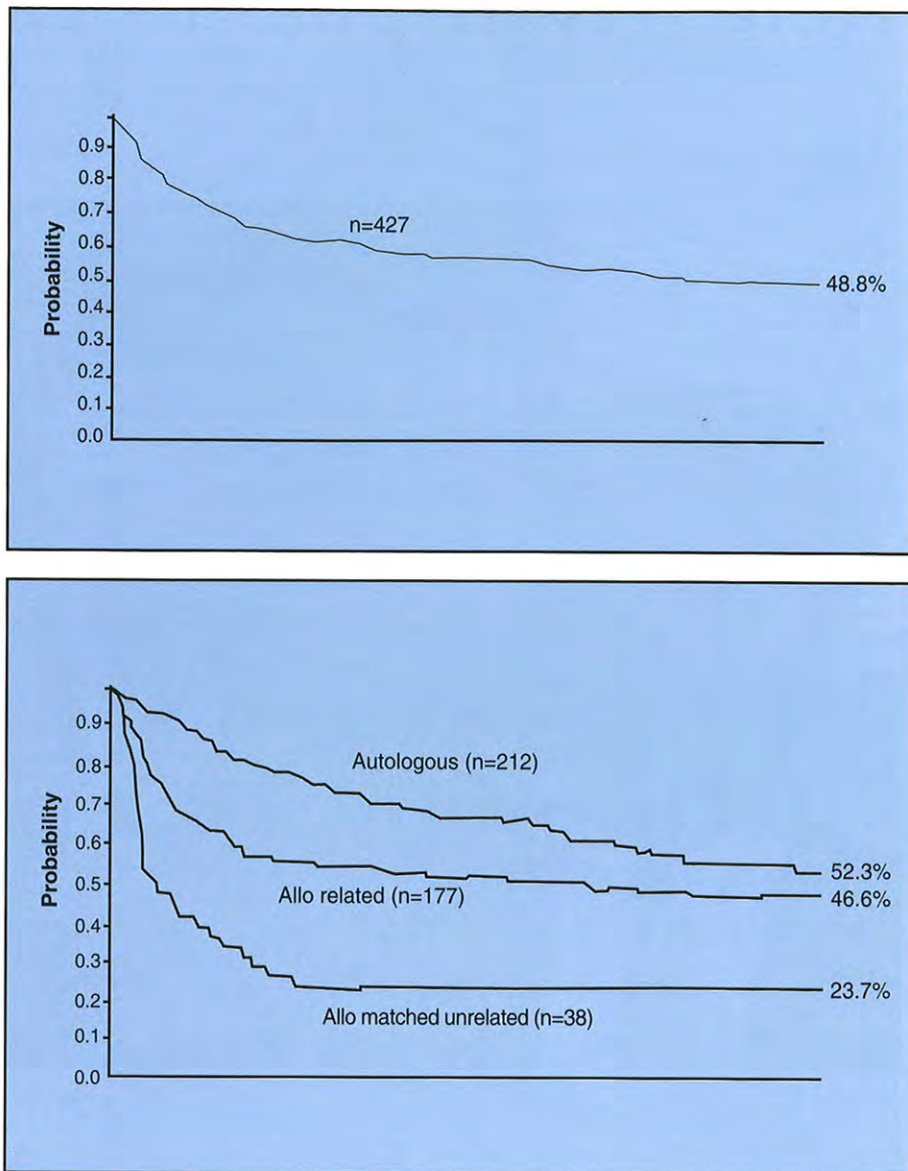
St Vincents initiated and now houses the **Australasian Bone Marrow Transplant Recipient Registry**. This registry receives data on all patients having blood stem cell transplants in Australia and New Zealand. This data is an important resource and has allowed important retrospective reviews of new transplant strategies. A recent comparison of allogeneic peripheral blood stem cells versus bone marrow stem cells has been completed. This revealed significantly faster engraftment with the blood stem cells and no increase in complications such as graft-versus-host disease. **The use of blood**

stem cells has now become standard at St Vincents.

BREAST CANCER

In NSW as many as one in fourteen women will develop breast cancer and in over a third it will present with metastatic disease. Transplants for breast cancer are a relatively new indication with the initial area of interest being **metastatic disease**. Most of these patients live only 18 to 24 months from diagnosis. Two randomised studies in patients with metastatic disease have demonstrated improved response and survival with blood stem cell transplant when compared to standard therapy. The early encouraging results in

PATIENT SURVIVAL, 1997



as scleroderma, lupus erythematosus and multiple sclerosis. Our own involvement in this area is an on-going clinical and laboratory research program looking at transplantation in the treatment of **rheumatoid arthritis**. Preliminary results which are awaiting publication look promising. The challenge will be to provide this therapy at the lowest cost and with minimal risk to the patient.

Figure 2: Survival of patients undergoing bone marrow and blood stem cell transplants at St Vincents from 1990 – 1996.

metastatic disease allowed the expansion of studies to **primary breast cancer with high risk of relapse**. The most convincing study in this group by Peters in North Carolina has demonstrated a better than 70% disease free survival beyond 5 years. Currently there are number of international randomised studies underway to confirm this result.

At St Vincent's Campus more than 44 transplants have been performed. Of the initial 44 patients, 19 had metastatic disease and 25 had primary high-risk disease (10 or more nodes positive). In the metastatic group the three year survival is 56% with two year disease free survival of 29%. In the high-risk group the four year survival is 95% with 69% disease free survival.

THE FUTURE

Blood stem cell transplantation has an exciting future as we learn to expand blood stem cells in vitro. This will enable small numbers of "clean" stem cells to be expanded to provide sufficient to do a transplant free of immunoreactive cells. The graft-versus-tumour effect will be enhanced by infusion of specific lymphocyte subsets. We will also learn more about the technology of **gene transfer** which will enable us to treat malignancies at the genetic level. Work is being carried out in our research laboratory in the Garvan Institute to explore some of these questions. Transplantation is being explored in **autoimmune diseases** such

**Drs Elliott Savdie and
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Renal Transplantation



HISTORICAL PERSPECTIVE

RENAL transplantation (allografting) was performed between identical twins in the nineteen fifties, but the modern era of cadaveric renal allografts began in the nineteen sixties in Boston and Paris, after the discovery of the immunosuppressive properties of 6-mercaptopurine.

Between 1960 and the late nineteen seventies, immunosuppression for renal allografts was standardised universally: a combination of the purine antagonist azathioprine and corticosteroids; and the treatment of acute rejection with larger doses of steroids, usually given parenterally. Polyclonal antilymphocyte or antithymocyte preparations were of weak efficacy but used in some units. With these protocols, the one-year survival rate for cadaveric renal transplants was about 60%.

In 1978, Sir Roy Calne described the use of the cyclical undecapeptide cyclosporin A in high dose (20mg/Kg/d) in combination with steroids, and a new era in renal transplantation began. One-year survival rates of 80% were soon reported. However, the big disadvantage of such large doses of cyclosporin was its nephrotoxicity. This was partly overcome in the early 1980s by the use of lower doses in combination with moderate doses of azathioprine and steroids, the so-called "triple therapy." Using this protocol, one-year survival rates of 80-90% became universal by the late nineteen eighties. The arrival of the first monoclonal antibody to be used in renal transplantation – muromonab-CD3 in 1986 – gave clinicians a further powerful new tool in the treatment of established acute rejection episodes, with significantly better results than using pulsed steroids.

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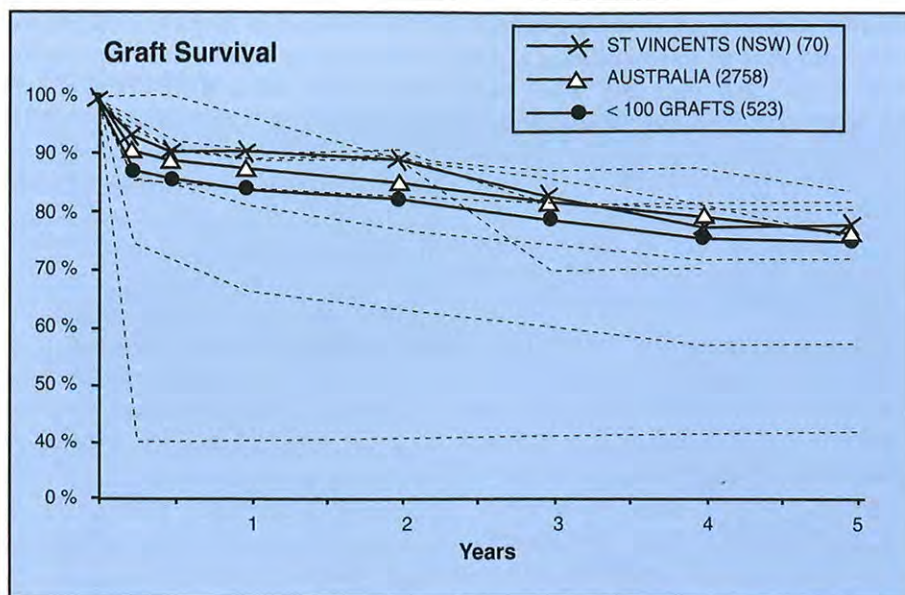


Figure 1. Percentage graft survival for renal transplants performed between 1991 and 1996 for St Vincent's Hospital versus all other Australian units as well as all Australian units performing less than 100 grafts over this period. The dotted lines represent individual hospitals other than St Vincent's, Darlinghurst.

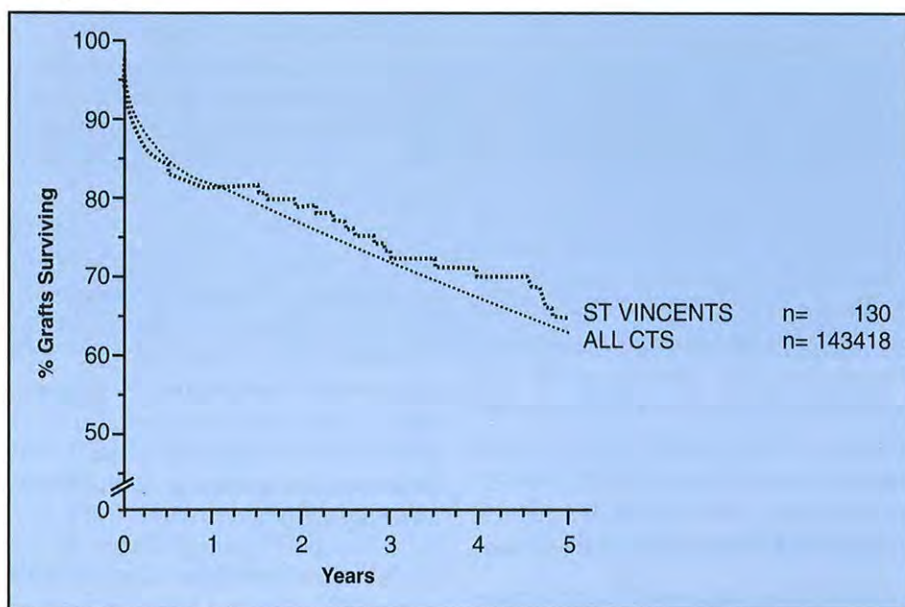


Figure 2. Percentage graft survival for renal transplants performed between 1982 and 1996 for St Vincent's Hospital versus all international units (CTS).

THE ST VINCENT'S EXPERIENCE

Professor Doug Tracy performed the first kidney transplant in New South Wales at Prince Henry Hospital in 1965. Professor Reginald Lord performed the first renal allograft at St Vincents in 1969 and since then approximately 300 kidney transplants have been performed at the hospital. The longest survival of a transplanted patient, who currently has a second graft, is 29 years. The longest surviving first allograft is 28 years.

Our renal transplant results are reported annually in the national or "ANZDATA" Registry and also the

international or "CTS" Registry in Heidelberg, Germany. Results from recent years show a renal allograft survival of 90% at one year and 75% at five years and these results compare favourably with the rest of Australia (Figure 1). When data since the early nineteen eighties are included the one-year graft survival is more of the order of 80% and the five-year graft survival just below 70%, comparing favourably with international units (Figure 2). Taken together, the data indicate that transplantation outcomes are improving with time.

The major current difficulty with transplantation is the dwindling number of cadaveric donors resulting in low

numbers of transplants and pressure to perform more living-related transplantations and to countenance xenografts.

THE FUTURE - NEW IMMUNOSUPPRESSANTS

As shown in the figures, there is a slow attrition of renal allografts with time which results in five-year survivals averaging about 50-60% nationally and internationally (although the St Vincents results are better). The reasons for this chronic rejection are complex but certainly in large part immunological. The triple therapy protocol continues to impart considerable adverse toxicity both on the immune system and other organs. Particularly with cyclosporin A, nephrotoxicity is a perennial problem, making management of renal allografts difficult. Hypertension is another big problem such that 90% of graft recipients require antihypertensive medication compared with 25% prior to the introduction of cyclosporin A.

The introduction of new immunosuppressant agents (Table) offers theoretical advantages, both in terms of efficacy and side-effects, over standard triple therapy. These drugs are now discussed in detail. Their future long-term use awaits ongoing trials to establish proof of efficacy: an improvement in survival and a reduction in side-effects.

Tacrolimus (FK-506)

Tacrolimus is a cyclic macrolide (erythromycin and sirolimus are other examples) first isolated and developed in Japan in the nineteen eighties. It has a very similar action to cyclosporin A even though it bears little structural similarity to it.

Tacrolimus' mechanism of action involves its intracellular cytoplasmic binding to a protein or "immunophilin" known as FKBP-12 (just as cyclosporin A binds to cyclophilin) to form a complex, leading to inhibition of T-cell-receptor-triggered gene expression of cytokines. Specifically, the FK506-FKBP12 complex inhibits calcineurin-calmodulin-induced phosphorylation of the cytoplasmic component of NF-AT

transcription factor for IL-2 and possibly other cytokines. The proliferation of lymphocytes, specifically T-helper cells is thus inhibited.

Tacrolimus appears more potent than cyclosporin A in suppressing T-cell-mediated immune responses. Certainly in liver transplantation, its use results in less acute and chronic rejection and it may become the preferred primary immunosuppressant. Its use in renal transplantation remains to be determined and no clear benefits over cyclosporin A have yet emerged, although some units have developed protocols involving conversion from cyclosporin A to tacrolimus in patients with severe or intractable rejection. St Vincents has used it on five occasions to "rescue" renal or combined renal-cardiac allografts with success in three instances.

Tacrolimus' side-effect profile is similar to that of cyclosporin A, including nephrotoxicity. It appears more likely to cause glucose intolerance, neurotoxicity and gastrointestinal side-effects. On the credit side, gingival hypertrophy does not appear to be a problem.

Sirolimus (Rapamycin)

This is another cyclic macrolide, originally derived from soil microorganisms from Easter Island or Rapa Nui. Its immunosuppressive potential was recognised in the nineteen seventies.

Despite its structural similarity to tacrolimus, sirolimus appears to work by a different mechanism wherein the T and B lymphocyte *response* to cytokines rather than the lymphocyte *synthesis* of cytokines is impaired. Rapamycin does bind to tacrolimus immunophilins (especially FKBP-25) but the resulting complexes have no affinity for the calcineurin-calmodulin complex and therefore do not affect the early activation genes of T-cells. Rather the sirolimus-FKBP25 complex blocks the second set of phosphorylation events that follow binding of IL-2 to its receptor and the cytokine-mediated signal transduction pathways in the late G1 phase of the cell cycle, inhibiting progression to the S phase.

Clinical phase III studies of sirolimus are underway in multiple centres in the USA and there is also a multicentre trial

in progress in Australia. The drug has yet to be used in renal transplantation at St Vincents, although its use has commenced in the heart transplant unit as part of a clinical trial.

Sirolimus may be *co-administered* with cyclosporin A (in contrast with tacrolimus which is usually *substituted* for cyclosporin A by virtue of its similar mechanism of action). However, since both sirolimus and cyclosporin A are metabolised by hepatic and intestinal cytochrome P450 enzymes, they may mutually hinder each other's degradation. Thus, blood levels of the two compounds must be closely monitored when used together, particularly when large doses are used such that the cyclosporin A concentration is >450 ug/L and the sirolimus >10 ug/L. Currently, sirolimus assays are sent to Princess Alexandra Hospital in Brisbane.

Mycophenolate Mofetil (MMF)

Mycophenolate Mofetil is the morpholinoethyl ester of its active compound mycophenolic acid (MPA). It is a century since this compound was isolated from *Penicillium* species, having been initially investigated for antibacterial and antifungal properties. Later, its antitumour and immunosuppressive activity became evident, and it was used in the clinical treatment of cancer and psoriasis.

MMF does not resemble cyclosporin A, tacrolimus or sirolimus in its structure or mode of action. Its mechanism of action is closest to that of azathioprine, i.e. it is primarily a purine antagonist; but it is a more potent and specific immunosuppressant than azathioprine.

MMF is converted to MPA, which is a potent, reversible, noncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH) and guanylate synthetase, two essential enzymes in *de novo* purine synthesis from ribose phosphate. As a result, cells become depleted of guanosine triphosphate (GTP) and deoxy-GTP. In lymphocytes, purines are synthesized largely by this *de novo* pathway, and their depletion due to MPA causes T and B lymphocytes to be fixed in the S phase of the cell cycle and unable to proliferate.

By contrast to lymphocytes, purine synthesis in most other cells depends on the so-called *salvage* pathway in which guanosine is rephosphorylated to GMP by HGPRTase or phosphoribosyl phosphatase (the enzyme absent in the Lesch-Nyhan syndrome). Therefore, the antiproliferative effect of MMF is theoretically lymphocyte-specific. Further, the type II isoform of IMPDH which predominates in proliferating lymphocytes, is four times more sensitive to MPA than the type I isomer expressed in most other cells. By contrast, azathioprine's mechanism of action is primarily via the *salvage* pathway, i.e. it has a weak antiproliferative activity in all dividing cell types.

Three large cadaver renal transplant trials comparing MMF in "triple therapy" regimes with cyclosporin A and prednisolone versus control regimes without MMF have indicated that the groups receiving MMF had a statistically significant reduction in acute rejection episodes; although graft and patient survival rates were no different. The main side effects of MMF were gastrointestinal intolerance (mainly abdominal pain and diarrhoea) and haematological toxicity was occasionally observed (anaemia, leukopaenia and thrombocytopaenia) despite the "lymphocyte-specificity" as proposed above. There was also a trend towards more CMV infections and less *Pneumocystis* infections in the MMF-treated patients.

Additional published data indicate that MMF may be a valuable agent in rescuing allografts exhibiting refractory rejection, and in reducing the number of multiple acute rejections. At St Vincents we have had a small but growing experience with MMF in renal allografts, principally in patients with refractory rejection. Its use has been valuable in about half the patients treated; but the haematological toxicity has been much higher than that claimed in the literature with up to 50% exhibiting cytopaenia and some patients having to cease the drug altogether.

Whether MMF eventually replaces azathioprine in triple therapy regimes will depend on further experience and published data. If it is shown eventually to produce better survival than azathioprine-containing regimens its use can be expected to increase

Immunosuppressive Agents Used In Organ Transplant Recipients

A. Established Drugs

Drug	Dose	Mechanism of Action	Specific Toxicity	Comments
Cyclosporin A	3 – 10mg/kg/d Adjusted to target whole blood concentration	Inhibition of IL2 synthesis	Hypertension Renal impairment Neurologic Hirsutism Gingival hyperplasia Glucose intolerance Hyperlipidaemia	Multiple drug interactions
Azathioprine	1.0 – 2.0 mg/kg/d	Inhibition of salvage purine synthesis	Marrow suppression Hepatotoxicity	Potential of effect with allopurinol
Prednisolone	0.1 – 0.2 mg/kg/d	Broad anti-inflammatory	Cushingoid Glucose intolerance Osteoporosis Avascular necrosis Growth retardation	Higher doses needed for acute rejection episodes
OKT3	5mg IV/d for 7 – 14 days	Murine CD3 antibody: lympholysis	Cytokine release syndrome CMV later	Possible increased lymphoma risk

B. Newer Drugs

Tacrolimus	0.05 – 0.15 mg/kg/d	Inhibition of IL2 synthesis	As for cyclosporin with exception of gingival hyperplasia	Similar drug interactions as cyclosporin
Sirolimus	0.5 – 7.0 mg/M2/d	Blocks response of lymphocytes to IL2	Leukopaenia Thrombocytopaenia	C450 metabolism. May lead to elevated cyclosporin levels
Mycophenolate mofetil (MMF)	1.0 – 3.0 gm/d	Inhibition of <i>de novo</i> purine synthesis	Gastro-intestinal intolerance Marrow suppression	Efficacy may be enhanced by blood level monitoring
Daclizumab	1 mg/kg IV pre graft then weekly for 1 month	Engineered IL2 receptor antibody	Low side-effect profile	Still under trial

Table 1

dramatically. Also of interest will be whether renal allografts can be managed with MMF (and steroids) without the use of azathioprine; if so, a lot of nephrotoxicity might be avoidable and renal transplants simpler to manage.

Daclizumab

Interleukin-2 (IL-2) and its ability to bind freely with its receptor on the surface of T-lymphocytes are pivotal to the proliferative response to allogeneic allografts. As outlined above several of the immunosuppressants have a mechanism of action whereby IL-2 production is decreased (cyclosporin A and tacrolimus) or its effects modified after it has bound to its receptor (sirolimus).

The IL-2 receptor is interesting in that it is only detectable on activated and not resting T-cells. Thus, the ability to impede or impair selectively the function of this receptor would in theory

have the dual advantages of disabling the T-cells involved in the allograft rejection response while sparing other immunocompetent cells and pathways.

While several rodent monoclonal antibodies to the IL-2 receptor have been developed and used in this regard they have been limited by their immunogenicity. A more promising advance has been the development of daclizumab, a genetically engineered "humanised" monoclonal antibody incorporating murine antigen-binding domains (10%) inserted into a human IgG1 immunoglobulin (90%). Daclizumab binds preferentially to the alpha domain of the IL-2 receptor (beta and gamma are the other subunits). The alpha domain is a 55kD peptide also known as T cell activation antigen or CD25, and it is this domain which is specifically expressed when T cells are activated.

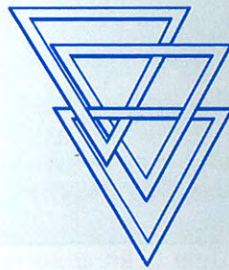
The recent publication of a controlled clinical trial of daclizumab in

renal transplant recipients has indicated it may indeed be useful in the prevention of acute rejection. A collaborative North American study group compared daclizumab with placebo in patients receiving standard "triple therapy." The antibody or vehicle was administered prior to the transplant thence alternate weekly for a total of five doses, the rationale being to maximise the dosage coincident with the expression of IL-2-receptor-alpha. Follow-up was for twelve months. The daclizumab-treated subgroup had a reduced incidence of biopsy-confirmed acute rejection episodes, although the graft survival after one year did not differ in the two groups. There were no adverse reactions to daclizumab (in contrast with the well-known dramatic systemic effects of the mouse monoclonal OKT3).

Daclizumab has only just become available in Australia. In the meantime, we continue to use OKT3 in the treatment of severe acute rejection in renal allografts.

ST VINCENT'S CLINIC

RESEARCH GRANT RECIPIENTS 1999



SR MARY BERNICE AWARD

Prof. D.D.F. Ma Identification of possible genetic factors for venous clots following hip and knee replacement surgery.

ANNUAL AWARDS

Dr A Meagher – Thalidomide in inflammatory bowel disease

Dr D Marriott – The use of molecular techniques to elucidate the epidemiology of the spread of MRSA on the St Vincent's Campus and to enable more rapid diagnosis of MRSA carriage or infection.

Professor R.S.A. Lord – Investigation of maturation of vascular dendritic cells in atherosclerotic lesions

Dr P.D. Stricker – Prostate Cancer: Causes, Cases, Mechanisms, Treatment

Dr T O'Connor – Development of a colorectal tumour registry at St Vincent's Campus

DI BOYD CANCER RESEARCH AWARD

Dr A.V. Biankin The Genetics of Pancreatic Cancer



The Mission of St Vincent's Clinic Foundation

The people of Sydney and beyond are indeed fortunate to benefit from one of the most comprehensive health care services available to date – the services of the Sisters of Charity through the St Vincent's Campus at Darlinghurst.

These facilities are part of the 17-strong health and aged care facilities under the direction of the Sisters of Charity of Australia.

Integral to the Darlinghurst campus are the services and facilities provided by St Vincent's Clinic and St Vincent's Clinic Foundation.

Established in 1992, St Vincent's Clinic Foundation strives to provide funds and support for medical research into matters of clinical significance.

Every advance in medical science has started with a commitment by a medical practitioner or scientist to alleviating the pain and suffering of humankind.

It is here that St Vincent's Clinic Foundation plays its role in medicine today.

Australia is rich in research bodies striving within the clinical laboratory setting, investigating the causes of disease.

However, funding is sparse for the establishment and carrying out of studies conducted in the course of patient care. This is where St Vincent's Clinic Foundation can focus some of the community's goodwill.

Already the Foundation has successfully supported vital research into disease and illness including cancer, diabetes, kidney disease, and heart disease, to name just a few.

However, your support is needed now to continue and maximise this effort.

Please support St Vincent's Clinic Foundation. We care and we know you do too.



St Vincent's Clinic Foundation

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All donations to St Vincent's Clinic Foundation are tax deductible and can be made in a number of ways.

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INTRODUCTION

Organ transplantation is now accepted therapy for end stage heart, lung, liver and renal failure.

With modern immunosuppressive drug regimens, the long term results are excellent and the complication rates acceptably low. Ocular complications following solid organ transplantation are uncommon but can be a major cause of morbidity as they can result in devastating loss of vision if not managed correctly.

The author has been involved in the management of patients with ocular complications following organ transplantation since the beginning of the transplant program at St Vincent's Hospital and has also been involved in the ocular management of patients undergoing liver transplantation at Royal Prince Alfred Hospital. This short review will highlight important ocular complications of solid organ transplantation based on research and clinical experience from St Vincents that has been published recently in the *British Journal of Ophthalmology*. In this study 19 out 860 patients (2%) undergoing heart lung or liver transplantation over a 12 year period, developed a symptomatic ocular complication requiring treatment.

Ocular complications are nearly always related to the immunosuppressive therapy essential for successful transplantation and can be classified into two broad groups based on the time of occurrence following transplantation. In one group, complications occur early following the transplant and are related to high grade immunosuppression and/or systemic infection. Retinal vasculitis and fungal choroiditis are typical manifestations in this group. In the second group, complications occur later and are related to the duration of immunosuppression rather than its severity. Herpes group viral infections are typical of this group of patients.

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St Vincent's Hospital
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Royal Prince Alfred Hospital

Ocular Complications of Organ Transplantation



PATHOGENESIS

Systemic immunosuppression results in a range of abnormalities of the immune response and these may involve the eye and visual system in a number of ways. Table 1 summarises the pathogenesis of various ocular complications seen in patients following organ transplantation.

SPECIFIC OCULAR COMPLICATIONS

Cataract

Cataract is by far the most common ocular complication of organ

transplantation and is the result of chronic systemic corticosteroid therapy following transplantation. Corticosteroids induce a characteristic posterior subcapsular cataract in a dose dependent manner. Based on studies in renal transplant patients up to 50% of patients will develop cataract following transplantation.

Cataract surgery in transplant patients is no different to that in the general population and the results from surgery are excellent. Modern microsurgical techniques using phacoemulsification, foldable intraocular lenses and assisted local anaesthesia allow safe surgery with rapid visual rehabilitation and an extremely low complication rate.

Opportunistic infections

In the St Vincents study, opportunistic infection was the most common ocular complication accounting for 65% of all complications. Herpes group viruses were the most frequent pathogens causing 88% of the infections

Herpetic retinitis

Herpes simplex, herpes zoster and cytomegalovirus can each produce a severe vision threatening retinal infection in patients following transplantation. Although such infections may occur at any time following transplantation, they typically are delayed and occur in the second and subsequent years following transplantation. Our data shows that the immunosuppressive regimens in patients with herpetic retinitis is no different to that of other patients and suggests strongly that it is the duration of immunosuppression that is associated with herpetic retinitis. There is some evidence that herpes simplex and zoster retinal infections may occur more frequently than cytomegalovirus infection.

Diagnosis of herpetic retinitis is clinical, however the increasing availability of polymerase chain reaction technology will aid greatly in the specific diagnosis of intraocular infection. The visual outcome depends on the extent of retinal involvement at the time of diagnosis and whether critically important areas of the retina such as the macula and optic nerve head are involved.

Acute retinal necrosis

Acute retinal necrosis is the clinical form of herpes simplex and herpes zoster retinal infection seen in transplant recipients. It is a clinical triad of retinal opacification and necrosis, florid retinal vasculitis and uveitis (Figure 1). It is acute in onset and rapidly progressive. Without treatment, the retinitis and associated inflammation can cause widespread retinal destruction with resultant retinal detachment and profound visual loss. Most patients develop bilateral involvement without treatment.

Early aggressive treatment with intravenous acyclovir is essential to

Pathogenesis of ocular complications following organ transplantation

Pathogenic mechanism	Ocular Complication
Opportunistic infection	Acute retinal necrosis, CMV retinitis, ocular candidiasis, herpetic keratitis
Autoimmunity	Retinal vasculitis
Neoplasia	Post transplant lymphoproliferative disorder, ocular lymphoma, actinic related eyelid cancers
Allergy	Drug hypersensitivity reactions
Drug toxicity	Cataract, Rifabutin associated uveitis, cyclosporin retinopathy

Table 1

control the retinitis, followed by 12 to 16 weeks of oral acyclovir to minimise the risk of second eye involvement.

Intensive local corticosteroid therapy and an increase in systemic corticosteroid dose may be necessary to control the uveitis. Retinal laser photocoagulation is needed to reduce the risk of retinal detachment which may occur in up to 80% of involved eyes as the retinitis resolves. The visual outcome is variable.

CMV retinitis

Cytomegalovirus retinitis has long been recognised in transplant recipients but has always been relatively uncommon. In sharp contrast, CMV retinitis is very common in patients with AIDS occurring in up to 40% of patients in advanced stages of infection when there is profound immunodeficiency. CMV retinitis becomes easily controlled if immune function improves with combination anti HIV therapy.

CMV retinitis has a characteristic clinical picture of haemorrhagic full thickness retinal opacification associated with little or no uveitis (Figure 2). The retinitis spreads relatively slowly and is far less likely to become complicated by retinal detachment. There are a number of drugs that are available to treat CMV including ganciclovir, foscarnet and cidofovir. These drugs are highly effective in transplant patients with CMV retinitis. As long as the optic disc and macula are uninvolved the visual prognosis is relatively good.

Herpetic keratitis

Corneal infection by herpes simplex virus is a common world wide ocular problem. Patients who develop herpetic corneal infection post transplant are more likely to develop large corneal epithelial ulcers and are probably at increased risk of developing recurrent corneal stromal disease. Transplant patients are treated similarly to other patients and selected patients with frequently recurrent or severe keratitis may benefit from the use of long term suppressive doses of oral acyclovir.

Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus occurring after organ transplantation is managed in the same way as in other patients with high dose oral acyclovir, valacyclovir or famciclovir.

Fungal intraocular infection

Intraocular infection by fungi is less common but in our series accounted for about 20% of the infections seen. In the immunosuppressed population, a wide range of fungi can be opportunistic pathogens and a high index of suspicion for fungal infection must be maintained especially in the first 6 to 12 months following transplantation. Candida and aspergillus species are among the fungi which we have seen in the Sydney series of patients (Figure 3). Diagnosis is made by microscopy and culture of intraocular fluids. Therapy with intraocular amphotericin and systemic antifungal drugs is necessary.

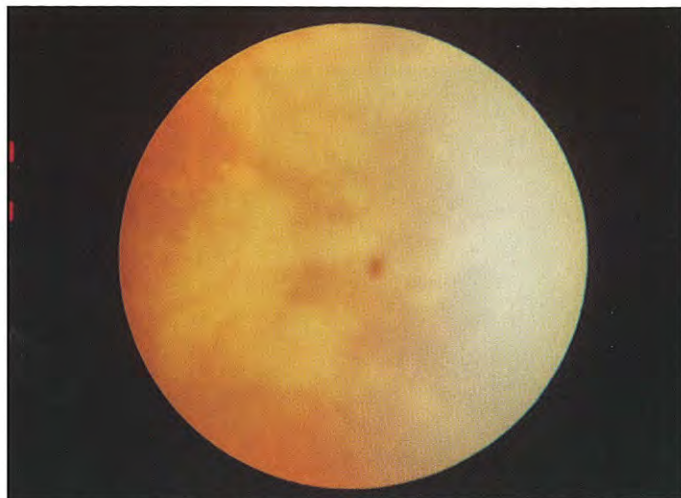


Figure 1: Acute retinal necrosis caused by herpes zoster infection. There is severe uveitis resulting in a poor view of the retina. There is a large area of retinal opacification.

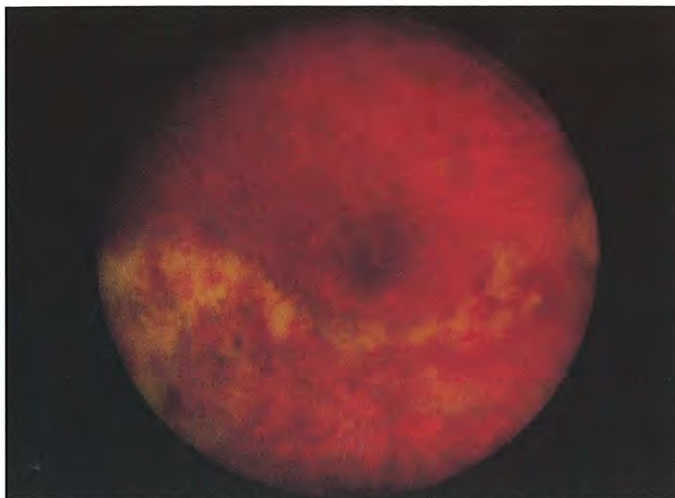


Figure 2: Typical CMV retinitis. Note the yellowish areas of retinal opacification and the prominent retinal haemorrhages. There is minimal uveitis and media opacity.

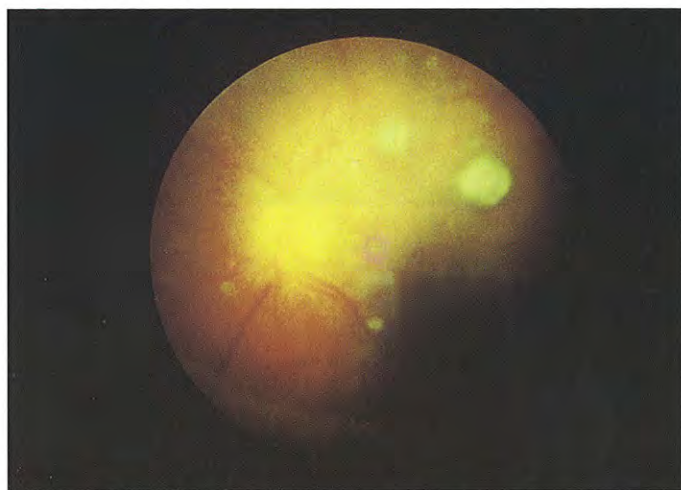


Figure 3: Classical clinical features of candida endophthalmitis with a localised area of retinochoroiditis and overlying vitreous "fluff balls"



Figure 4: Hypopyon and severe anterior uveitis in a patient with rifabutin associated uveitis

Neoplasia

Post transplant lymphoproliferative disorder is a recognised syndrome following transplantation and is a B cell lymphoproliferative disorder that may rarely involve the eye. In our series we have had a liver transplant patient develop slowly enlarging multifocal choroidal infiltrates that were diagnosed histologically following full thickness eye wall biopsy as post transplant lymphoproliferative disorder. The lesions resolved without sequelae following reduction of immunosuppression.

Autoimmune and Allergy

Retinal vasculitis and drug allergies involving the eye may occur in patients following transplantation due to dysregulation of the immune system following immunosuppression.

These disorders are uncommon and are managed using the same principles as in other patients.

Drug toxicity

As discussed earlier, corticosteroid ocular toxicity resulting in cataract development is overwhelmingly the commonest ocular complication post transplant. Occasionally other drugs may produce ocular toxicity. High dose cyclosporin can produce a transient ischaemic vasculopathy involving the retinal circulation that can result in visual loss. Rifabutin, an antibiotic used to treat mycobacterial infection, may produce a dose dependent acute anterior or panuveitis that presents dramatically with a hypopyon and profound visual loss but usually resolves without sequelae (Figure 4).

CONCLUSION

As organ transplantation is only performed at a few specialised centres in Australia, transplant recipients who develop ocular complications most

commonly present to ophthalmologists geographically remote from the transplant unit. The development of ocular symptoms in transplant recipients warrants careful ophthalmic assessment as they may result from a variety of opportunistic ocular infections or other ocular diseases. Failure to recognise and treat ocular infection appropriately can result in devastating permanent visual loss.

An understanding of the type and frequency of ocular complications associated with transplantation is needed by both transplant units and general ophthalmologists to avoid the devastating visual consequences of inaccurate or delayed diagnosis. Physicians managing transplant patients who develop ocular complaints should seek urgent ophthalmic assessment.

Uncertainty regarding the diagnosis should lead to prompt consultation with the transplant unit and its ophthalmologist.



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