



Clinical Renal Transplantation: Where Are We Now, What Are Our Key Challenges?

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ABSTRACT

Today transplant patients have a risk of death a log order higher than someone of the same age but without end-stage renal failure and a prognosis akin to the normal population with a diagnosis of cancer. Graft losses are mostly from chronic allograft nephropathy, and death arises from cardiac disease, malignancy, and infection. Most immunosuppression protocols are designed to minimize acute allograft rejection, through heavy induction strategies, powerful but toxic maintenance therapies, and equally powerful and expensive prophylaxis against resultant infections. However, despite all efforts, the 20-year survival of renal allografts has not improved much over the past 30 years. New metrics and new thinking are needed to change the long-term outcomes. The biological consequences of immunosuppression currently require a balance between controlling the allograft response and reducing toxicity. To improve, we must both control rejection and remove the long-term problems of toxicity and infection. In the early period after transplantation, we need maximum immunosuppressive efficacy with minimal ischemia-reperfusion injury. Later, we need less immunosuppressive efficacy, to avoid risk factors for chronic toxicity, cardiovascular disease, and malignancy. One of the key challenges for the next few years will be to learn how to individualize therapy using surveillance biopsies and then to validate and use noninvasive technologies to guide therapeutic decisions. There is also an urgent need to determine the relevant early indicators for measuring long-term success to help design better management strategies. The multiplicity of alternatives testifies to the absence of a single dominant strategy.

PATIENTS WITH END-STAGE KIDNEY DISEASE have a worse prognosis than those in the normal population diagnosed with cancer.¹ The prognosis is better for patients who are suitable for placement on the transplant waiting lists and who then actually receive a renal transplant, than for those who remain on the waiting list on dialysis. Relative risk of mortality is a straightforward and measurable indicator of success of the therapy, and it is a statistic that the patient can identify with as relevant. The second outcome measure that provides a useful comparator between therapeutic options is of course survival of the graft. However, the patient's own assessment includes not only his or her survival and the graft survival, but also improvement in the quality of life that transplantation provides compared to dialysis. We have singularly failed to develop a reliable and accurate indicator of the relative quality of life, despite application of a number of indices validated in general populations.

The basis of the success that we can provide through renal transplantation has been won not only through the

major Nobel Prize-winning achievements of many scientists over the past 100 years, but also progressively through clinical experimentation. If we are to achieve further improvements, we must define the major challenges that face us today and then focus energy on their resolution. **Table 1** provides one approach to defining the key challenges in renal transplantation over the next 10 years.

ACCESS TO RENAL TRANSPLANTATION

There are few if any countries in the world where the rate of organ donation is sufficient to meet the needs of the

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Table 1. Major Challenges in Renal Transplantation for the Next Decade

- Increasing the number of transplants
- Measuring and improving quality of life
- Improving patient survival through
 - Preventing and treating malignancy
 - Preventing and treating cardiovascular disease
 - Preventing and treating infections
- Improving graft survival through
 - Preventing rejection
 - Resolving renal vascular disease
 - Preventing, diagnosing, and treating chronic rejection
 - Improving immune monitoring technologies
- Reducing the cost and complexity of transplantation

population with end-stage kidney disease. Spain and Norway perhaps come the closest to providing as many grafts as the incident population requires and thus keep waiting lists from growing. Waiting lists are growing in most countries, and there are efforts under way to increase the availability of both living and deceased organs. Data from the World Health Organization show that the actual rate of transplantation correlates with the development and wealth of the country, but it is also apparent that there is a wide spread of access to transplantation even within bands of the Human Development Index.² This diversity is perhaps most apparent in the wealthiest parts of the world, where countries like Japan have very low transplant rates while equally wealthy countries in Europe far surpass them. It is clear that the transplantation rates depend upon the wealth and development of countries, but also on community and government determination to increase rates, community and professional attitudes to organ donation, and the availability of skilled teams for both organ donation and organ transplantation programs. The solutions are spread across the orga-

nizational, religious, and community spectrum with no one right answer.

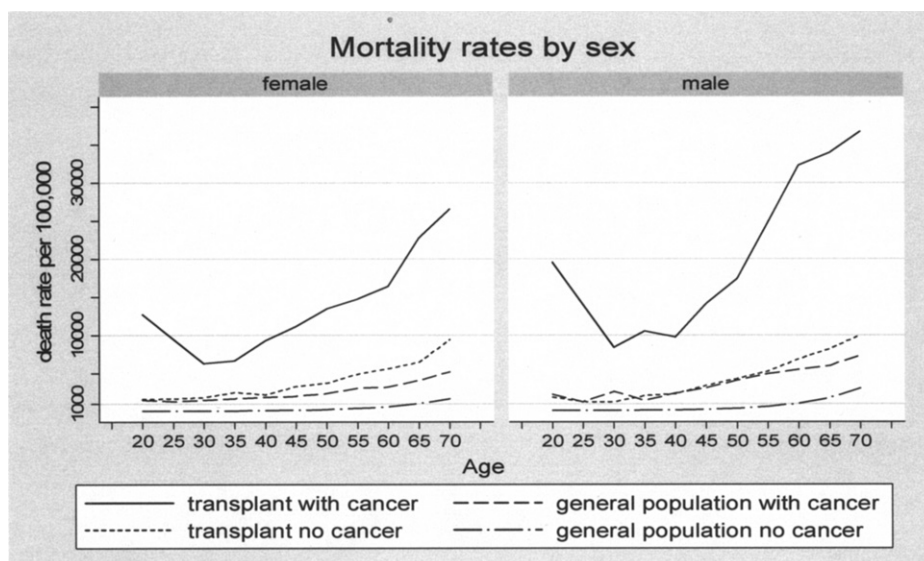
PATIENT SURVIVAL

Standardized mortality ratios describe the difference between the observed and expected rates of death by sex and age compared to the normal population. In Australia, the standardized mortality ratio for transplant recipients has fallen from around 12 for females and 8 for males in the late 1980s to around 8 and 5, respectively, in the last few years. There is thus evidence that we have improved the outcome of individuals over that time, but it also makes clear that there is still much work to be done to bring life expectancy in line with the general population at a ratio of 1 (Fig 1).³

The main causes of death after transplantation are cardiovascular disease, infection, and malignancy with the rank order of prominence varying with the country and perhaps also the selection criteria for transplant waiting lists. In much of Asia, infection reigns supreme as the cause for death, with an abundance of tuberculosis and fungal infection, while across Australia, North America, and much of Europe, cardiac disease is dominant. In a recent analysis of the Australian data, the time dependency of cardiac deaths has become evident, as has the trend to improvement with era of transplantation.³ A number of factors are well known to be associated with an increase in cardiac disease, such as poor renal function, high blood pressure, and diabetes, while the beneficial treatment effects of antihypertensives and statins have become evident.^{4,5} It is thus possible that with diligent attention to these factors, it will prove possible to still further improve outcomes.

Malignancy has become an increasing burden especially as the average duration of survival after transplantation has increased. There is a constant increase in the prevalence of cancer after transplantation for most cancers. The two

Fig 1. Death rate per 100,000 people by age cohorts of the general Australian population with and without cancer compared with the Australian renal transplant population with and without cancer. Reproduced from the ANZDATA Report, 2008.



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