GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

From the perspective of a potential kidney transplant recipient:

- Kidney transplantation using either live or deceased donors is worthwhile for an individual with renal failure if it significantly improves their quality of life and/or long-term survival.
- The potential benefit of live donor transplantation needs to be weighed up against the likely outcome with the alternative options. For the individual recipient, factors to consider include the eventual or continuing need for dialysis, the suitability and possible outcome of deceased donor transplantation, as well as the likely waiting time for a deceased donor organ.
- When compared with deceased donor transplantation, living donor kidney transplantation is associated with similar or even superior recipient outcomes. Living donor kidney transplantation therefore represents an excellent option for many individuals requiring renal replacement therapy.
- In Australia, while there is a short supply of deceased donor kidneys, live donation can be justified if the risk of harm to an individual donor is very low and there is the likelihood of a benefit for the individual recipient.
- For some individuals (i.e. older recipients, those with multiple comorbidities, the immunologically sensitized) living donor kidney transplantation may provide significant benefits over deceased donor transplantation. In some cases, live donation may be the only reasonable transplant option available.
- Pre-emptive (i.e. prior to dialysis) live donation is associated with excellent recipient outcomes and should be strongly considered in appropriate recipients who have suitable live donors.

From the perspective of a potential kidney donor:

To justify live kidney donation, the risk of harm to the individual donor should be very low and the potential benefit to the recipient should be significant with a reasonable likelihood of success. Each case needs to be assessed individually with the potential risks and benefits being carefully examined.

- There is a general lack of data regarding the overall safety and long-term outcome for donors who fail to meet the strict criteria for suitability (e.g., donors who are overweight, mildly hypertensive, smokers, those with minor urinary abnormalities). As part of the informed consent process, it is essential that these potential donors be made aware of this lack of data regarding long-term safety and outcomes.
- In some individuals (e.g., parents, partners) there is a very strong desire to donate, despite the risks involved. These individuals may experience significant psychological and personal gains when donation has been successful in improving the life of their intended recipient. In these situations, special care is required during the informed consent process to ensure that donors are fully aware of the potential risks involved.
- Failure to donate (for example on medical or psychological grounds) may result in psychological harm (e.g., guilt, depression) and efforts must be made to provide or arrange for appropriate support and education in these cases (see ‘Psychosocial care of living kidney donors’).
- Live donation can only be justified if general ethical principles arising from the assessment and care of the donor are not compromised. High ethical standards need to be maintained throughout the process and the rights of the donor should be strongly considered at all times. Important elements of this include:
  - Donor autonomy: Donors should be as fully informed as possible regarding the risks they are undertaking. Consent should be freely given by the donor, without pressure, coercion or inducement from medical personnel, the family, or the recipient. Donors should be seen separately, in the absence of the potential recipient and their family and their expectations and willingness should be gauged as early as possible in the assessment process.
  - Confidentiality: The principle of confidentiality implies that efforts will be made for this to be maintained between the donor and recipient. It is accepted...
that some information will always be shared (e.g. cytomegalovirus (CMV) status, human leukocyte antigen (HLA) issues, renal vascular anatomy and functional results); however, the need for sharing information that is potentially sensitive in nature should be made explicit to each individual and consent obtained.

- Donor advocacy: Independence between the clinicians or team members responsible for the donor, and those responsible for the recipient is highly recommended. This will help minimize concerns regarding a conflict of interest between the care of the recipient and the care of the potential donor.

From the perspective of the transplant team:
- There should be general agreement between team members regarding a decision to proceed with a particular live donor transplant. When there is a conflict, additional independent assessments of donor/recipient suitability should be sought.
- The transplant team has rights and responsibilities also. Although donors and recipients may be fully aware of their risks and accept these, the team has the right to refuse to perform a transplant if it feels the risk is unacceptable. Once again, additional independent assessment of donor/recipient suitability should be sought in these circumstances.

IMPLEMENTATION AND AUDIT

1. Short- and long-term live donor outcomes need to be closely monitored.
2. Live donor transplant outcomes need to be closely monitored.
3. Deceased donor rates and transplant list waiting times need to be closely monitored.

BACKGROUND

The key objective of this guideline was to examine evidence assessing whether the practice of living kidney donation in Australia and New Zealand is an acceptable and justifiable option for those with kidney disease. In defining what is 'acceptable', the medical and psychological impact on the donor was seen to be of paramount importance as was the outcome for recipients, relative to their alternative options of dialysis and/or deceased donor transplantation.

To justify living donation as an option in the care of those with kidney disease, the situation would ideally satisfy the following criteria:

i) there would be no risk to the living kidney donor
ii) the transplant recipient would benefit significantly, and
iii) dialysis or waiting for a deceased donor kidney would be much worse alternatives.

If all of these conditions could be clearly met, then live donation would very easily be justifiable. Unfortunately, even in the simplest or least complicated of situations, none of these three criteria can be absolutely achieved or completely and accurately quantified. In practice, if conditions go to a reasonable extent to satisfying the above criteria, then live donation has usually been deemed acceptable to potential donors, recipients and transplant teams.

From the perspective of the recipient, it is well established that transplantation is associated with significant benefits. Furthermore, live donation is clearly very successful and may present several benefits over deceased donor transplantation. There is little dispute over these 'recipient' issues and data can be obtained from registries including ANZDATA and from cohort studies that strongly support these statements (even though it is not Level I or II evidence). Furthermore, in the presence of a significant shortage of deceased kidney donors and the likelihood of otherwise waiting for several years for a deceased donor, it becomes very easy to justify live donor kidney transplantation – for the recipient.

When we consider the live donor, things are not quite as clear. Although live donation has been occurring for some decades and the practice is generally perceived to be very safe for most individuals in Australia, New Zealand and other developed countries, it is not without some risk. The direct benefit to the donor is either non-existent or often much harder to perceive. However, in some cases a benefit to the donor is clearly present and may be an important consideration (e.g. the partner who will benefit their whole family by donating; or the parent who benefits psychologically from helping their child). In most cases, the justification rests on the perception of safety for the donor. Is this safety clearly established – particularly long term? Probably, but one could argue that this is only with fairly strict adherence to the donor acceptance criteria. We must also consider what degree of risk is 'acceptable' for a donor as opposed to that for a recipient. As would be expected, the criteria for each are very different. For some donors that fall out of the usual limits for acceptance and are perceived as being 'marginal', ethical issues become a very major part of the assessment process, particularly when the desire to donate is very strong. The data helping us to justify live donation in these 'marginal' situations is particularly lacking and requires much more study. The perceived safety of live donation in a general sense does not mean that it is necessarily safe for all potential donors.

Long-term follow up studies of donors are generally lacking and those that exist are often flawed to some extent (e.g. lack of an appropriate control group, loss to follow up). The recent establishment of the ANZDATA Live Donor Registry should help significantly in further assessing long-term donor outcomes.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for living donors and combined with MeSH terms and text words for mortality, prognosis, graft survival, survival analysis and cohort studies. The search was carried out in Medline (1966 – September Week 2, 2006).
Recipient and graft survival – recipient and donor factors influencing outcome

Various studies have assessed the success of live donor kidney transplantation relative to the donor source (e.g., related, unrelated, spousal). In general, graft survival is excellent and equivalent regardless of whether the donor is related or unrelated. Mismatched, unrelated live donor transplants show similar or superior results compared with deceased donor transplants. Gjertson and Cecka analyzed United Network for Organ Sharing (UNOS) Registry data and found that 5-year graft survival rates for spousal, living unrelated and parental donation were all similar (75%, 72% and 74%, respectively). Graft half-lives were 14, 13 and 12 years, respectively.

Mandal et al analyzed USRDS data and compared primary deceased donor to primary live donor transplantation for different racial groups. The outcomes for recipients aged over 60 years (n = 5,142) demonstrated that live donation was associated with a better outcome. Comparing deceased donor with live donor renal transplant in the older age group, the relative risk of death was 1.72 and the relative risk of graft failure was 1.64.

Living donor renal transplantation for recipients aged 18–59 years was also generally associated with better outcomes compared with deceased donor renal transplantation. In some instances, however, deceased donor renal transplant was associated with a better outcome. This occurred when all of the following criteria were met: recipient age 18–59 years, deceased donor age less than live donor age, and deceased donor HLA match better than live donor HLA match. The impact of waiting on dialysis was not taken into account in this analysis.

The impact of waiting time on the success of transplantation has been examined in several studies. Meier-Kriesche et al analyzed United States Renal Data System (USRDS) data from 73,103 primary adult renal transplants performed between 1988 and 1997. There was a progressive rise in the risk of death and death-censored graft loss with increasing time on dialysis prior to transplantation. The increases in mortality risk for waiting relative to preemptive transplantation were as follows: 0–12 month wait, 21%; 12–24 month wait, 28%; 24–36 month wait, 41%; 36–48 month wait, 53%; and >48 month wait, 72%. In another publication, Meier-Kriesche and Kaplan reported that waiting for a live donor transplant for more than 2 years while on dialysis reduced graft survival to the same level as that for deceased donor transplants performed within 6 months of commencing dialysis. Using USN Registry data, Gjertson reported that pre-transplant dialysis time accounted for 12–13% of the variation seen in 1-year graft survival rates for both live and deceased donor transplantation. Also using USN Registry data, Kasiske et al. reported that the relative risk of death or graft failure, was lower in deceased donor and live donor recipients who were transplanted pre-emptively, compared with those transplanted following commencement of dialysis. Racial minority groups and those with a lower level of education were less likely to be transplanted pre-emptively.
With regards to recipients who are less than 18 years old, a study by Ishitani et al. examined the success of live, related donor transplantation in paediatric recipients using UNOS Registry data. When compared with pre-emptive transplantation, there was a relative risk of graft failure of 1.77 in those transplanted after dialysis had commenced. Kennedy et al. used ANZDATA to examine graft outcomes in transplanted adolescents, and also reported improved outcomes with pre-emptive transplantation.

Patient survival – comparison between dialysis and transplantation

Wolfe et al. compared the survival of those on the waiting list with those for individuals receiving a primary deceased donor transplant. Standardized mortality ratios were derived from an analysis of 228,552 subjects on dialysis. A total of 46,164 individuals were on the waiting list, of whom 23,275 received a primary deceased donor transplant over a 7-year period of observation. The annual death rate for those on the waiting list was 6.3 per 100 patient-years. By comparison, those transplanted had a long-term annual death rate of 3.8 per 100 patient-years. The improvement in relative risk of mortality was most pronounced for young, white recipients (20–39 years) and for people with diabetes. It should be noted that there was an initial elevation in the relative risk of mortality related to the early transplant period. The mortality risk was equal in the two groups by day 106 of follow-up, and improved in the transplanted group thereafter.

McDonald and Russ have reported similar findings using ANZDATA. An analysis of the period 1991–2000 found an 80% lower long-term risk of mortality between those transplanted and those remaining on the waiting list.

Quality of Life – comparison between analysis and transplantation

Cameron et al. have performed a meta-analysis examining the effect of transplantation on overall quality of life. Successful kidney transplantation was associated with improved general wellbeing and less distress, when compared with continued haemodialysis or peritoneal dialysis. There are several individual studies that have examined quality of life issues in more detail. Evans et al. reported that 79.1% of transplant recipients describe near normal physical function, compared with only 50% of dialysis patients. Mental function scores were also higher in transplant recipients. Studies by both Gorlen et al. and Laupacis et al. found that the quality of life improvements associated with transplantation were sustained long term. However, transplantation continued to affect quality of life relative to normal. This was attributed to the side effects of immunosuppression, comorbid conditions and the stress associated with the possibility of losing graft function.

Cost effectiveness of transplantation

A detailed analysis of the relative costs of dialysis and transplantation has been performed by Kidney Health Australia. Estimates of the cost of home or satellite-based dialysis (haemodialysis and peritoneal) for an individual are approximately $45,000–$60,000 per year. Hospital-based haemodialysis is estimated to cost approximately $83,000 per year. Although the initial cost of transplanting an individual is estimated to be relatively high ($62,000 for the first year) the cost falls significantly thereafter (approximately $11,000 per year for year 2 and onwards). The estimated costs associated with an individual live donor transplant are similar to those for an individual deceased donor transplant. A Canadian report estimated that transplanting an individual would result in savings of CAN$104,000 over a 20-year period.

Overall safety for live donors

Only a brief account of the overall safety data will be summarized here; a much more detailed analysis of the literature regarding donor safety will follow in subsequent sections of these Living Kidney Donor guidelines. By and large, live kidney donation is considered to be safe for the majority of healthy donors. This contention, however, is based predominantly on large retrospective studies, which demonstrate that unilateral nephrectomy in healthy subjects is generally associated with a very low level of long-term risk. A meta-analysis published by Garg et al. has examined the development of proteinuria in donors. It concluded that there is a small increase in urinary protein excretion; however, glomerular filtration rate (GFR) was well preserved over a 15-year follow-up period. Another meta-analysis, by Boudville et al. examined the effect of donation on blood pressure. This concluded that donors may have a 5 mmHg increase in blood pressure within 5–10 years of donation.

Ibrahim et al. assessed the vital status and lifetime risk of end-stage kidney disease (ESKD), GFR, urinary albumin excretion, prevalence of hypertension, general health status and quality of life in 3698 kidney donors. Survival and risk of ESKD was not significantly different to those in the general population. Most donors had a preserved GFR, normal albumin excretion and an excellent quality of life.

It is important to point out that the absence of any large prospective, well-controlled, long-term follow-up studies on live donors is seen as a significant deficiency. Furthermore, long-term studies regarding live donors with isolated abnormalities (e.g. hyperlipidaemia, mild hypertension, obesity) are also lacking, and the long-term risks in these subjects remain particularly ill defined. It is hoped that the recently established ANZDATA Live Donor Registry will help in further clarifying the true long-term donor outcomes in Australia and New Zealand.

With regards to the short-term risks, these are predominantly related to the surgical procedure. The risk of perioperative mortality is generally regarded as being approximately 1 in 3000 – a figure derived from large American surveys and several single centre reports. Although Australian and New Zealand registry data are currently lacking, of approximately 5000 live kidney donations that
have occurred in Australia and New Zealand to date, the transplant community is currently aware of two perioperative deaths (anecdotal reports).

The risk of non-fatal major perioperative complication is also generally felt to be low, approximating 2–4% in most published series (see later subtopics for a detailed account of the supporting literature). The majority of these complications have been haemorrhagic episodes, although a variety of other events have been reported including bowel obstruction, bowel injury, thromboembolic events, pulmonary oedema, hernia development and rhabdomyolysis.

Prasad et al. performed an observational cohort study of 58 living donors to 6 months post-donation for changes in 24 h ambulatory blood pressure profile, kidney function, urine protein excretion, body mass index, glucose intolerance and fasting lipid profiles. No significant changes in blood pressure, protein excretion, body mass index, glucose and lipids were found. Estimated glomerular filtration rate declined significantly ($P < 0.0001$).

**SUMMARY OF THE EVIDENCE**

Most of the data presented here comes from Registries and from large retrospective cohort studies. There is a lack of prospective long-term data regarding live donor safety, particularly in relation to consequences of donation in certain donor subgroups.

To summarize this guideline topic:
- Live kidney donation is currently justifiable in Australia and New Zealand based on:
  i) the current overall success of kidney transplantation;
  ii) the demand for donor organs, which far outweighs the supply from deceased donors;
  iii) the detrimental effects of waiting on dialysis for several years; and
  iv) the apparent low level of risk to the majority of healthy donors.
- It is acknowledged that there is a need for more precise information regarding long-term risks faced by donors. This would ideally be obtained from prospectively collected live donor registry data.

**WHAT DO THE OTHER GUIDELINES SAY?**

National Health & Medical Research Council (Australia):

Two recently published documents cover various aspects of the information presented here. The first document – for health professionals – outlines important ethical principles, and details the rights and responsibilities of donors, health professionals and institutions. The second document – for potential donors – provides information regarding the assessment, a discussion of the risks and also outlines important ethical issues. Both discuss the rationale behind live kidney donation. These are available at: [www.nhmrc.gov.au/publications/subjects/organ.htm](http://www.nhmrc.gov.au/publications/subjects/organ.htm)

British Transplant Society/British Renal Association:

An extensive, 100-page document has been produced outlining similar issues to those discussed here. The full version of these British Live Donor Guidelines is available at: [www.bts.org.uk](http://www.bts.org.uk) and at [www.renal.org](http://www.renal.org)

The Canadian Council for Donation and Transplantation:

A 70-page document has been published outlining similar issues to those discussed here. A full version of these guidelines is available at: [www.ccdt.ca](http://www.ccdt.ca)

The Amsterdam Forum:

An International Forum on the Care of the Live Kidney Donor, comprising 100 experts from 40 countries, produced a short manuscript outlining similar issues to those discussed here.

**SUGGESTIONS FOR FUTURE RESEARCH**

1. Assess long-term donor risks: medical and psychosocial. Prospective studies are required. The risks in various donor subgroups need to be better assessed (e.g. those with isolated abnormality such as mild hypertension, obesity, etc.).
2. Survey Australian and New Zealand transplant centres regarding live donor outcomes to date. Known major adverse events to be collated and reported.
3. Examine the barriers to donation for live donors in Australia and New Zealand (e.g. financial, social, community attitudes, awareness).
5. Examine Australian and New Zealand transplant centre practice regarding live donor assessment (handling of ethical issues, informed consent process).

**CONFLICT OF INTEREST**

John Kanellis has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

**REFERENCES**

### APPENDIX

#### Table 1 Characteristics of included studies

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<td>Fehrman-Ekholm et al. 1997</td>
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<td>Donor survival (Kaplan–Meier analysis)</td>
<td>1964–1994, national registry, Sweden</td>
<td>Survival after &gt;20 years: donors 85%, expected survival (Hakulinen’s method) 66%</td>
<td>No long term risk to live kidney donors (better survival likely due to health of persons accepted for donation)</td>
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<td>Goldfarb et al. 2001</td>
<td>70</td>
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<td>1963–1975, single centre, US</td>
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<td>Renal function well preserved after donor nephrectomy</td>
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<td>Kasiske et al. 2002</td>
<td>38 36</td>
<td>Analysis of cadaver and living donor transplants (χ², logistic regression, Kaplan–Meier analysis)</td>
<td>1995–1998, United States Renal Data System Registry, US</td>
<td>Pre-emptive transplantation associated with a lower rate of delayed graft function compared with non pre-emptive transplantation: cadaver (8.4 vs 25.6%) and living donor (2.6 vs 6.1%)</td>
<td>Pre-emptive transplantation is associated with improved patient and graft survival</td>
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<td>Mandal et al. 2003</td>
<td>31 909</td>
<td>Cox proportional hazards model to approximate risk associated with CRT, LRT</td>
<td>1995–1998, United States Renal Data System Registry, US</td>
<td>Cadaveric versus live donor (younger patients): graft failure uncensored for death RR 1.49 (95% CI: 1.41–1.61), risk of death 1.64 (95% CI: 1.49, 1.82)</td>
<td>Elderly recipients with an imminent LRT should not be offered CRT. CRT may be preferable in younger recipients</td>
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<td>Matas et al. 2003</td>
<td>10 828</td>
<td>Survey sent to transplant centres listed with UNOS</td>
<td>1991–2001, 171/234 UNOS-listed kidney transplant programs</td>
<td>Death from surgical complications 0.02%, mortality rate 0.03%</td>
<td>Morbidity and mortality for living kidney donor nephrectomy is low</td>
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<td>Najarian et al. 1992</td>
<td>57</td>
<td>Comparison of donors and their siblings</td>
<td>20 years, single centre, USA</td>
<td>Hypertension drugs: donors 32%, siblings 44%</td>
<td>Perioperative mortality after living donor nephrectomy is low</td>
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<tr>
<th>Study ID</th>
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<th>Study methods</th>
<th>Data sources</th>
<th>Results</th>
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<td>Ramcharan et al. 2002 and Matas et al. 2003</td>
<td>464</td>
<td>Living donor outcomes – cross sectional</td>
<td>1963–1979, single centre, USA</td>
<td>Survival 89.9%, normal kidney function in surviving donors 99.2%</td>
<td>Most kidney donors have normal renal function at &gt;20 years follow up</td>
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<td>Rizvi et al. 2005</td>
<td>736</td>
<td>Retrospective analysis of living related kidney donation</td>
<td>2000–2004, single centre, Pakistan</td>
<td>Creatinine clearance: 87% of pre-nephrectomy value, hypertension 10.3%, proteinuria &gt; 150 mg/24 h 24.3%, ESKD in one donor.</td>
<td>Donor nephrectomy has minimal adverse effect on overall health status</td>
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<td>Simforoosh et al. 2006</td>
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<td>Survival analysis (Kaplan–Meier analysis)</td>
<td>1984–2004 transplant data, single centre, Iran</td>
<td>15-year graft survival: LRD 53.4%, LURD 59.0%; 15-year patient survival: LRD 73.9%, LURD 76.4%</td>
<td>Long term results for living unrelated kidney transplantation comparable with living related kidney transplantation</td>
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<td>Terasaki et al. 1995</td>
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<td>Graft survival rates (Kaplan–Meier analysis)</td>
<td>UNOS Renal Transplant Registry</td>
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<td>High rate of graft survival in kidney donations from spouses and parents</td>
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<td>Voiculescu et al. 2003</td>
<td>62</td>
<td>Transplant data (Fisher’s exact test, Mann–Whitney U-test)</td>
<td>Transplant data, single centre, Germany</td>
<td>Acute rejection: LRD 52.2%, LURD 54.2%; delayed graft function: LRD 15.8%, LURD 4.2%; number of patients with rejection: LRD 52.5%, LURD 54.2%</td>
<td>Kidney transplantation from emotionally related living donors is a valuable option</td>
</tr>
</tbody>
</table>

CI, confidence interval; CRT, cadaveric donor renal transplantation; ESKD, end-stage kidney disease; LRD, living related donor; LRT, live donor renal transplantation; LURD, living unrelated donor; RR, relative risk; UNOS, United Network for Organ Sharing.