Donor sepsis

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GUIDELINES

There is no contraindication to general allocation of CMV (+) organs, however, the donor should be made aware to enable CMV prophylaxis, particularly for CMV (–) recipients. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **Uncontrolled donor sepsis should be a contraindication to kidney donation.**

- **Donor sepsis, once controlled with appropriate antibiotic therapy, is not a contraindication to kidney donation (Level III evidence).**

- **Transmission of virus/es from donor to recipient is possible and the risk of this should be minimised by donor assessment and allocation as follows:**
  HIV: exclusion if antibody (+) or high-risk behaviour (IV drug abuse, commercial or male-male sex during previous 6 months).

  Hepatitis B: HB surface Ag (+) and isolated HBV core Ab+ unsuitable for general donation, consider for HB surface Ag+ recipients. HBV core Ab+ with HBV surface Ab+ (previous infection) allocate to any HBV surface Ab+ (immune) recipient with specific consent.

  Hepatitis C: anti-HCV (+) – allocate only to anti-HCV (+), RNA (+) recipient with specific consent.

  Epstein Barr Virus: EBV (+) – no contraindication to general allocation however, recipient requires notification as EBV (-) recipients may incur increased risk of primary infection and post-transplant lympho-proliferative disease.

  HTLV I & II and CJD occur at extremely low frequencies in Australia and New Zealand, and are not screened for.

  HSV, HZV, HHV6 and HHV8 are prevalent and may be transmitted, but are not screened for.

- **Transmission of syphilis, malaria, rabies and other parasites are unlikely due to rarity of these infections in Australia. However, if donor infection is suspected, appropriate testing and treatment should be given to both donor and recipient.**

- **A donor will be excluded in the presence of uncontrolled sepsis. If sepsis has occurred but has been controlled with antibiotics, donation should proceed provided the recipient is treated with appropriate antibiotics for at least 3 days post-transplant, and that specific informed consent is obtained from the recipient.**

- **HIV (+) donors, or those deemed to be at high risk (IV drug abuse, prostitution, male-male sex within the past 6 months) should be excluded from donation.**

- **Hepatitis B: HB surface Ag+ or isolated HBV core Ab+ unsuitable for donation; HBV core Ab+ and HBV surface Ab+ allocate to any HBV surface Ab+ recipient with specific consent. HBV immunisation should be given to seronegative patients with end-stage kidney disease (ESKD) prior to transplant.**

- **Hepatitis C: anti-HCV (+) – allocate only to anti-HCV (+), RNA (+) recipient with specific consent.**

- **Cytomegalovirus: CMV (+) – no contraindication to general allocation however, donor should be made aware to enable CMV prophylaxis, particularly for CMV (-) recipients (Level II evidence).**

- **Epstein Barr Virus: EBV (+) – no contraindication to general allocation however, recipient requires notification as EBV (-) recipients may incur an increased risk of primary infection and post-transplant lymphoproliferative disease.**

- **HTLV I & II and CJD occur at extremely low frequencies in Australia and New Zealand, and are not screened for. Donors from areas where HTLV is endemic (e.g. Caribbean basin) should be screened.**

- **HSV, HZV, HHV6 and HHV8 are prevalent and may be transmitted, but are not screened for. Varicella immunisation should be considered for seronegative patients with ESKD prior to transplant, but not post-transplant.**

- **Syphilis: Transmission of syphilis is possible, however, donation may proceed in the presence of a positive serological test for syphilis (e.g. RPR) provided a two-week course of penicillin is given to the recipient and specific consent is obtained.**

- **Tuberculosis: Active mycobacterial infection is a contraindication to transplantation. Donor chest X-ray is recommended to enable risk assessment and in the deceased donor, any suspicious lesions should undergo biopsy and microscopy. In the live donor situation, chest X-ray is also recommended and any suspicious lesions should be assessed by a respiratory specialist.**

Background

Bacterial sepsis

Sepsis is common among deceased donors at some stage of their pre-terminal illness (Freeman et al 1999). Transmission of bacterial infection from donors to kidney allograft recipient has been documented (Doig et al 1975; Weber et al 1979; Nelson et al 1984). Sepsis remains a common cause of morbidity, and occasionally mortality, among kidney transplant recipients. This guideline will discuss available data and recommend a practical approach to minimise the risk of sepsis transmission from donors to recipients, while maximising donor utilisation.

Viral infection

Chronic viral infections that are transmissible via kidney transplantation are highly prevalent (CMV, EBV, BK/Polyoma, HSV, Varicella), present in a minority (Hepatitis B & C, HIV, HHV 6 & 8) or are rare (HTLV I & II, CJD) among potential kidney donors in Australia. Viral infections may be associated with fulminant viraemia and organ dysfunction (EBV, CMV, Varicella, HSV, HBV), with chronic organ damage (HBV, HCV), kidney transplant damage (BK nephropathy, HCV, CMV), increased risk of bacterial or opportunistic sepsis (HIV, HCV, HBV, CMV), or malignancy (EBV, HIV, HPV, HSV, HBV, HCV). This guideline will review the literature and consider local epidemiology to propose practical guidelines to maximise organ use yet minimise viral risk.

Search strategy

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for bacterial infections and viral diseases and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline (1966 – April Week 3 2005). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 4 May 2005.

What is the evidence?

Transmission of bacterial infection from kidney donor to recipient

There are no randomised controlled trials (RCTs) examining transmission of infection, due to logistic and ethical impediments. Transmission of bacterial infection by kidney transplantation has been reported, resulting in recipient complications including anastomotic disruption and death (Doig et al 1975; Weber et al 1979; Nelson et al 1984; Delmonico & Snydman 1998). However, once identified, treatment of donor (pre-organ harvest) and recipient (from the time of transplantation) with appropriate antibiotics has resulted in transplantation without transmission of infection or other adverse consequences for the recipient, even when the primary infection was the cause of donor death, such as meningitis (Delmonico & Snydman 1998; Little et al 1997).

Two recent cohort studies have reported the impact of transplanting organs retrieved from donors who were identified as having bacteraemia either before or after organ retrieval (Freeman et al 1999; Zibari et al 2000). The two key findings were: (1) organs are commonly allocated despite donor sepsis acquired prior to or within the Intensive Care Unit (ICU) setting; and (2) current practices, including antibiotic treatment of both donor and recipient in cases of donor sepsis, have provided excellent clinical outcomes with no significant transmission of sepsis to kidney recipients and patient and graft survival equal to that following allocation of organs from non-septic donors. It should be noted that both studies were retrospective, and that only those donors with positive blood cultures were identified as septic. Donors and potential donors who exhibited evidence of sepsis, such as fever, haemodynamic compromise or organ infiltration, in the absence of positive blood or urine cultures, appear not to have been included in either study. Thus, guidelines on the use of donors who have appeared to be septic, have responded to broad-spectrum antibiotics, but for whom no pathogen was identified, cannot be made on the basis of existing literature.

On this basis, it appears reasonable to allocate kidneys when donor sepsis has been identified on clinical and microbiological grounds and treated with a satisfactory clinical response. Organs may then be implanted provided the recipient is given antibiotic coverage according to the clinical setting and sensitivities of the organism. In cases when no microbiological diagnosis has been obtained (in the opinion of this reviewer), use of the donor organs should be considered when clinical resolution of all evidence of sepsis has been achieved for at least 48 hours prior to organ retrieval, and the recipient provides specific informed consent and receives similar broad spectrum antibiotic coverage for the first 3–7 days post-transplant.

Transmission of viral infection

Human immunodeficiency virus (HIV)

HIV transmission from donor to recipient has been extensively reported, both from seropositive (Kumar et al 1987) and seronegative 'window period' donors (Simonds et al 1992), resulting in the development of acquired immunodeficiency syndrome (AIDS) post-transplant.

Hepatitis B virus (HBV)
This highly infectious agent is readily transmitted from donors who are chronic carriers (HBV surface Ag+) to recipients. Although transmission rates are less than 100%, this may be due to a degree of protection afforded by HBV immunisation among ESRD patients on dialysis (Chan et al 1992; Natov & Pereira 2002).
Donors who are HBV core Ab+, but HBV surface Ag- and HBV surface Ab+ or – may have persistent virus within hepatocytes, but little or none in the bloodstream. Consistent with this, HBV has been transmitted from such donors to recipients of liver transplants. However, there have been no reported cases of transmission to over 50 kidney recipients from HBV core Ab+ donors recorded in Australia. A major review of the UNOS database has demonstrated sero-conversion from HBV core Ab negative to positive in a minority of recipients, but no cases of HBV surface Ag seropositivity and no increase in significant liver disease after transplantation from HBV core Ab + donors to HBV core Ab- recipients. Again, the high rate of HBV immunisation among dialysis patients may have afforded protection (Fong et al 2002). Allocation of HBV surface Ag+ kidneys to HBV surface Ag+ recipients has been advocated however, long-term outcome data is lacking.

Hepatitis C virus (HCV)
Hepatitis C is prevalent among donors (range: 1%– 2% (Natov et al 2002) and is transmissible from donors who are viraemic or RNA+, constituting approximately half of all HCV Ab+ donors (Natov et al 2002; Mathurin et al 1999). Recipients who are HCV+ experience similar short-term, although inferior long-term outcomes, compared with HCV- kidney transplant recipients (Roth et al 1994; Legendre et al 1998). Whether outcomes differ between those who acquire HCV prior to versus at the time of transplantation is unclear.

Allocation of HCV Ab+ kidneys to HCV Ab+ RNA+ recipients has been advocated (Natov et al 2002). HCV Ab+ RNA- recipients are excluded, as they may have cleared the virus and transplantation would result in reinfection. For RNA+ recipients, transplantation entails risks including super-infection with a different genotype. Long-term assessment of the efficacy of this strategy is awaited.

Cytomegalovirus (CMV)
The majority of donors are CMV IgG+ (> 80%). However, effective prophylaxis is available and may significantly reduce the risks of CMV disease post-transplant (Lowance et al 1999). Thus, knowledge of donor and recipient status is useful.

Compliance with valacyclovir may be compromised by the large number of tablets required for patients with good kidney function (up to 16 tablets per day). If compliance is problematic, or if valacyclovir is contraindicated or causes side-effects, valgancyclovir appears to be an effective alternative, however, prospective head to head comparison data for this agent compared with valacyclovir is currently lacking.

Epstein Barr virus (EBV)
EBV may be transmitted to seronegative recipients, and the primary infection that follows is associated with an increased risk of post-transplant lymphoproliferative disease (PTLD) (Haque et al 1996).

Transmission of parasitic infestation

Syphilis transmission is probably inhibited by the temperature and penicillin present in organ preservation fluids, and successful transplantation of organs from an RPR (+) donor has been reported, with the recipient being treated with penicillin and remaining free of syphilis (Caballero et al 1998).

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

British Renal Association: 8.39. Renal transplant recipients are susceptible to opportunistic infections such as cytomegalovirus, pneumocystis and tuberculosis. The early detection of and/or prophylaxis against these infections in high-risk patients (e.g. cytomegalovirus (CMV) -ve recipient of a CMV +ve kidney) is possible, and their use must be judged taking into account potential hazards and expense. Guidelines on the prevention and treatment of cytomegalovirus infection transplant recipients have recently been published by the British Transplantation Society.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: Eliminating the risk of infections: Screen donors for HIV, HBV, HCV, HTLV1, and CMV. Exclude donation if HIV+ or high-risk behaviour during past 2 months. HBV+ donors acceptable for HBV+ recipients. HCV+ donors acceptable for HCV+ recipients who are also RNA+. Testing for EBV and CMV may be useful to guide donation, to determine whether anti-CMV prophylaxis should be used post-transplant, and to assess risk of PTLD (increase in EBV D+R- cases).

Donation is acceptable following the identification of donor sepsis, provided control of sepsis is achieved with antibiotics and antibiotics are administered to the recipient for 3-6 days. (Nephrol Dial Transplant 2000; 15 (Suppl 7): S41–S42).

International Guidelines: No recommendation.

Implementation and audit

Set up a register of kidneys discarded due to sepsis (suggestion only).

Suggestions for future research

1. Perform a prospective follow-up of all cases of suspected or proven donor sepsis referred for donation to see: (1) usage rate / discard rate, (2) recipient antibiotic use, and (3) recipient sepsis, delayed graft function, kidney function, and patient and graft survival at 1 year. Compare to same outcomes among all non-septic donors for same time period (deceased donors only).

2. Studies of viral transmission outcomes unlikely to be useful given small numbers involved in Australia, other than to document outcomes prospectively for HCV+ donors to HCV+ recipients, and HBV+ donors to HBV+ recipients, if this strategy is implemented in Australia.

References

Caballero F, Domingo P, Rabella N et al. Successful transplantation of organs retrieved from a donor with syphilis. Transplantation 1998; 65: 598–99.

Chan PC, Lok AS, Cheng IK et al. The impact of donor and recipient hepatitis B surface antigen status on liver disease and survival in renal transplant recipients. Transplantation 1992; 53: 128–31.

Delmonico FL, Snydman DR. Organ donor screening for infectious diseases: review of practice and implications for transplantation. Transplantation 1998; 65: 603–10.

Doig RL, Boyd PJ, Eykyn S. *Staphylococcus aureus* transmitted in transplanted kidneys. Lancet 1975; 2: 243–45.

European Renal Association–European Dialysis and Transplant Association. European Best Practice Guidelines. Section II: Evaluation and selection of donors. Nephrol Dial Transplant 2000; 15 (Suppl 7): 39–51.

Fong TL, Bunnapradist S, Jordan SC et al. Impact of hepatitis B core antibody status on outcomes of cadaveric renal transplantation: analysis of the United Network of Organ Sharing database between 1994 and 1999. Transplantation 2002; 73: 85–89.

Freeman RB, Giatras I, Falagas ME et al. Outcome of transplantation of organs procured from bacteremic donors. Transplantation 1999; 68: 1107–11.

Haque T, Thomas JA, Falk K et al. Transmission of donor Epstein-Barr virus (EBV) in transplanted organs causes lymphoproliferative disease in EBV-seronegative recipients. J Gen Virol 1996; 77: 1169–72.

Kumar P, Pearson JE, Martin DH et al. Transmission of human immunodeficiency virus by transplantation of a renal allograft, with development of the acquired immunodeficiency syndrome. Ann Intern Med 1987; 106: 244–45.

Legendre C, Garrigue V, Le Bihan C et al. Harmful long-term impact of hepatitis C virus infection in kidney transplant recipients. Transplantation 1998; 65: 667–70.

Little DM, Farrell JG, Cunningham PM et al. Donor sepsis is not a contraindication to cadaveric organ donation. QJM 1997; 90: 641–42.

Lowance D, Neumayer HH, Legendre CM et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. N Engl J Med 1999; 340: 1462–70.

Mathurin P, Mouquet C, Poynard T et al. Impact of hepatitis B and C virus on kidney transplantation outcome. Hepatology 1999; 29: 257–63.

Natov SN, Pereira BJ. Transmission of viral hepatitis by kidney transplantation: donor evaluation and transplant policies (Part 1: hepatitis B virus). Transpl Infect Dis 2002; 4: 117–23.

Nelson PW, Delmonico FL, Tolkoff-Rubin NE et al. Unsuspected donor pseudomonas infection causing arterial disruption after renal transplantation. Transplantation 1984; 37: 313–14.

Roth D, Zucker K, Cirocco R et al. The impact of hepatitis C virus infection on renal allograft recipients. Kidney Int 1994; 45: 238–44.

Simonds RJ, Holmberg SD, Hurwitz RL et al. Transmission of human immunodeficiency virus type 1 from a seronegative organ and tissue donor. N Engl J Med 1992; 326: 726–32.

The Renal Association and the Royal College of Physicians of London. *Treatment of adults and children with renal failure. Standards and audit measures*. 3rd edition. London: The Lavenham Press Ltd; 2002.

Weber TR, Freier DT, Turcotte JG. Transplantation of infected kidneys: clinical and experimental results. Transplantation 1979; 27: 63–65.

Zibari GB, Lipka J, Zizzi H et al. The use of contaminated donor organs in transplantation. Clin Transplant 2000; 14: 397–100.