

Deceased Kidney Donor Suitability Guidelines

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Non-heart–beating donors

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Guidelines

No recommendations possible based on Level I or II evidence.

Suggestions for clinical care

(Suggestions are based on Level III and IV sources)

- **Non-Heart Beating (NHB) donors should be considered as an extra source of deceased donor kidneys for transplantation, with acceptable patient and graft survival, in spite of an increased incidence of delayed graft function.**
- **Results using kidneys from NHB donors may be improved by using ‘controlled’ donors younger than 60 years of age and by minimising warm and cold ischaemic times (? use kidneys locally).**
- **Transplant Centres are encouraged to develop protocols which satisfy local and regional ethical and legal requirements.**
- **All NHB donation procedures occur as an emergency and require a team including transplant co-ordinators and surgeons available urgently 24 hours a day.**

Background

The objective of this guideline is to explore the option of using non-heart beating donors (NHB) for renal transplantation.

NHB donors are used by a number of centres as a means of overcoming the shortage of kidneys available for transplantation. NHB donors can make a significant

contribution to transplant numbers: in Maastricht (Netherlands), 40% of transplants and in Leicester (UK) 22% of transplants are derived from NHB donors. However, in both centres there has been no increase in the overall transplant rate and it could be argued that the effort and resources dedicated to these programmes has resulted in a decrease of kidneys from other and potentially better sources (Brook & Nicholson 2003).

NHB donors have higher rates of primary non-function compared with heart beating (HB) donors (5.8% vs 1.3%) and higher rates of delayed graft function (DGF, 42.4% vs 23.3%) (Rudich et al 2002). However, there are similar rates of acute rejection and allograft survival is not significantly different between NHB and HB donor transplants (Brook & Nicholson 2003, Cho et al 1998). Patient survival is similar for NHB compared with HB recipients at 6 years (80.9% vs 77.8%, Rudich et al 2002).

The use of NHB donors raises many ethical and logistical issues which must be clarified prior to commencing this programme. To avoid a negative impact on HB donor programmes, it is important be clear that NHB donors are in addition to and not instead of HB donors. What category of NHB donors should be used? Potentially up to 50% of kidneys are discarded following procurement because of technical problems making them unsuitable for transplantation which can be difficult for donor families. Acceptance of NHB donor programmes by the community and hospital staff can be challenging. Is it acceptable to perform cannulation and in-situ perfusion prior to obtaining consent from the next-of-kin? In the Netherlands, this has been passed with legislation but in the UK this depends on the Coroner (Brook & Nicholson 2003).

All NHB donation procedures occur as an emergency and it is essential to have a team including transplant co-ordinators and surgeons available 24 hours a day. This is a major consideration for the implementation of a NHB programme and a disincentive to many units (Brook & Nicholson 2003).

Criteria for NHB donors (Maastricht)

- 1) Duration of circulatory arrest < 30 min without professional cardiac massage and ventilation
- 2) Professional cardiac massage and ventilation not exceeding 2 hours
- 3) Age limit 65 years
- 4) No signs of IV drug use
- 5) No systemic infection/sepsis
- 6) No history of kidney disease, uncontrolled hypertension, or malignancy other than primary, non-metastasizing CNS tumours.

Preservation of organs should take place soon after the declaration of death to limit ischaemic damage. When death is declared on cardiac criteria, a period of non-action is observed before commencing mechanical resuscitation and preservation of the kidneys by in-situ cooling. There is variation between units in how this is performed (Oomen et al 1996).

Categories of NHB donors (Maastricht)

The common situation is that all NHB donors have sustained irreversible cardiac arrest.

Category 1: 'Dead-on-arrival' at hospital – cause of death is obvious (e.g. serious head injury) and no resuscitation is given. This is an unusual event and rare source of NHB donors.

Category 2: 'Unsuccessful resuscitation' – an individual is brought to Accident & Emergency while being resuscitated but this is not effective or arrest occurs on the hospital ward and they are unable to be resuscitated. These are relatively common events and represent the largest potential pool of NHB donors.

Category 3: 'Awaiting cardiac arrest' – e.g. severe brain damage without brain death has occurred. Patients are mostly ventilator-dependent and after consent from relatives, the ventilator is switched off and cardiac arrest awaited. The agonal period is limited to 2 hours to avoid damage from hypotension and hypoxia.

Category 4: 'Cardiac arrest while brain dead' – these patients are in the process of being diagnosed brain dead and do not respond to cardiopulmonary resuscitation.

Search strategy

Databases searched: MeSH terms and text words for kidney transplantation and cadaveric organs were combined with MeSH terms and text words for diabetes, hypertension, viruses, bacterial infections, non-heart beating, marginal donor, paediatric donor, aged donor, and donor with prior cancer. These were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and search filters for identifying prognosis and aetiology studies. The search was carried out in Medline (1966 – November Week 2 2003). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 12 December 2003.

What is the evidence?

There are no randomised controlled trials for this subject and they would be difficult to perform. The information comes from individual centre reports and Registry reports and the numbers are small.

Summary of the evidence

The Maastricht categories can be classified more simply into controlled and uncontrolled donors depending on whether cardiac arrest was anticipated or not. In uncontrolled donors, there is little time to organise donation but in controlled donors there is often more chance to organise in-situ perfusion and organ retrieval. This

results in longer warm ischaemic time (30–60 minutes) prior to in situ cooling in uncontrolled donors with almost inevitable DGF (Brook & Nicholson 2003).

In NHB donors, the kidneys will inevitably sustain a more prolonged period of ischaemia than HB donors but the aim is to limit this time. Various methods of renal perfusion and cooling exist. Some programmes apply mechanical ventilation and cardiac massage until procurement with preservation of the kidneys on the back table. Other methods use in-situ cooling to limit the ischaemia. Alternatively, a rapid laparotomy may be performed with intra-aortic cannulation and core cooling. Another technique is cardiopulmonary bypass and use of an extracorporeal machine for total body cooling (Alvarez et al 2000). In situ perfusion using a Double-Balloon-Triple-Lumen catheter is widely used and is relatively simple. This is the method used in Maastricht. After confirmation of irreversible cardiac arrest (by doctors who are independent of the transplant team) and consent from the family for organ donation, the catheter is placed via the femoral artery into the aorta and perfusion with 5L perfusion solution is commenced. Nephrectomy can be performed in theatre subsequently (Oomen et al 1996).

Machine perfusion of the donor kidneys is used in Maastricht as a way of minimising further damage to the organ and to allow an opportunity to assess the kidneys on the basis of several pressure-related and biochemical tests. The reliability of these tests is limited. Machine perfusion has also been widely used in the US but it is not common in the UK. Three comparisons of cold storage and machine perfusion for NHB donors showed no difference in DGF (Brook & Nicholson 2003).

Donor selection

The two most important selection criteria are donor age and warm ischaemic time and these should be considered together (Brook & Nicholson 2003). Most NHB programmes use 60 years as the upper limit for donor age and greater than 30–45 minutes of warm ischaemia time as an exclusion criterion. Prolonged warm ischaemic time (> 30 min) is more common with 'uncontrolled' donors and results in DGF in almost all cases. However, if a very young donor is used, successful transplantation may be possible even after 60 minutes warm ischaemic time (Brook & Nicholson 2003).

In addition to the usual contraindications to organ transplantation such as extracranial malignancies, hepatitis, HIV etc., donors with diseases such as uncontrolled diabetes and hypertension should be avoided because of potential adverse effects on the kidneys.

Results

Significant factors for allograft loss for NHB donor recipients include organ used for repeat transplant, DGF, donor older than 35 years and donor as a result of head trauma (Rudich et al 2002).

In Newcastle (UK), the results of transplantation from NHB donors have varied according to the category of donor used. Excellent results have been obtained (90.5% success) using Maastricht Category III donors. However, success was only

obtained in 45.5% of transplants using Category II donors but this can be dramatically improved to 92.3% by the use of machine perfusion and glutathione S transferase enzyme analysis. This has the advantage of further increasing the donor pool (Balupuri et al 2000).

In Leicester (UK), NHB donor renal function falls into two groups: about half of the recipients achieve a normal serum creatinine and the other half have a creatinine between 200–300 $\mu\text{mol/mL}$ at three months, which remains stable for years (Brook & Nicholson 2003).

United Kingdom Transplant has written there is increased early renal graft loss in NHB donor transplants followed by parallel rates of graft survival over the first year. One-year transplant survival was not significantly different at 82% with NHB donors versus 85% with HB donors (UK Transplant Activity Report 2001).

In Singapore, two-year patient and graft survivals were very similar in both HB and NHB donor transplants (100% vs 98% and 98% vs 96%). The incidence of DGF was also comparable (41% vs 50%). This is despite significant differences in donor age (23.7 vs 34 yrs) and warm and cold ischaemic times (Lau et al 1999).

A Japanese series of 125 NHB renal transplants demonstrated DGF in 78.4% of patients, which lasted a mean of 16 ± 21 days (range: 3–37 days). Primary non-function occurred in 8.8% of grafts and acute rejection in 51.2% of recipients (Tanabe et al 1998). Local figures for HB donor transplants were not given.

Increasing donor age (> 55 years) showed a significant correlation with raised serum creatinine ($P < 0.001$) and prolonged post-transplant dialysis ($P < 0.01$) in a separate Japanese study. Renal transplants from non-cerebrovascular disease NHB donors had significantly lower creatinine than from cerebrovascular donors ($P < 0.0001$). Ten-year graft survival rates were almost identical in the NHB donor grafts, the UNOS cadaveric renal grafts, and Japanese living-related grafts (Hoshinaga et al 1998).

UNOS data demonstrates that one-year graft survival was better from NHB donors who died of trauma (89%) compared with NHB donors from other causes of death (78%, $P < 0.04$). Need for dialysis was higher in recipients of NHB donor kidneys compared with HB donors (48% vs 22%) but this did not affect graft survival (Cho et al 1998).

Summary

NHB donor renal transplantation is a possible way of increasing allograft numbers. It results in good short- and long-term graft survival at the cost of an increase in DGF, increased need for dialysis, and the discarding of organs which are considered unsuitable for transplantation after procurement. Machine perfusion of the organs and testing for viability should be optimal. Legal and ethical issues are potential barriers.

What do the other guidelines say?

The CARI guidelines are in agreement with the guidelines from the European Renal Association-European Dialysis and Transplant Association.

British Transplantation Society: Guidelines relating to solid organ transplants from NHB donors were published in 2004 and conclude that summarising the predicted outcome following kidney transplantation with kidneys retrieved from NHB donors is not straightforward. It is anticipated that the risks of primary non-function and delayed graft function are increased and there is reduced graft survival.

Kidney Disease Outcomes Quality Initiative: No recommendation.

British Renal Association 2002: Purchasers should fund efforts to increase the number of cadaver organs made available by the setting up of transplant coordination and organ procurement teams, and they should ensure that adequate educational programmes are in place; an important part of this is improved communication with intensive care units. (Good Practice)

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines 2000:

II.2 Cadaveric non-heart beating donors (NHBD):

- A. Non-heart beating donors should be considered as a valuable source of kidneys for transplantation, despite shorter graft survival and higher serum creatinine in recipients compared with those transplanted from classical cadaveric donors. (Evidence level B)
- B. Young donors who die from trauma can be safely considered as non-heart beating donors. (Evidence level B)
- C. To optimize this promising alternative, it is recommended that centres start and accumulate experience. (Evidence level C)

II.1.2 Determination of brain death:

- A. It is recommended that the procurement centres encourage standardization of the management of the brain-dead donor including easy-to-use forms to assist the responsible physician in the emergency situation, and in line with national (or regional) laws and regulations which determine the criteria and methods for diagnosing terminal and irreversible loss of brain functions, i.e. brain death. (Evidence level C)

International Guidelines: No recommendation.

Implementation and audit

1. Approval will be needed from the hospital ethics committee, the coroner and community to commence using NHB donors for renal transplantation.
2. Consideration needs to be given as to which categories of NHB donors to accept.
3. Appropriateness of cannulation and in-situ perfusion prior to consent from next-of-kin needs to be discussed.
4. Survey of attitudes and education of hospital staff and community needs to occur.

5. NHB donation should be performed by surgical procurement teams familiar with the techniques required.
6. Availability of a 'donor' team needs to be established.
7. Conferences with ICU physicians, surgeons, transplant physicians, and lawyers would be worthwhile.

Audit

1. To ascertain potential donor numbers need to perform data collection from Trauma Units.
2. Collect data on potential 'missed donors', both heart-beating and non-heart-beating.
3. Procured kidneys vs transplant rate (i.e. discard rate) needs to be established.
4. Warm and cold ischaemic times should be monitored.
5. Rates of primary non-function, DGF, acute rejection, graft and patient survival should be monitored.
6. Impact of using NHB donors on transplant numbers should be established.

Suggestions for future research

1. Role of machine perfusion should be established.
2. Community attitudes to using NHB donors for renal transplantation should be established.

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Appendix

Table 1. Studies of kidney transplantation from donors without a heartbeat

Reference	No. of Transplantations from Donors Without a Heartbeat	First Year of Program	Duration of Study (yr)	Matched Patients	Graft Survival		
					Time after transplantation (yr)	Donors with a heartbeat (%)	Donors without a heartbeat (%)
Wijnen et al 1995	57	1980	12	Yes	5	55	54
Gonzalez Segura et al 1995	52	1985	10	No	5	77	68
					9	66	50
Pacholczyk et al 1996	76	1986	9	Yes	1	90	82
Balupuri et al 2000	47	1988	10	No	5	83	88
Sanchez-Fructuoso et al 2000	95	1989	10	No	5	84	83
Cho et al 1998	229	1994	2	No	1	86	83
Sanchez-Fructuosa et al 2003	188	1995	7	Yes	7	87	93

Source: BTS 2004. Guidelines relating to solid organ transplants from non-heart beating donors, p 21.