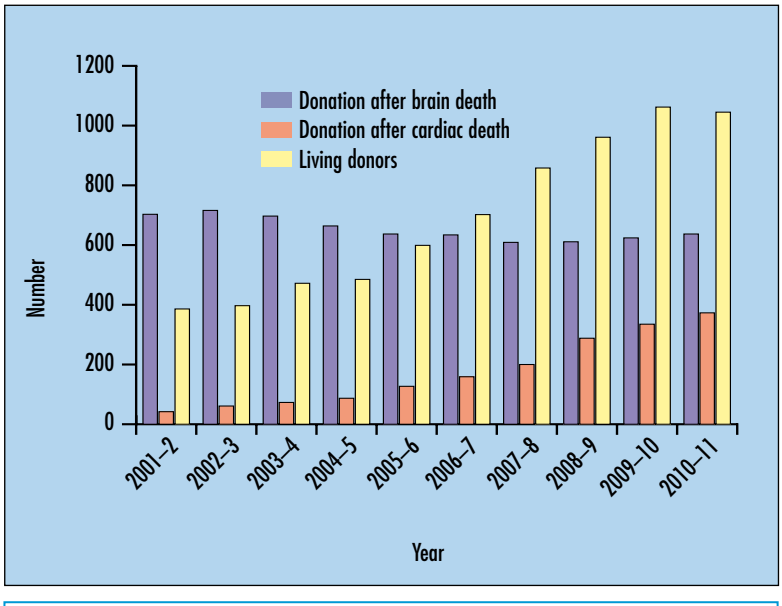
# Allocation of kidney transplants in the UK

***Live and donation after cardiac death has increased markedly recently. The allocation system for donation after brain death reserves the least mismatched organs for young people. Live donors most often donate to relatives but a scheme tries to 'exchange' live donor kidneys when direct transplantation is not possible.***

Renal transplantation offers a vastly improved quality of life and almost certainly a significant survival advantage compared with being treated with dialysis. Strictly, given that there will never be a randomized controlled comparison of transplantation *vs* dialysis, the survival advantage could be considered unproven but registry data implies that a patient with a successful renal transplant 1 year post-procedure has a third the mortality risk of patients who were wait-listed for transplantation but remained on dialysis. In the UK as well as in much of Europe and North America in recent years the absolute number of kidney transplants retrieved from living donors has increased, as has the absolute number of kidneys retrieved from individuals who died after cardiac death, whereas the proportion of kidneys retrieved from patients who have died following brain death has decreased. This change is illustrated in *Figure 1*. In the UK the allocation rules differ depending on the category of donor.

***Figure 1. Number of deceased and living donors in the UK, 1 April 2001–31 March 2011. From NHS Blood and Transplant (2011a).***

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## Tissue type and mismatching

Before describing the allocation rules it is necessary, albeit briefly, to explain the concept of tissue matching and mismatching. All nucleated mammalian cells have on their surface antigens called the human leucocyte antigens (HLA). These are explained to patients as being analogous to a personal barcode which is unique for each individual, apart from the very rare circumstance of identical twins. Historically this point is of interest as the first successful live donor renal transplant was between identical twins. During fetal and early neonatal life an individual's immune system learns to recognize self and as a consequence people do not generate antibodies against their own tissue type.

For renal transplant allocation all systems have processes that work to a degree to minimize the degree of mismatch between the donor and the recipient. For renal transplant allocation in the UK the 'tissue type' for renal transplantation is defined by using HLA loci A, B and DR. There are other so-called minor histocompatibility antigens (C, DP, DQ) and these are critically important in, for example, bone marrow transplantation but are not used in the algorithm for cadaveric renal transplant allocation.

Each individual inherits one antigen at each locus from their mother and one from their father. It follows then if a donor and recipient have the same tissue type then the mismatch at A, B and DR would be expressed as 000. At the other end of the scale the maximum mismatch would be two mismatched antigens at A, B and DR, expressed as a 222 mismatch. If there were only one mismatch at, say, the B and DR loci the mismatch grade would be expressed as 011. Given the pattern of inheritance it would be expected that any individual would be a 111 mismatch with either parent. It is of course possible to inherit the same antigen from both parents – this happens most often for common antigens. If 45% of a population have the A2 antigen then it can be seen that to inherit A2 from both parents making the offspring homozygous at the A locus would not be unusual.

In allocation algorithms that attempt to minimize the degree of mismatch individuals who are homozygous (at any locus) are at a disadvantage, because for a recipient to receive a zero mismatched donor he/she requires a homozygous donor of the same type. A recipient who is

homozygous (say for A2) will be a one mismatch with donors who are A2 plus another antigen. But there will be many other recipients who are one mismatch either for A2 or for the other antigen carried by the donor. This means that any particular donor can be an equal mismatch to a much larger recipient pool than just the homozygous recipient. Recipients who are homozygous are therefore at a disadvantage for allocation in those circumstances.

It is possible to develop antibodies against HLA antigens, most easily understood following a mismatched organ transplant where a recipient's immune system will often develop antibodies against foreign HLA antigens expressed on the surface of the cells in the organ. This is also seen following pregnancy where the mother is exposed to the 'foreign' paternal antigens carried by the fetus. The development of HLA antibodies can occur following blood transfusion where nucleated white blood cells are transfused. This is now rare with leukodepletion of whole blood used for transfusion. Finally on occasions individuals are found to have developed HLA antibodies when there have been no identifiable risk factors. The term commonly used to indicate the presence of antibodies is to describe the patient as being sensitized to the antigens.

If a renal transplant is carried out where the recipient has antibodies against HLA antigens carried by the donor this results in complement fixation and lysis of the donor cells with hyperacute rejection and prompt failure of the transplant, often in the operating theatre. An important part of the transplant work-up process, and this has a significant influence on allocation, is the determination of HLA antibodies circulating in the recipient's serum; when patients are registered on national waiting lists these antigens to which a recipient has antibodies are declared as 'unacceptable'. This means that a potential recipient is not eligible to receive a transplant from a cadaveric donor who has an HLA antigen to which the recipient has an antibody to avoid the hyperacute rejection described above.

The frequency of HLA antigens varies in the population with some antigens being relatively common. As HLA A2 is present in 45% of UK donors, if a potential recipient has an A2 antibody this in effect means about 45% of the cadaveric kidneys donors in the UK are not 'available' to be transplanted for that individual. So the development of HLA antibodies greatly influences the chances of someone receiving a renal transplant. Some potential recipients have antibodies against so many HLA antigens that they have to wait for many years before receiving a cadaveric transplant offer or may never receive an offer. The 'breadth' of antibodies that an individual has is expressed as 'percentage sensitization'. If a patient has antibodies that react to (in the order of) 85% of the population he/she is deemed as 'highly sensitized'.

Although minor histocompatibility antigens (C, DP, DQ) are not part of the allocation algorithm for cadaveric renal transplant, if recipients have antibodies to these antigens they are not offered kidneys that carry those antigens because transplantation in those circumstances would be expected to lead to early graft failure, or at the best aggressive rejection.

## Allocation of kidneys following donation after brain death

There is a national scheme that operates in the UK and Northern Ireland for the allocation of kidneys retrieved from this donor source. Once the tissue type of the donor is known – and this is often before retrieval – a matching run is performed which lists recipients in priority order. This is administered by NHS Blood and Transplant based near Bristol. The national scheme is complex and allocates based on five tiers:

1. 000 mismatched paediatric patients – highly sensitized* or HLA-DR homozygous
2. 000 mismatched paediatric patients – others
3. 000 mismatched adult patients – highly sensitized* or HLA-DR homozygous
4. 000 mismatched adult patients – others and favourably matched paediatric patients (100, 010, 110 mismatches)
5. All other eligible patients.

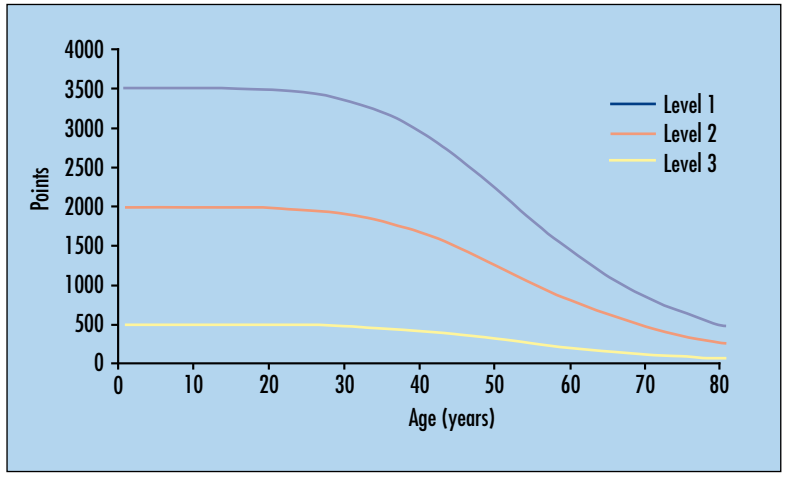
*≥85% calculated reaction frequency (based on comparison with a pool of 10 000 donor HLA types on national database).

Paediatric patients in tiers one and two are prioritized according to waiting time. In the remaining tiers, patients are prioritized according to a points score based on seven criteria. These are calculated as shown:

1. Waiting time points = number of days of waiting time accrued (see definitions)
2. HLA match and age points combined are calculated as: 3500/(1+(age/55)5) if level 1 mismatch
   2000/(1+(age/55)5) if level 2 mismatch
   500/(1+(age/55)5) if level 3 mismatch

Points scores are illustrated in *Figure 2* and mismatch levels are shown in *Table 1*.

***Figure 2. Point scores for HLA and age. From NHS Blood and Transplant (2006).***



3. Age difference points = – ½ (donor–recipient age difference)$^2$
4. Location points are 900 for patients at the same centre as the donor or 750 for patients at another centre within the local area. The areas are A – Bristol, Cardiff, London (Guy's, Royal Free, Royal London, St George's and the West London Renal Transplant Centre), Oxford, Plymouth and Portsmouth; B – Belfast, Birmingham, Coventry, Cambridge, Leicester, Nottingham and Sheffield; C – Edinburgh, Glasgow, Leeds, Liverpool, Manchester and Newcastle
5. HLA-DR homozygous points = 500 for all HLA-DR homozygous patients (where HLA level>1)
6. HLA-B homozygous points = 100 for all HLA-B homozygous patients (where HLA level>1)
7. Blood group points = –1000 for blood group B patients when the donor is group O (tiers D and E only).

The principles behind the scheme include recognizing that matching is particularly important in children as they may require more than one kidney transplant during their lifetime and a good match the first time will mean less difficulty in finding a suitable donor in the future. The principles behind the points allocation are to:

- Favour patients who have waited longest
- Favour well-matched transplants for younger patients
- Favour closer age matches between donor and recipient
- Favour patients who are geographically closer in order to minimize the transportation time of the kidney
- Include three other factors relating to blood group match and rareness of the patient's tissue type.

There are separate prioritization rules for when a pancreas is retrieved where one of the kidneys is also taken for implantation for a patient who is on the kidney/pancreas waiting list. Kidneys from donors aged 4 years and under are retrieved and offered to be transplanted together with only a minority of transplant centres in the UK participating in such implantations. If a kidney needs to be re-allocated because the patient for whom the kidney has been accepted cannot receive the transplant, much the most commonly because of occult intercurrent illness, there is a system to re-allocate to the next person on the matching run until it has been more than 20 hours since retrieval at which point the centre holding the kidney uses the organ in a patient of their choice. This, like the use of en bloc kidneys, is relatively rare.

## Allocation of kidneys following donation after cardiac death

At the present time most often these kidneys are allocated by the local transplant centre responsible for the retrieval. In some regions (and in Scotland) the kidneys are allocated to a pooled recipient list shared by more than one centre. Many centres in the UK use either the national allocation scheme described above or one based upon the national allocation scheme with some modifications. In this situation where there are two kidneys to be allocated to a single centre's waiting list, often one of the kidneys is allocated largely according to the national scheme and the other using the national allocation scheme as a prioritization but offering the kidney to a patient who does not require, on the day of transplant, a particular (time-consuming) test to ensure that the recipient has not developed any antibodies that could lead to early graft failure. This is with the aim of reducing the period the kidney is exposed to cold ischaemic injury after retrieval and before re-implantation. It is likely that a national scheme will be developed in the relatively near future that will need to balance the need to keep cold time short to minimize injury to the graft but also ensure equity of access to this donor source in the UK.

## Live donors

The vast majority of live donors are 'directed' in that there is a named individual to whom they wish to donate their kidney. For about two thirds of the time this is a family member, although in approximately a third there is not a 'blood' relationship. Most commonly 'non-blood relatives' donate to their spouse, but other relationships including that of friendship may be the link.

There are a number of individuals who wish to act as altruistic or Good Samaritan live donors, similar in concept to blood donation, where they donate a kidney with no specified recipient. These kidneys currently are allo-

**Table 1. Categorization of HLA mismatch combinations into levels for purposes of donation after brain death allocation**

| Level | HLA mismatch summary | HLA mismatch combinations included |
|---|---|---|
| 1 | 000 | 000 |
| 2 | [0 DR and 0/1 B] | 100, 010, 110, 200, 210 |
| 3 | [0 DR and 2 B] or [1 DR and 0/1 B] | 020, 120, 220, 001, 101, 201, 011, 111, 211 |
| 4 | [1 DR and 2 B] or [2 DR] | 021, 121, 221, 002, 102, 202, 012, 112, 212, 022, 122, 222 |

From NHS Blood and Transplant (2011b)

cated as if they have come from donors after brain death and allocated through the national matching scheme. In order to ensure the best quality of these kidneys the recipient is identified a short while before planned surgery and the necessary pre-surgery blood tests and work up carried out in the fortnight before the surgery. In other respects the allocation mimics that following donation after brain death.

For a number of live donors and recipients pairs it is either not possible or very difficult to offer a direct transplant between them. Most typically this is because of the presence of donor-specific HLA antibodies or of blood group incompatibility. In this situation there is a scheme called the paired exchange scheme in which donor/recipient pairs can be registered. Four times a year all the individuals in this scheme in the UK enter into a complex algorithm which broadly tries to calculate the maximum number of transplants possible. For example, it may be that a donor in Leeds cannot donate to his wife but can donate to a man in London, that man's sister can donate to a woman in Manchester, and the woman in Manchester's husband can donate to the first donor's wife in Leeds. The logistics of organizing this surgery are considerable and the number of transplants performed has been smaller than had been hoped. This is mostly because the individuals enrolled in this scheme are more highly sensitized than is the average and so it is harder to find satisfactory donors for them.

The particular problem with this scheme is that it is internal, in that to be eligible to receive the kidney you must be within the scheme and have a live donor. In early 2012 a modification is planned such that an altruistic donor can be considered for donation to a recipient in this scheme and the final donor in this, what is called cascade donation, donates to someone on the cadaveric transplant waiting list. This would mean, to use the above example, that an altruistic donor donates to a woman in Leeds, her husband donates to a man in London, the sister of the man in London donates to a woman in Manchester, the husband of the Manchester recipient then donates to an individual on the cadaveric waiting list. This final allocation would following the allocation rules used for donation after brain death described above. The big potential advantage is that the pool to receive that final donation is now all the individuals registered on the UK list, so it is very likely that someone suitable will be found. This is a big advantage over trying to match to just the individuals who are entered in the paired exchange scheme which is very much smaller than the number of people on the whole UK waiting list.

## Conclusions

Renal transplant allocation following donation after brain death is a complex process. The allocation schemes have evolved over time as more data have become available in particular information about what influences outcome post-transplantation. The scheme attempts to ensure best use of a scarce resource while achieving equity of access to cadaveric transplants. The UK scheme in common with all schemes has to accept a number of compromises while respecting those broad principles. The allocation has to be speedy as all the time a kidney is being stored without a blood supply and hypoxic it is being injured. One 'compromise' then has to balance the advantage of minimizing the mismatch by allocation to the least mismatched patient against the damage done to the kidney by the (time-consuming) transportation of the kidney to a distant part of the country. The local schemes for allocation after donation after cardiac death follow similar principles to the national donation after brain death scheme. In live donation although the majority are directed to family members there is a pairing scheme and a system for allocating after live altruistic donation. The website for NHS Blood and Transplant – organ donation (www.organdonation.nhs.uk/ukt/), which is the source of some of the text in this article as well as the two figures and table, is a good resource to keep updated with alterations to the various schemes. **BJHM**

Figures 1 *and* 2 *are reproduced courtesy of NHS Blood and Transplant.*
*Conflict of interest: none.*

NHS Blood and Transplant (2006) *Deceased Donor Kidney Allocation Scheme.* www.uktransplant.org.uk/ukt/about_transplants/organ_allocation/kidney_%28renal%29/renal_organ_sharing_principles/kidney_organ_allocation_scheme_2006.jsp (accessed 15 November 2011)

NHS Blood and Transplant (2011a) *Transplant activity in the UK, 2010-2011.* www.organdonation.nhs.uk/ukt/statistics/transplant_activity_report/transplant_activity_report.jsp (accessed 15 November 2011)

NHS Blood and Transplant (2011b) *Paired donation matching scheme.* www.organdonation.nhs.uk/ukt/about_transplants/organ_allocation/kidney_%28renal%29/living_donation/paired_donation_matching_scheme.jsp (accessed 15 November 2011)

## KEY POINTS

- Renal transplantation offers substantial quality of life and almost certainly a survival advantage compared to dialysis.
- There is a national scheme in the UK for allocating kidneys from the majority of cadaveric donors.
- The scheme achieves the best tissue-matched kidneys for young people and uses a number of other priorities in the overall allocation system.
- There are schemes to try to achieve transplantation when there is a live donor who cannot donate directly to his/her family member.