Finding the perfect match: the living donor paired exchange system

Patients on the kidney transplant waiting list can often face substantial waiting times for an organ from a deceased donor. Furthermore, the number of patients requiring a kidney transplant is increasing. This article discusses an emerging solution – the living donor kidney exchange system.

Transplantation is the preferred option for treatment of end-stage renal disease as it is less expensive than long-term dialysis, reduces patient mortality and substantially improves quality of life (Wolfe et al, 1999). Organs for transplantation are obtained from deceased and living donors, with deceased donors being further characterized by the donor's mode of death: cardiac or brain death. There is a limited supply of organs for patients waiting on the transplant list who are not part of the living donor programme. This inevitably leads to a substantial waiting time for many patients. Excluding patients who receive kidneys from living donors, the median waiting time for a kidney transplant in the UK is 1156 days (NHS Blood and Transplant, 2013a). In 2013, 6079 patients were waiting for a kidney-only transplant (NHS Blood and Transplant, 2013b).

Furthermore, the number of patients requiring a kidney transplant is increasing, and despite the rise in donations from living donors over recent years, demand still greatly exceeds supply. One solution is to pool kidneys offered by living donors who are incompatible with their preferred recipient. Once the incompatible pairs have entered the pool, they can be compared with other donors and recipients and compatible pairs identified. This is known as the living donor paired exchange system and operates in many countries throughout the world. This article discusses the programme in its current form, the problems encountered and the various modifications that have been adopted and proposed to improve its success.

Clinical history

A 67-year-old computer management consultant was diagnosed with hypertension by her GP. Blood tests performed as part of her initial investigations revealed a raised creatinine level and she was diagnosed with early stage chronic kidney disease. After a progressive decline over 10 years, she developed stage 5 renal failure and was treated with peritoneal dialysis initially and then haemodialysis. By this point, three possible living donors for a kidney transplant had come forward, but none were found to be compatible. Eighteen months later, a matching pair was identified, also consisting of an incompatible donor and recipient. The donor in this pair was able to provide a compatible kidney for the patient on the waiting list. In turn, the recipient in this pair could receive a kidney from one of the patient's incompatible donors. This paired exchange subsequently took place without complication and, as a result, the patient's time on the waiting list was reduced compared to standard waiting times for a deceased donor kidney.

The need for more living donors

There is a growing gap between the number of patients requiring a kidney transplant and the supply of organs. Increasing the pool of living donors is an attractive option as donated kidneys from this group show better transplanted organ (graft) survival than organs from deceased recipients. In 2013, 969 living donor kidney transplants were performed in the UK, accounting for 55% of all kidney transplants that year (NHS Blood and Transplant, 2013b). Five-year graft survival is 91% for living donor kidneys and 85% for deceased donor kidneys respectively (NHS Blood and Transplant, 2011). Overall, 5-year patient survival in recipients of a living donor kidney is 96% compared to 87–9% in those who receive a deceased donor kidney (NHS Blood and Transplant, 2011).

Therefore, increasing the living donor pool of kidneys offers a number of benefits: meeting the demand for kidney transplants, reducing the time spent on the waiting list receiving renal replacement therapy, and also improving the outcome for recipients. Time spent on dialysis before transplantation is an important factor in determining the success of a kidney transplant, with a worse prognosis conferred by a longer time spent on dialysis (Meier-Kriesche and Kaplan, 2002).

Paired kidney donor exchange: the UK system

Many patients on the renal transplant waiting list have one or more friends or relatives who would be willing to

Dr Jennifer Hunter *is Foundation Year 1, North Middlesex Hospital, London,* **Mr Mohammad Heetun** *is Year 5 Specialist Trainee in General Surgery in the Department of General Surgery, Poole NHS Foundation Trust, Poole, Dorset BH15 2JB and* **Mr Sanjay Sinha** *is Consultant Transplant Surgeon at Churchill Hospital, Oxford University Hospitals, Oxford*

Correspondence to: Mr M Heetun (heetun@hotmail.com)

donate a kidney, but with whom they are incompatible for a transplant. This is the result of either blood group (ABO) incompatibility or the presence of a 'positive crossmatch' in which the patient possesses antibodies against antigens on the donor organ, in particular HLA antigens. These antibodies are produced after sensitizing events such as previous blood transfusions, previous transplants and pregnancy.

The living donor paired exchange system allows living donor kidneys to be transferred between two or more incompatible pairs to create the same number of compatible pairs, as shown in *Figure 1*. In this system, a living donor and his/her incompatible recipient in need of a transplant are entered as a pair into a centralized list for a country or region.

Paired donor exchange was first suggested by Rapaport in 1986 and the first paired kidney transplants were carried out in Korea in 1991, where the supply of cadaveric kidneys is severely limited and kidney transplantation is highly dependent on living donors (Rapaport, 1986; Kwak et al, 1999). Paired kidney transplants are now performed in many countries including the United States, Holland and the UK.

Paired kidney exchange was first made possible in the UK in 2006 after a legal framework for the process was created by the Human Tissue Act 2004 and the Human Tissue Act 2006 (Scotland). The responsibilities of the Human Tissue Authority include regulation of living donor transplantation. NHS Blood and Transplant, a special health authority established in 2005, maintains a waiting list and matching system. These organizations provide the basis for centralized regulation and coordination of paired living donor exchange in the UK. Every 3 months, the list of registered pairs is processed to determine combinations that will maximize the number of transplants performed and the likelihood of a successful outcome. This is termed a 'matching run' and is achieved using an algorithm (based on the criteria in *Table 1*), which assesses the likelihood of success in transplanting organs from all possible two- or three-way paired exchanges.

Each possible exchange is allocated a number of points based on these criteria, and the combination which maximizes the total number of points is selected to proceed. In the initial four matching runs in the UK, only two-way exchanges were considered, but three-way exchanges are now common in all matching runs. The relevant transplant centres are notified about the matching pair, allowing cooperation between centres to ensure that all the relevant investigations and preoperative assessments can be carried out before a planned transplant. In 2012–13, 55 paired living kidney donor transplants took place compared with 51 in 2011–12 (NHS Blood and Transplant, 2013c).

In the UK, it is recommended that donor nephrectomies and recipient transplants take place at the centre

Figure 1. Principles of paired kidney donation. Each pair represents an incompatible donor/recipient pair.

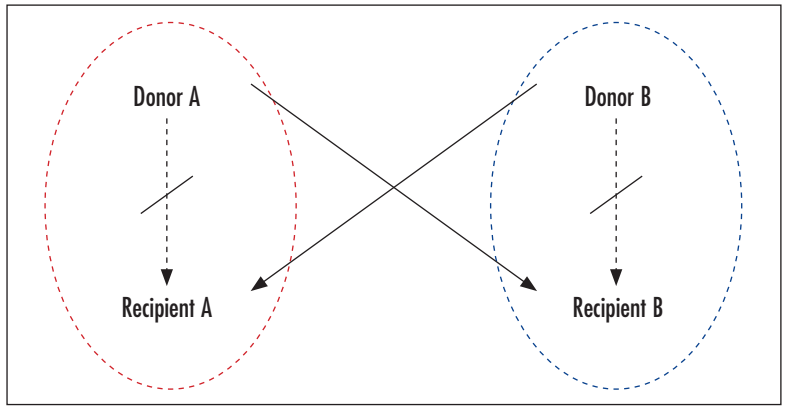


Table 1. Criteria used in UK paired donation scheme

Factor	Points	Description
Geographical proximity of donor to recipient	20 points if same centre/area	Based on five areas of UK. Prioritizes nearby exchanges
Calculated HLA antibody reaction frequency	0–50 for 0–100% calculated HLA antibody reaction frequency	Priority to sensitized patients. Calculated HLA antibody reaction frequency is determined at UK Transplant by comparing patient's unacceptable HLA specificities with HLA types of donors of identical blood group in a pool of 10 000 donors on UK Transplant database. The % of blood group identical donors who are incompatible with the recipient determines the level of calculated HLA antibody reaction frequency
HLA-A, B, DR mismatch (mm) of transplant	000 mismatch – 15 points; 0 DR mismatch and <2 B mismatch – 10 points; (0 DR mismatch and 2 B mismatch) or (1 DR mismatch and <2 B mismatch) – 5 points; (1 DR mismatch and 2 B mismatch) or (2 DR mismatch) – 0 points	Prioritizes well match transplants. Four mismatch levels as used in decreased donor allocation scheme
Donor–donor age difference	3 points if ≤20 years, otherwise 0 points	As a tie-breaker, to prioritize a 'fair' exchange

All blood group-compatible exchanges considered except O donor kidneys are only allocated to group O recipients. HLA = human leukocyte antigen. From Johnson et al (2008)

where the donors and recipients are based respectively and that the kidneys are transferred accordingly. The rationale for the kidney rather than the donor travelling is that it helps to preserve anonymity between donors and recipients of different pairs.

Potential problems with paired donor kidney exchange

While this system considerably expands the pool of living donors for kidney transplants, there can be problems. For example, an imbalance between the number of donors of a particular blood group and the number of recipients of that blood group can significantly reduce the number of possible paired matches. Another issue is that although HLA compatibility is assessed between donors and recipients, other compatibility parameters such as lymphocyte or antibody crossmatch are not always assessed initially and a later discovery of incompatibility can prevent a potential transplant going ahead. In the UK, there have been 27 matching runs to date (as of October 2013) with the most recent run identifying 35 possible transplants. Of these, 11 did not proceed to transplantation (Organ Donation and Transplantation, 2014). In the Dutch system, crossmatching is performed centrally and included in the algorithm used to select optimal combinations of paired exchanges (de Klerk et al, 2008).

Furthermore, there is the risk that one of the kidneys involved in the exchange may be irreparably damaged in the process of harvesting it from the donor. This can lead to an unbalanced situation in which one recipient does not receive a kidney despite their paired donor having donated one.

The 'blood group O problem' and use of desensitization

The current system for matching pairs in the UK will allow any blood group-compatible exchange with the exception that blood group O donor kidneys are donated only to blood group O recipients (blood group A and B patients can receive organs from B and A donors respectively as well as O donors, whereas O patients can only receive organs from O donors) (Glander et al, 2010). To overcome this restriction and allow transplants between blood group-incompatible patients to occur, it is possible to desensitize O group patients before transplantation, removing antibodies against group A and B antigens. A number of desensitization protocols have been developed. Tydén and colleagues (2005) developed a protocol using immunoadsorption to remove antibodies from recipients in conjunction with rituximab (an anti-CD20 monoclonal antibody), that reduces B-cell and antibody levels after antibody depletion. In 2005, they reported that 12 patients had been successfully transplanted with kidneys from blood group-incompatible donors with no significant side effects from treatment at 1-year follow up (Tydén et al, 2005).

Desensitization has also been suggested as a means of overcoming a positive crossmatch and there are currently two main protocols: high dose intravenous immunoglobulin alone, and low dose intravenous immunoglobulin combined with plasmapheresis. Rituximab has been used with both protocols to increase their efficacy. These protocols have successfully allowed patients to receive kidneys from donors with whom they have a positive crossmatch, and the transplants appear to have good short-term outcomes (Montgomery, 2010; Vo et al, 2010). Montgomery (2010) found that performing living donor kidney transplants after desensitization using low dose intravenous immunoglobulin and plasmapheresis provided a significant survival benefit over waiting for a compatible kidney while on dialysis, with the survival advantage more than doubling at 8 years.

Desensitization of patients with anti-HLA antibodies on the deceased donor waiting list remains debatable because of the uncertain availability of deceased donor kidneys. However, Vo et al reported the successful transplantation of 76 highly sensitized patients using rituximab and intravenous immunoglobulin. At study entry, the mean time on dialysis among recipients of a transplant from a deceased donor was 144±89 months. Following desensitization, the time to transplantation was 5±6 months (Vo et al, 2008). In a further study, the same authors found that the same regimen could reduce the time on the waiting list for deceased donor recipients from 95±46 months to 4.2±4.5 months after treatment (Vo at al, 2010).

The costs of desensitization for a potential transplant vary from country to country, but in the United States for example, patients who are entered into a desensitization programme can expect this to cost an additional $20 000–30 000 above the cost of a kidney transplant that does not required desensitization (University of Wisconsin Hospitals and Clinics Authority, 2014).

Paired donation and desensitization

Desensitization and paired exchange have traditionally been considered as competing strategies, but increasingly, paired exchange is becoming integrated into desensitization protocols. Montgomery (2010) proposed a transplant modality algorithm to identify which donor/recipient phenotypes would benefit from each of these modalities (*Figure 2*). Patients with a positive crossmatch to a live donor who have phenotypes that are easy-to-match (O donor; narrow sensitization) and/or difficult to desensitize (high titres of donor-specific antibodies) would benefit from paired donor exchange. Those who are difficult to match (AB donor; broad sensitization) and/or easy to desensitize (low donor-specific antibody titres) should be considered for desensitization protocols. However, phenotypes that are both difficult to match and difficult to desensitize may benefit from a combination of paired exchange and desensitization in which they are paired with a more immunologically suited donor.

Altruistic donors

Altruistic donation, also called non-directed donation, is becoming increasingly common (Matas et al, 2000). Conventionally, these have been individuals who have offered to donate a kidney to anyone on the waiting list for a deceased donor kidney. However, it has been suggested that, if willing, the kidney could be more usefully used in starting off a chain of paired donor exchange transplants (*Figure 3*). The kidney from the donor of the final pair is given to a patient on the waiting list for a deceased donor kidney.

Given the nature of altruistic donation, it is vital that the donor is thoroughly evaluated both physically and psychologically and that he/she is motivated only by altruism. For example, centres may have to contend with donors requesting that their organs be given to recipients with particular characteristics such as religion or background.

Despite these issues, use of altruistic donors to start chains of paired kidney exchanges could increase the number of living donor kidney transplants as well as provide an end organ for a recipient on the cadaveric waiting list. Altruistic non-directed kidney donation was made legal in the UK in 2006, and in 2012–13, the Human Tissue Authority approved 104 altruistic cases compared to 38 in 2011–12 (Human Tissue Authority, 2013).

A further benefit of using altruistic donors in paired kidney donations is that they mitigate the type O imbalance in incompatible pairs, potentially reducing the need for desensitization. Altruistic donors are more similar to the general population and, consequently, approximately 48% of altruistic donors are expected to have blood type O compared to 25% of donors in incompatible pairs (Gentry et al, 2011).

Exchanges involving more than two pairs

As discussed previously, the UK matching system now allows exchange between three pairs (*Figure 4*). This modification was made because of the small number of potential transplants yielded by the original two-pair exchange system and studies suggest that the optimal maximum chain length permitted by a matching run algorithm is three (Saidman et al, 2006; De Klerk et al, 2010). There have been many cases of paired exchange transplants involving more than three pairs, particularly in the United States where paired exchange has existed for much longer.

Unbalanced paired kidney exchange

A variation of the paired exchange programme involves introducing a compatible but not identical pair with an incompatible pair. For example, an A donor and O recipient (incompatible pair) could be paired with an O donor and an A recipient (compatible but not identical). This leads to two compatible living donor kidney transplants. In practice, this requires a high degree of altruism

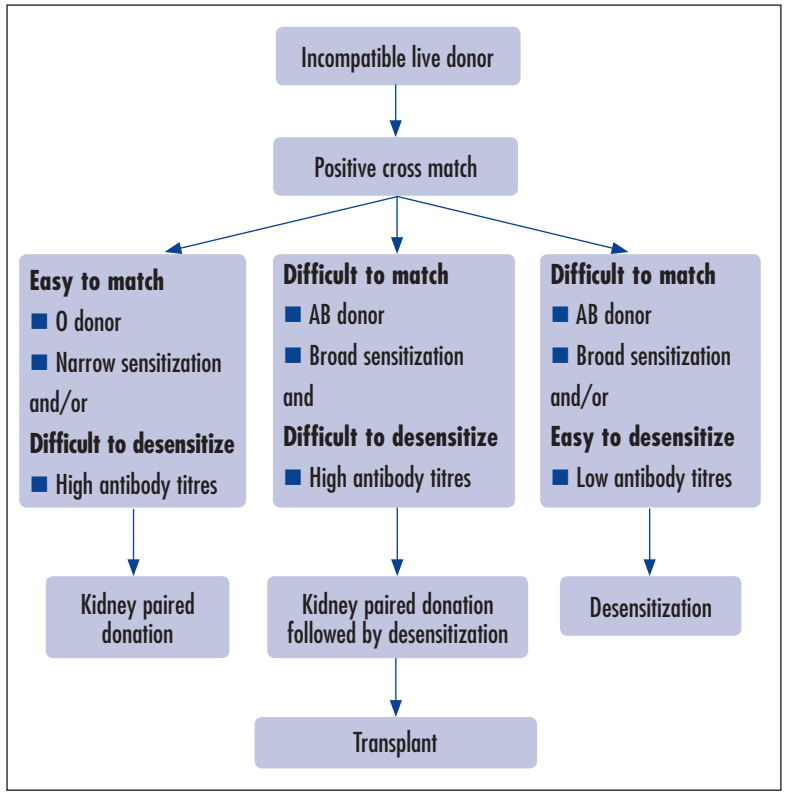


Figure 2. Transplant algorithm incorporating kidney paired donation and desensitization. Reproduced from Montgomery (2010).

Figure 3. Altruistic donation: the altruistic donor starts a chain of paired donor transplants.

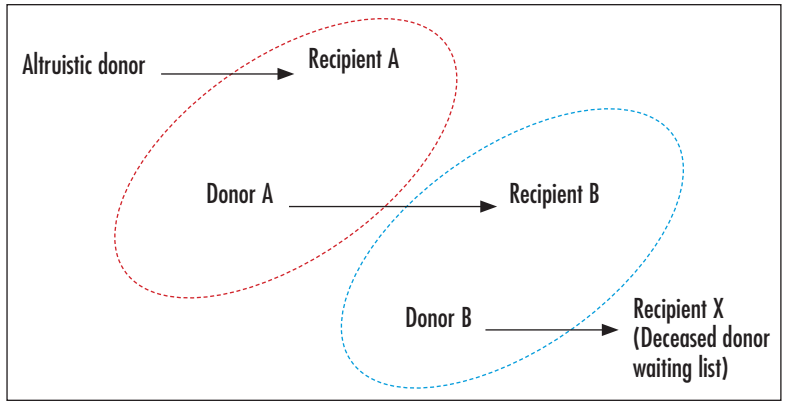
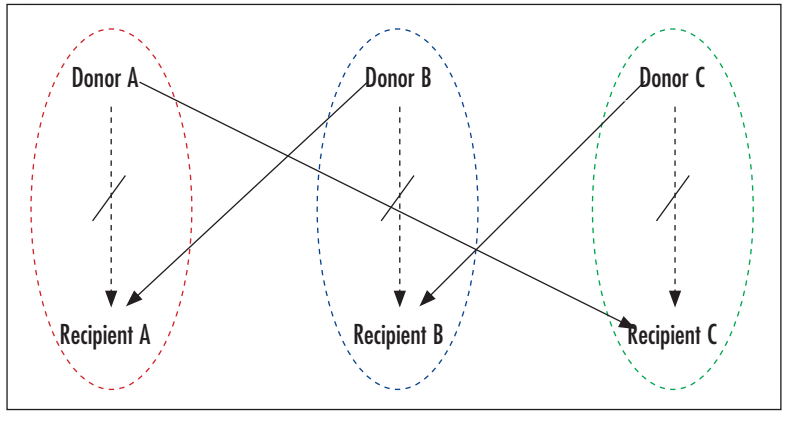


Figure 4. The principle of three-way paired exchange.



on the part of the compatible pair. Although an improved match might be available to the recipient through paired exchange, a compatible direct donation is already possible and may seem like the preferable option rather than going through a matching run (Ferrari and de Klerk, 2009). Kranenburg and colleagues in the Netherlands investigated the willingness of matched donors and recipients to participate in a paired donor exchange despite a direct donation already being possible and found that a third would be willing to do so (Kranenburg et al, 2006). Although not widespread practice, this option could potentially increase the number of compatible living donor kidney transplants, particularly for blood group O donors.

Conclusions

The living donor paired kidney exchange system has been established in the UK and a number of other countries as a method of increasing the availability of organs for renal transplantation. Modifications to the system have been both adopted and proposed to increase the pool of living donors. Although more long-term data are required to determine the role and effectiveness of these interventions, the living donor kidney exchange programme represents a ray of hope for the many patients in need of an organ on the transplant waiting list. **BJHM**

The authors would like to thank Lisa Burnapp, Consultant Transplant Nurse, Guys and St Thomas' NHS Foundation Trust for her assistance in writing this article.

Conflict of interest: none.

de Klerk M, Witvliet MD, Haase-Kromwijk BJ, Weimar W, Claas FH (2008) A flexible national living donor kidney exchange program taking advantage of a central histocompatibility laboratory: the Dutch model. *Clin Transpl:* 69–73

De Klerk M, Van Der Deijl WM, Witvliet MD, Haase-Kromwijk BJ, Claas FH, Weimar W (2010) The optimal chain length for kidney paired exchanges: an analysis of the Dutch program. *Transpl Int* **23**(11): 1120–5

KEY POINTS

- Organ transplantation is an established treatment for end-stage renal failure.
- The demand for kidneys from patients on the transplant waiting lists continues to exceed supply.
- The living donor exchange programme offers a solution by pooling incompatible organs from living donors so that these are more widely available to other potential recipients.
- Paired kidney transplants are now performed throughout Europe, Asia and the United States.
- Numerous modifications to the programme have been adopted and proposed to further increase the number of potentially successful transplants. These include desensitization and altruistic donation.

Ferrari P, de Klerk M (2009) Paired kidney donations to expand the living donor pool. *J Nephrol* **22**: 699–707

Gentry SE, Montgomery RA, Segev DL (2011) Kidney paired donation: fundamentals, limitations, and expansions. *Am J Kidney Dis* **57**(1): 144–51

Glander P, Budde K, Schmidt D, Fuller TF, Giessing M, Neumayer HH, Liefeldt L (2010) The 'blood group O problem' in kidney transplantation--time to change? *Nephrol Dial Transplant* **25**(6): 1998–2004

Human Tissue Authority (2013) Huge rise in altruistic donor numbers, says HTA. www.hta.gov.uk/newsandevents/htanews.cfm/1143-Huge-rise-in-altruistic-donor-numbers--says-HTA.html (accessed 30 March 2014)

Johnson RJ, Allen JE, Fuggle SV, Bradley JA, Rudge C; Kidney Advisory Group, UK Transplant NHSBT (2008) Early experience of paired living kidney donation in the United Kingdom. *Transplantation* **86**(12): 1672–7

Kranenburg LW, Zuidema W, Weimar W et al (2006) One donor, two transplants: willingness to participate in altruistically unbalanced exchange donation. *Transplant Int* **19**: 995–9

Kwak JY, Kwon OJ, Lee KS, Kang CM, Park HY, Kim JH (1999) Exchange-donor program in renal transplantation: a single-center experience. *Transplant Proc* **31**(1-2): 344–5

Matas AJ, Garvey CA, Jacobs CL, Kahn JP (2000) Nondirected donation of kidneys from living donors. *N Engl J Med* **343**(6): 433–6

Meier-Kriesche HU, Kaplan B (2002) Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. *Transplantation* **74**(10): 1377–81

Montgomery RA (2010) Renal Transplantation across HLA and ABO antibody barriers: integrating paired donation into desensitization protocols. *Am J Transplant* **10**(3): 449–57

NHS Blood and Transplant (2011) Survival Rates Following Transplantation. www.organdonation.nhs.uk/statistics/transplant_activity_report/current_activity_reports/ukt/survival_rates.pdf (accessed 30 March 2014)

NHS Blood and Transplant (2013a) Waiting time to transplant. www.organdonation.nhs.uk/about_transplants/waiting_time_to_transplant/ (accessed 30 March 2014)

NHS Blood and Transplant (2013b) Organ Donation and Transplantation Activity figures for the UK as at 12 April 2013. www.organdonation.nhs.uk/statistics/downloads/annual_stats.pdf (accessed 30 March 2014)

NHS Blood and Transplant (2013c) Kidney Activity. www.organdonation.nhs.uk/statistics/transplant_activity_report/current_activity_reports/ukt/kidney_activity.pdf (accessed 30 March 2014)

Organ Donation and Transplantation (2014) Renal Transplant Services Meeting Presentations. www.odt.nhs.uk/transplantation/advisory-groups/kidney/RTSM_2014/) (accessed 30 March 2014)

Rapaport FT (1986) The case for a living emotionally related international kidney donor exchange registry. *Transplant Proc* **18**: 5–9

Saidman SL, Roth AE, Sönmez T, Unver MU, Delmonico FL (2006) Increasing the opportunity of live kidney donation by matching for two- and three-way exchanges. *Transplantation* **81**: 773–82

Tydén G, Kumlien G, Genberg H, Sandberg J, Lundgren T, Fehrman I (2005) ABO-incompatible kidney transplantation and rituximab. *Transplant Proc* **37**(8): 3286–7

University of Wisconsin Hospitals and Clinics Authority (2014) Kidney Desensitization Program Frequently Asked Questions. www.uwhealth.org/transplant/kidney-desensitization-program-frequently-asked-questions/10618 (accessed 30 March 2014)

Vo AA, Lukovsky M, Toyoda M et al (2008) Rituximab and intravenous immune globulin for desensitization during renal transplantation. *N Engl J Med* **359**(3): 242–51

Vo AA, Peng A, Toyoda M et al (2010) Use of intravenous immune globulin and rituximab for desensitization of highly HLA-sensitized patients awaiting kidney transplantation. *Transplantation* **89**(9): 1095–102

Wolfe RA, Ashby VB, Milford EL et al (1999) Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* **341**(23): 1725–30