

CLINICAL REVIEW

Renal transplantation

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Epidemiological data from the past decade suggest that the global burden of patients with renal failure who receive renal replacement therapy exceeds 1.4 million and that this figure is growing by about 8% a year.^{1,2} The UK renal registry from 2009 estimated that over 47 000 people received renal replacement therapy in the UK.³ Renal transplantation increases survival and improves the quality of life for patients with end stage renal failure.^{4,5} A recent UK estimate found that transplantation conferred a cost saving of £25 000 (€29 000; \$40 000) a year per patient with end stage renal failure.⁶ In the UK rates of renal transplantation are increasing (fig 1), and since 2006 the number of patients waiting more than five years for a transplant has halved, but there are still a large number (about 7000) of patients on the transplant waiting list (fig 1).^{7,8}

We review the process of selecting patients eligible for renal transplantation and the care of patients after renal transplantation for the primary care physician. This article is based on evidence from large registries, case series, clinical trials where available, and national guidelines.

Who is eligible for a kidney transplant?

Guidelines recommend that all patients with chronic kidney disease at stage 5 or stage 4 (glomerular filtration rates <15 mL/min and 15-30 mL/min respectively) with progressive disease likely to require renal replacement therapy within six months should be considered for transplantation.^{9,10} The mean estimated glomerular filtration rate of patients starting renal replacement therapy is 8.6 mL/min/1.73 m².¹¹ A minority of patients with end stage renal failure are deemed unsuitable for transplantation. Absolute contraindications to transplantation are few, but include untreated malignancy, active infection, untreated HIV infection or AIDS, or any condition where life expectancy is under two years.^{9,10} Relative contraindications and special considerations for transplantation are listed in box 1 and discussed in detail in the web extra appendix on bmj.com.

Patients should have access to transplantation if they are medically fit for surgery. Ineligible patients will remain on long term dialysis. Patients who are awaiting a kidney transplant will be regularly reassessed. About 5% of patients are removed from the transplant list each year, typically because they are deemed too unwell for transplant.⁷

Pre-emptive kidney transplantation is transplantation before the need for maintenance dialysis arises. It is the treatment of choice in patients nearing renal replacement therapy in both national and international guidelines because pre-emptive kidney transplantation is associated with improved allograft and patient survival,^{9,12-16} reduced dialysis related cardiovascular morbidity and sensitisation events, cost savings on dialysis, and better quality of life.¹⁷ In the UK in 2008 only 5.3% of the 6639 patients who met guideline criteria for kidney transplantation received a pre-emptive transplant.³ Most pre-emptive transplants are living donations. If no suitable living donor can be found patients are placed on the deceased donor waiting list when their glomerular filtration rate falls below the cut-off value. Patients with type 1 diabetes should also be listed for a simultaneous kidney-pancreas transplant.

How are donor kidneys sourced?

Brain or cardiac death donors

Most transplanted kidneys in the past four decades have come from “donation after brain death” donors. However the number of kidneys derived from “donation after cardiac death” donors has increased in recent years in the UK and comprised 34% (n=567) of all deceased donor kidney transplants in 2010-1 compared with 66% (n=1100) from “donation after brain death” donors.⁷ Kidneys transplanted from “donation after cardiac death” donors have a longer warm ischaemia time and higher rates of both delayed graft function and primary non-function but similar long term patient outcomes and graft survival.¹⁸

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Extra material supplied by the author: how kidneys are allocated for transplantation in the UK, special considerations for transplantation, and ethical issues in transplantation (see <http://www.bmj.com/content/343/bmj.d7300/suppl/DC1>)

Summary points

- The global burden of end stage renal disease is increasing
- Renal transplantation increases patient survival and quality of life and reduces costs of care for patients with end stage renal disease
- Most donor kidneys come from "brain death" or "cardiac death" donors, but donations from living donors are increasing
- Pre-emptive transplantation from a living donor is the best treatment choice for patients with end stage renal disease and has been associated with improved allograft and patient survival
- Long term outcomes in kidney transplantation are improving

Sources and selection criteria

We searched PubMed, the Cochrane Database, and ScienceDirect using the key words "kidney transplantation." The search was limited to those journals published in the English language. The data were mainly derived from large registry descriptions, multiple case series, and clinical trials. We have combined our knowledge with that of recently published guidelines and reviews identified by the previously mentioned PubMed searches on kidney transplantation.

Box 1: Relative contraindications to transplantation

- Comorbid condition
- Age >65 years
- Untreated coronary artery disease
- Obesity
- HIV infection
- Previous malignancy
- Chronic hepatitis B or C

Living donors

Living donor transplantation has also increased over the past decade, with one in three transplants in the UK now from a living donor.⁷ Living donor kidney transplantation has reduced the gap between demand and supply of kidneys. Donors include those who are genetically related to the recipient or emotionally related (such as spouse, partner, or close friend). A long term series from the US found that living transplants are associated with reduced rates of delayed graft function and better allograft and patient survival.¹⁹ The United Network for Organ Sharing (UNOS) reports five year allograft survival of 79.9% for living donor kidneys compared with 66.5% for deceased donor kidneys. With improvements in surgical nephrectomy techniques (laparoscopic and mini-open donor), reduced postoperative pain, shorter hospital stay, and faster return to work, living donation has become more acceptable.²⁰ More complex procedures with living donors are now being considered in certain centres, such as transplantation from obese donors with a body mass index >35 and from older donors and transplants with multiple vessels. A "matched pair donation" scheme exists whereby a relative, friend, or partner of a potential recipient can donate an incompatible organ by being matched with another incompatible donor-recipient pair, enabling both people in need of a transplant to receive a compatible organ. Pooled donation is a form of matched pair donation involving more than two living donor pairs. Altruistic non-directed donation occurs when a kidney is donated by a healthy person who does not have a relationship with the recipient and is not informed who the recipient will be.

What are the consequences of live kidney donation for the donor?

A large follow-up study of live kidney donors from one centre found that donors showed a 25% reduction in glomerular filtration rate, glomerular hyperfiltration, and proteinuria, which were not clinically important.²¹ An increase in protein excretion by the remaining kidney, particularly in male donors, is well

described, but in the absence of a correlation between protein excretion and blood pressure or renal function, the clinical importance of this finding is unclear.²² Long term outcomes of uninephrectomy have found no major adverse consequences.²³ The lifespan of a kidney donor seems to be similar to that for the general population of similar age, and there is no increased risk of developing end stage renal disease.^{24 25}

How is a patient with renal disease prepared for transplant surgery?

Patients are counselled about the risks of surgery and the risks, complications, and side effects of immunosuppressive therapy. Patients must be clearly informed about their mortality risk, rates of graft survival, and the potential impact of transplantation on their employment activities. Explaining the potential risk of recurrent kidney disease in an allograft is also important. Individual risks may change with the length of time that a person waits for a procedure, and patients may need repeated re-evaluation and counselling.

It is important to remember that the mean age of patients starting renal replacement therapy is 64 years. Patients require a full cardiac and respiratory assessment, including an assessment for the presence of peripheral vascular disease. A formal urological assessment is done (ultrasound, voiding cystourethrogram, cystoscopy) to exclude pre-existing disease that may compromise the function of the graft, such as bladder outflow obstruction, ureteric reflux, or congenital abnormality. Avoid blood transfusions in patients awaiting transplant surgery. Antibodies are measured regularly while patients are waiting for a procedure.

The renal transplant operation

Techniques for performing a donor nephrectomy are not discussed here as this article is aimed at generalist physicians, but Gibbons and Nicol provide details.²⁶ Living donors may be referred to the British Kidney Patient Association (BKPA)²⁷ and

to Morgan and Ibrahim²³ for information on the long term effects of donating a kidney.

The procedure for a renal transplant has not changed much since the original operation described by Kuss et al in 1951.²⁸ The most common approach is a pelvic operation with extraperitoneal placement of the kidney. The right side is usually chosen, as the iliac vessels on the right are more superficial than on the left. The transplant involves three important anastomoses: the donor renal artery is anastomosed to the recipient external iliac artery (end-to-side); the donor renal vein is anastomosed to the external iliac vein (end-to-side); and the donor ureter is reimplanted to the recipient's bladder forming a ureterocystostomy with a J-J ureteric stent left in situ. The J-J stent is removed 8–12 weeks postoperatively under local anaesthetic via flexible cystoscopy.²⁹

What are the potential short and medium term complications of renal transplantation?

Early and late complications of renal transplant are presented in box 2.

Surgical complications

Surgical complications after a renal transplant have reduced over time as techniques have been refined. Reported rates of surgical complications are low (5–10%) compared with liver and pancreas transplantation.³⁰

Bleeding is uncommon and is usually from vessels not ligated at the hilum or from small retroperitoneal vessels of the recipient. Vascular complications can involve the donor vessels (renal artery thrombosis (<1%), renal artery stenosis (1–10%), renal vein thrombosis) or the recipient vessels (iliac artery thrombosis, pseudoaneurysm, deep vein thrombosis (5%)).³⁰ Urological complications present as a leak or obstruction (2–10%), often as a result of ischaemia of the transplant ureter. The incidence of lymphocele (fluid filled collections from cut lymphatics) is 0.6–18%, which can be reduced by careful ligation of all lymphatics. Wound complications are the most common surgical complication after a renal transplant; these include wound infections (5%) and fascial dehiscence or incisional hernias (3–5%).³⁰

Medical complications

The main complications in the first few weeks after transplantation are rejection and infection. Risk of rejection can be determined to some extent before transplantation. High risk patients include those who are blood group incompatible or who are transplanted against a positive cross match and who have antibodies against the donor kidney before transplantation. Such patients require antibody removal before the operation. For other patients, risk is determined by whether the patient is sensitised or how well matched the donor kidney is to the recipient. To prevent rejection, the recipients receive induction at the time of transplant with either depleting or non-depleting monoclonal or polyclonal antibodies directed against T cells. Such agents include anti-CD3 (antithymocyte globulin), anti-CD25 (basiliximab), or anti-CD52 (alemtuzumab). Maintenance immunosuppression is then required in the long term to prevent rejection. Transplant centres use different induction and maintenance regimens. The table[↓] provides a summary of commonly used immunosuppressant agents.

Infectious complications are highest in the early postoperative period. Two particularly important infections that require special mention are cytomegalovirus and pneumocystis pneumonia. Cytomegalovirus has a broad clinical spectrum (presenting with symptoms of fever and malaise sometimes associated with leucopenia, thrombocytopenia, gastroenteritis, pneumonitis, and hepatitis) after transplantation and can prove fatal.³¹ Transplant units either give patients cytomegalovirus prophylaxis with valganciclovir for three to six months after transplantation or adopt a strict surveillance protocol and treat only when cytomegalovirus DNA is detected. Pneumocystis pneumonia is also most likely to occur in the first six months after transplantation, and most patients receive co-trimoxazole prophylaxis.

In the longer term the most common cause of graft failure is chronic alloimmune injury, and, with failure, other complications of renal disease emerge such as anaemia, bone disease, and fluid imbalance. Transplant patients are also at risk of malignancy and cardiac disease—the former as a result of long term immunosuppression, and the latter being multifactorial in nature.

Patients increasingly present with renal disease in the allograft now that modern immunosuppression means fewer acute rejections, and this accounts for about 5% of allograft loss.³² Primary focal segmental glomerulosclerosis, IgA nephropathy, mesangiocapillary glomerulonephritis type II, and diabetic nephropathy are the commonest causes of recurrent disease in an allograft. The impact of recurrent renal disease on allograft survival depends on the underlying cause.

What are the long term outcomes for renal transplantation?

The average lifespan of a renal transplant is now 8–15 years, depending on the type of graft.³ Data from the NHS Blood and Transplant registry show that one year and 10 year graft survival rates are 89% and 67% for adult kidneys from “brain death donors,” and 96% and 78% for kidneys from live donors (fig 2[↓]).⁷ Survival of the transplant recipient at 10 years for cadaveric and live donor transplants is 71% and 89% respectively.

What are the considerations for long term follow-up?

Regular follow-up of the transplant recipient by the transplant clinic for the life of the allograft is routine, and the specialist unit will offer advice regarding any patient who becomes acutely unwell. Patients' general practitioners plays an important role in monitoring risk factors for cardiovascular disease and maintaining a high level of suspicion for incident malignancy. In one national cohort of adult kidney transplant patients, new onset diabetes occurred in 16% within three years of transplantation.³³ The potential for hazardous drug interactions in patients undergoing long term immunosuppression means that particular care is needed with prescribing. We include a list of tips for non-specialists, but advice from the patient's specialist transplant unit should be sought if in doubt.

Fertility is impaired in patients with end stage renal failure, but gonadal function improves and ovulation resumes within a few months of renal transplantation.³⁴ Current recommendations advise that, after a year of stable graft function, pregnancy is likely to be safe.³⁵ In women with normal graft function, pregnancy usually has no adverse effects on graft function and survival. Women require preconception counselling, particularly regarding optimisation of immunotherapy and other drugs that may be teratogenic, and any patient wanting to conceive should

Box 2: Complications after renal transplantation*Surgical complications**Early*

- Haemorrhage
- Renal artery thrombosis
- Renal vein thrombosis
- Recipient vasculature injury
- Urine leak
- Lymphocele
- Wound complications

Late

- Ureteral obstruction
- Transplant renal artery stenosis

*Medical complications**Early*

- Acute rejection—acute cellular, antibody mediated
- Infection—bacterial, viral (cytomegalovirus), fungal (pneumocystis)

Late

- Immunosuppression related— specific side effect profile, malignancy, chronic alloimmune injury
- Allograft related—recurrent disease
- Renal disease— anaemia, bone disease
- Cardiovascular disease
- Infections—polyoma virus

Tips for non-specialists*Do's*

- Strictly manage cardiovascular risk factors
- Encourage self examination and attendance at national screening programmes (such as cervical smear tests)
- Encourage avoidance of sun exposure
- Vaccinate against influenza and pneumococcus
- Refer to transplant unit for preconception management
- Promptly refer to transplant unit in context of febrile episode

Don'ts

- Administer live vaccines
- Prescribe drugs that induce or inhibit cytochrome P450 activity if patient is taking sirolimus, tacrolimus, or ciclosporin
- Prescribe nephrotoxic agents (such as non-steroidal anti-inflammatory drugs)

be referred early to the transplant unit. Pregnancy after transplantation is considered high risk and is managed accordingly. These pregnancies are more likely to be complicated by preterm labour (30–50%), pre-eclampsia (30–37%) and intrauterine growth restriction (20–33%).³⁶ The transplanted kidney does not usually obstruct labour, but caesarean section is required in half of women.

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Ongoing challenges in renal transplantation

Reducing transplant demand

- Early detection and prevention of progression of chronic kidney disease
- Patient education of risk factors
- Improve diabetic management

Improving organ utility

- Match donor and recipient age and organ quality
- Increase live donor transplantation as an alternative to transplant waiting list
- Machine organ perfusion—optimising cadaveric organs
- Improve organ retrieval—reducing organ damage
- Increase use of non-heart beating donor kidneys

Increasing organ availability

- Better training for donor coordinators
- Greater number of donor coordinators managing the donation process
- Increase number of donor card carriers
- Greater use of "extended criteria donors"
- Increase numbers of paired exchange and altruistic donors
- Encourage organ donation from ethnic minority groups
- Change legislation—"opt out" or mandated choice organ donation

Optimising immunosuppression

- Development of more specific monoclonal antibodies
- Corticosteroid sparing regimens

ABO or HLA incompatible kidney transplantation

- Long term outcomes for ABO incompatible kidneys similar to those for antibody compatible kidneys

Patients' perspectives (living donor transplant)

The donor

When I first offered to be a kidney donor for my friend Paul it was a decision that just felt right. I had a little understanding of what might be involved, and a knowledgeable partner who—while naturally a little apprehensive—did appreciate that the risks to me were very small. So I volunteered for the donor programme at the Hammersmith Hospital without very much thought as to what was actually involved.

Not having attended any donor seminars, I had not expected the very thorough work-up by the transplant team. During the several visits that spring, every part of my body was checked out. It felt odd, but reassuring, visiting the hospital when I didn't feel ill. A slight alarm when the cardiac test picked up an anomaly, but a subsequent angiogram showed it to be treatable with drugs and not something that would prevent the transplant. I was very happy that a potentially significant condition had been picked up early—an unexpected bonus that I am still grateful for to this day.

The day arrived, and as I was wheeled into surgery I was strangely calm. I was about to go under the knife, but the knowledge that I was going to change Paul's and Barbara's lives forever was with me as I slipped into unconsciousness. The operation was totally successful for both Paul and myself, and the recovery period in hospital and at home was made so much easier by the wonderful care provided by the medical and nursing teams.

Three years on, I have little left to show for the experience other than a tiny scar and a great sense of pride that I did something that made a real difference.

The recipient

Since 18 years old, I had known that I would need either to be put on dialysis or have a kidney transplant—just like my father in the early 1980s. I had been observed on an annual basis until my creatinine level reached 500 (when I was aged 50), and I was then transferred to the renal team at the hospital.

My clinical issue is hereditary polycystic kidney disease, and I was informed of what might happen, but I soon realised that things had changed from the 1980s. The transplantation team at the hospital were so supportive; they have become almost like family. My operation (a live, blood group incompatible transplant) went well, and, while in the care of the high dependency unit, I progressed well to being discharged after only seven days.

Since then, my health has returned to normal. I see the team every eight weeks and take great comfort from knowing that I am being kept under the watchful eye of a great group of people. My experience shows what miracles can be performed and, with a team including family and friends in support, life can return to normal really quickly.

The role of the live donor coordinator

The live donor work-up process is a team effort, involving a range of healthcare professionals working together with donors and recipients to ensure the best outcome. We are responsible for the coordination of the management and care of the donors; from their first contact with us, through the assessment process, surgery, and follow-up. We are responsible for ensuring that our patients are fully informed about the work-up process and understand the realities and risks of live donor transplantation.

The initial assessment is essential to identify any problems for either the donor or recipient and address them at an early stage to enable us to proceed to transplantation. Each pair's experience is individual, depending on the complexity of the situation, and our role is to keep the process running smoothly and support donors and recipients through an experience which is full of highs and lows. Whether pairs can proceed to transplantation or are unable to proceed as planned, the coordinators are there to provide support and care to the patients and their families throughout the process. Seeing a recipient and donor after the operation looking fit and healthy and being able to enjoy life again is the most rewarding part of our role.

Jen McDermott, lead live donor coordinator, Imperial College NHS Trust

Additional educational resources*For healthcare professionals*

- Renal Association (www.renal.org/home.aspx)
- British Transplantation Society (www.bts.org.uk)
- Transplantation Society (www.tts.org/)
- UK Renal Registry (www.renalreg.com/)
- American Society of Nephrology (www.asn-online.org/)
- European Society of Organ Transplantation (www.esot.org)

For patients

- British Kidney Patient Association (www.britishkidney-pa.co.uk)
- Kidney Patient Guide (www.kidneypatientguide.org.uk)
- UK National Kidney Federation (www.kidney.org.uk)
- Transplant Support Network (www.transplantsupportnetwork.org.uk)
- American Association of Kidney Patients (www.aakp.org)
- American Kidney Fund (www.akfinc.org)

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Table

Table 1 | Immunosuppressant agents and adverse effects

Agent	Mechanism of action	Adverse effects
Corticosteroids	Inhibit cytokine production	Diabetes, osteoporosis, weight gain, hypertension
Ciclosporin	Calcineurin inhibitor	Hirsutism, gum hypertrophy, hypertension, diabetes, nephrotoxicity
Tacrolimus	Calcineurin inhibitor	Diabetes, nephrotoxicity, neurotoxicity (tremor)
Mycophenolate mofetil	Inosine monophosphate dehydrogenase inhibitor	Gastrointestinal disturbance (diarrhoea), haematological (anaemia, leucopenia), mouth ulcers
Azathioprine	Purine synthesis inhibitor	Myelosuppression, hepatitis
Sirolimus	Mammalian target of rapamycin (mTOR) inhibitor	Peripheral oedema, poor wound healing, hypertriglyceridaemia, anaemia, proteinuria

Figures

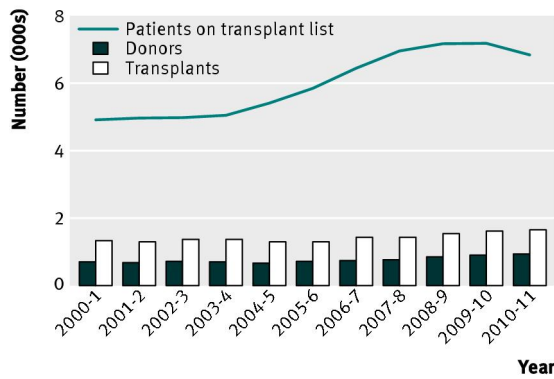


Fig 1 Deceased donor kidney programme in the UK, 1 April 2000-31 March 2010. Number of donors, transplants and patients on the active transplant list at 31 March.

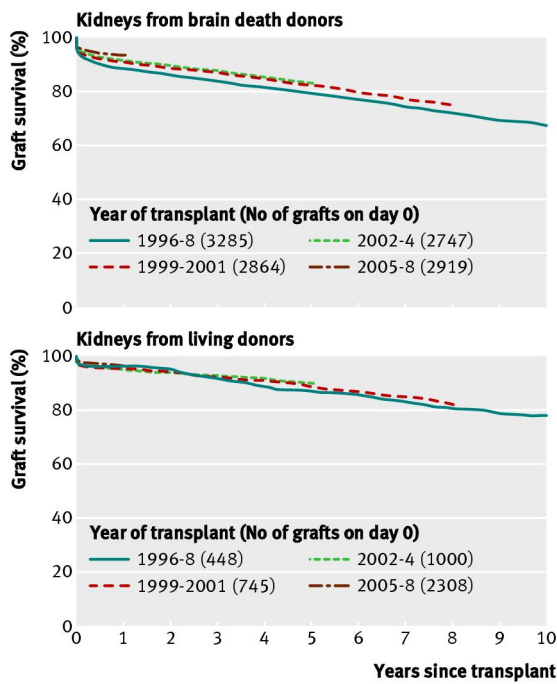


Fig 2 Long term graft survival after first kidney only transplantation from "brain death donors" and live donors