Renal transplantation

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Abstract

Renal transplantation is established as the preferred form of renal replacement therapy as it improves quality of life and usually increases longevity. Unfortunately, owing to excessive co-morbidities, only 30% of patients who develop end-stage renal failure are fit enough to be listed for transplantation. Early attempts at kidney transplantation were blighted by immunological rejection, but the advent of potent immunosuppressive agents has raised 1-year graft survival rates to >90%. This success is also attributable to improvements in histocompatibility testing, organ procurement, preservation methods and perioperative care. Chronic deterioration of graft function remains a problem; long-term outcome has shown only minor improvement over the last two decades, although this should be considered in the context of deteriorating organ quality as deceased donors become older with increasing co-morbidity. An overall increase in deceased donors has boosted transplant activity in the UK, and this trend could continue with the adoption of an 'opt-out' consent system and the potential use of virally infected organs. Living donor activity remains stable, but the use of non-directed altruistic donation and the living donor exchange scheme have reduced the need for higher risk ABO- and human leukocyte antigen (HLA)-incompatible transplantation. It is important to appreciate that kidney transplant recipients swap one chronic illness for another, which usually gives them a better and longer life, free of the need for regular dialysis.

Keywords Complications; infection; ischaemia–reperfusion; MRCP; neoplasia; outcomes; rejection; renal transplantation; tissue typing; transplant immunology

Key points

- Renal transplantation is the optimal form of renal replacement therapy for fitter patients
- Organ donation from deceased donors will probably continue to increase, aided by 'opt-out' legislation
- Improved living donor transplant outcomes have been facilitated by the use of sharing schemes
- The perfusion and reconditioning of donor organs is being vigorously investigated
- Chronic antibody-mediated rejection is a major cause of graft loss, and effective treatment is urgently required
- Management of the continually expanding population of transplant recipients requires careful service planning

Epidemiology

About 5% of the UK population have chronic kidney disease, and the prevalence of end-stage renal failure (ESRF) is approximately 1000 per million. Kidney transplantation is the preferred option for renal replacement therapy for patients with ESRF as it usually improves quality of life, increases survival and is more cost-effective.

As a result of successful organ donation strategies, the number of deceased donors has nearly doubled over the last decade, but there remains a gap between supply and demand (Figure 1). As of 31 March 2018, 7738 patients were on the UK adult kidney transplant waiting list, while approximately 3300 transplants are performed annually. Median waiting time for adults awaiting a deceased donor kidney is approximately 2 years (755 days), being longest for patients with blood group O or B. Contemporary results of renal transplantation in the UK are shown in Table 1. Further efforts are required to increase deceased organ donation, and the following three areas are among the most promising:

- 'Opt-out' legislation means that, from spring 2020, every adult in England will be considered willing to donate their organs after they die unless they have recorded a decision not to donate. This change has been in effect in Wales since 2015 and has delivered a significant increase in organ donation.
- Use of organ perfusion and 'reconditioning' techniques may restore viability to marginal donor organs.[1]
- Use of kidneys from hepatitis C-infected donors is becoming a possibility as the advent of extremely effective antiviral drugs has increased the chance of using infected organs in uninfected recipients with prompt antiviral treatment.

Selection and work-up

Not all patients with ESRF are fit enough to undergo listing for renal transplantation. The excellent results described above have been achieved by carefully selecting patients deemed fit for surgery and postoperative immunosuppression. The basis for this screening has been epidemiological evidence that early mortality and morbidity after surgery are largely related to cardiovascular events. As a result, patients are usually stratified by risk before being listed for transplantation, and investigations are planned accordingly.

As a result of accumulating evidence that time on dialysis is detrimental to patient survival, there has been increased

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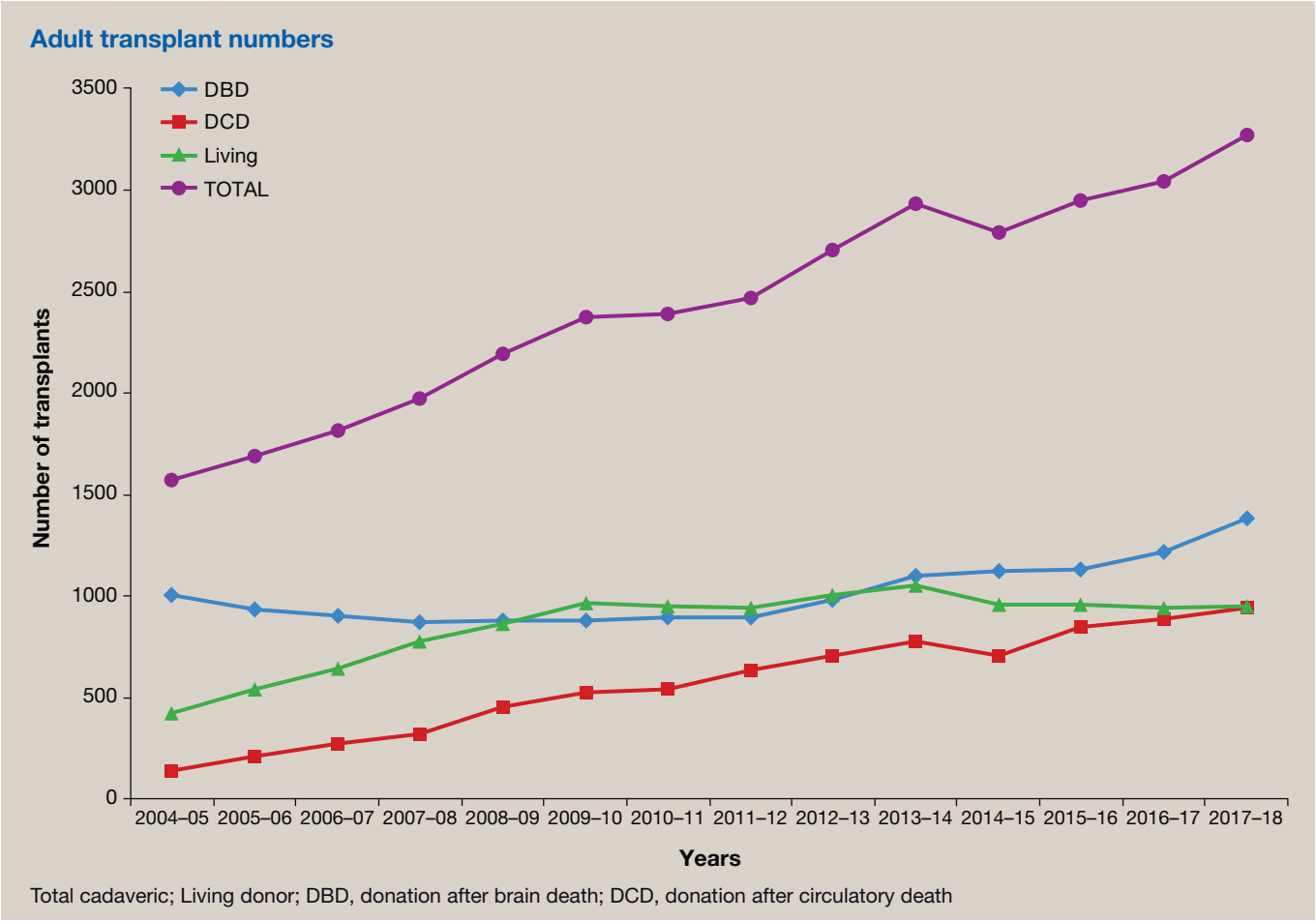

Figure 1

emphasis on listing (and transplanting) patients before they start on dialysis (pre-emptive listing). Currently (2017–2018), around 16% of deceased and 40% of living donor transplants are carried out pre-emptively in the UK.

The waiting list and allocation

Once accepted for listing, patients undergo histocompatibility testing to determine their (HLA) type and serum screening to detect the presence of anti-HLA antibodies, which are then registered centrally with NHS Blood and Transplant. When a donor kidney becomes available, its HLA type is determined and the available kidneys are matched to a blood group-compatible recipient using a complicated algorithm that takes account of the HLA mismatch as well as other variables such as waiting time, recipient age and donor–recipient age difference. A revised algorithm was introduced in summer 2019 to deliver more equitable access to deceased donor kidneys, as well as to better match the expected longevity of the kidney with that of the recipient.

Survival rates for adult first kidney transplants in the UK

	Deceased donor		Live donor	
	Graft survival	Patient survival	Graft survival	Patient survival
1 year	94%	97%	98%	99%
5 years	86%	87%	93%	94%

Data courtesy of NHS Blood and Transplant.
1-year survival cohort: 1 April 2013–31 March 2017; 5-year survival cohort: 1 April 2009–31 March 2013.

Table 1

HLA-matching, sensitization and cross-match testing

The targets for the host immune response are the cell surface glycoproteins of the major histocompatibility complex (MHC), represented in humans by HLAs. These are polymorphic and inherited in a Mendelian fashion from both parents. MHC class I molecules (encoded by genes at the *HLA-A*, *-B* and *-C* loci) are present on all nucleated cells, whereas MHC class II molecules (encoded by genes at the *HLA-DR*, *-DP* and *-DQ loci*) are more restricted in their distribution but can be upregulated during inflammation.

The degree of 'mismatch' between donor and recipient tissues at the HLA-A, HLA-B and HLA-DR loci (ranging from 0 to 6, because there are two haplotypes at each locus) has been shown to have an important impact on kidney transplant outcomes.

Consequently, one of the key components of the UK kidney allocation scheme aims to minimize mismatches between donor and recipient HLAs. There has been much interest in studying the physicochemical attributes of mismatched antigens at a molecular level to try to predict why some combinations are more immunogenic than others, and this remains an active field of research.

A potential recipient may have been sensitized to a foreign HLA through pregnancy, blood transfusion or previous transplantation, resulting in the development of antibodies to HLA. These pre-formed antibodies can result in hyperacute rejection of a subsequent transplant bearing the same HLA; hence their presence can severely restrict the pool of possible donors and limit the likelihood of finding a suitable match. A final cross-match test is performed immediately before transplantation, using donor tissue to determine whether the recipient has any significant antibodies to donor HLA that would cause hyperacute rejection (i.e. donor cells mixed with recipient serum *in vitro* looking for cell lysis).

Where there is no history of previous sensitization and no HLA antibodies are detected on serial screening, it is possible to predict which transplants will be cross-match negative ('virtual' cross-match). Increasing use of this technique avoids the 4–6 hours it takes to perform a physical cross-match, enabling the kidney to be transplanted sooner with a shorter cold ischaemic time. An intermediate between direct cross-match and virtual cross-match, used when prior recipient serum screening is inadequate, involves screening the recipient serum obtained on admission using single-antigen beads to determine any reactivity to HLA on the donor, thus avoiding the need to wait for donor tissue.

Types of donor

Deceased donors

There are two types of deceased organ donation: donation after brain death (DBD – formerly called heart-beating donation) and donation after circulatory death (DCD – formerly non-heart-beating donation). For DBD donors, after confirmation of death by brainstem death tests, the donor is transferred to theatre while being given cardiorespiratory support. The organ recovery operation begins while the organs continue to receive a blood supply. Once sufficient dissection has occurred, the aorta is cross-clamped and ice-cold preservation solution is flushed through the aorta to cool the organs, which can then be removed. Thus, there is no period during which the organs are still warm and not receiving a blood supply, in contrast to DCD donation.

A DCD donor has usually sustained a severe cerebral injury, but is not brain dead.[2] In this case, life-sustaining treatment is withdrawn, typically by stopping any inotropes and removing ventilatory support, in either the intensive care unit or theatre suite. Five minutes after circulatory arrest has occurred, death can be verified and the donor transferred to the operating room, where the organs are flushed *in situ* with cold preservation solution and then removed. There is thus an inevitable period of at least 5 (usually 10–20) minutes when the organs are warm but starved of blood, so-called 'warm ischaemia'. Although the period of cold storage ('cold ischaemia') causes reperfusion injury in the transplanted kidney, the additional period of warm ischaemia results in even greater reperfusion injury. This manifests as acute tubular necrosis and is characterized by a need for continued dialysis, a phenomenon termed delayed graft function (DGF); the incidence of this in DCD kidneys is >50%, compared with 25% in DBD kidneys.

Much of the recent increase in transplantation activity in the UK has been accomplished by increasing the number of DCD kidney transplants. This has widened the gap between the average quality of living and deceased donor organs. Decreasing mortality rates in adults aged <70 years in the UK compound this problem. This has had three important consequences. First, there has been increasing interest in improving donor management before organ retrieval, although the scope for intervention is limited under current UK law. Second, there has been burgeoning interest in improving the perfusion of deceased donor organs by techniques including *in situ* and *ex situ* hypothermic perfusion and normothermic perfusion (Figure 2). Finally, close scrutiny has been placed on the consent process so that potential recipients are given as much information as possible about donor organ quality.

Increasing donor age, a history of hypertension and a history of cardiac disease all predict poorer long-term graft survival. When assessing the suitability of a donor organ, other complicating factors include a history of previous malignancy or behaviour that puts the donor at risk of contracting hepatitis or HIV infection; in each case, the risks of using a donor kidney should be balanced against the benefits to the potential recipient, in particular the avoidance of the excess mortality that remaining on dialysis might entail. The main avoidable factor contributing to poor long-term function is the duration of cold ischaemia – the period after the kidney has been removed from the donor and before it is reperfused in the recipient. Risk–benefit decisions have been helped in recent times by the derivation of metrics for organ quality and relating such metrics to predicted outcome. These metrics have been adopted into the kidney allocation scheme in the USA and into the 2019 UK scheme.

Living donors

Living donors provide better quality organs than deceased donors. The most successful outcomes occur when (Table 1):

- donors are generally younger and fitter (better quality kidneys)
- transplantation can be planned and performed on a chosen date before the patient needs to start dialysis
- there is no occult organ damage as a consequence of the catecholamine and cytokine storm that characterizes brain death and circulatory arrest
- the duration of cold ischaemia is shorter, thereby minimizing ischaemia–reperfusion injury (IRI)
- transplantation is performed electively by senior staff in normal working hours.

However, the living donation process involves a fit individual who does not otherwise need an operation, and entails a significant risk, with a mortality rate of 1 in 3000, and a major and minor complication rate of approximately 2% and 20%, respectively. Consequently, the education and consent process is rigorous and in line with the principles laid out in the Human Tissue Acts (2004 and 2006 (Scotland)).

Living donation requires careful medical and psychological assessment of the potential donor to assess the suitability and

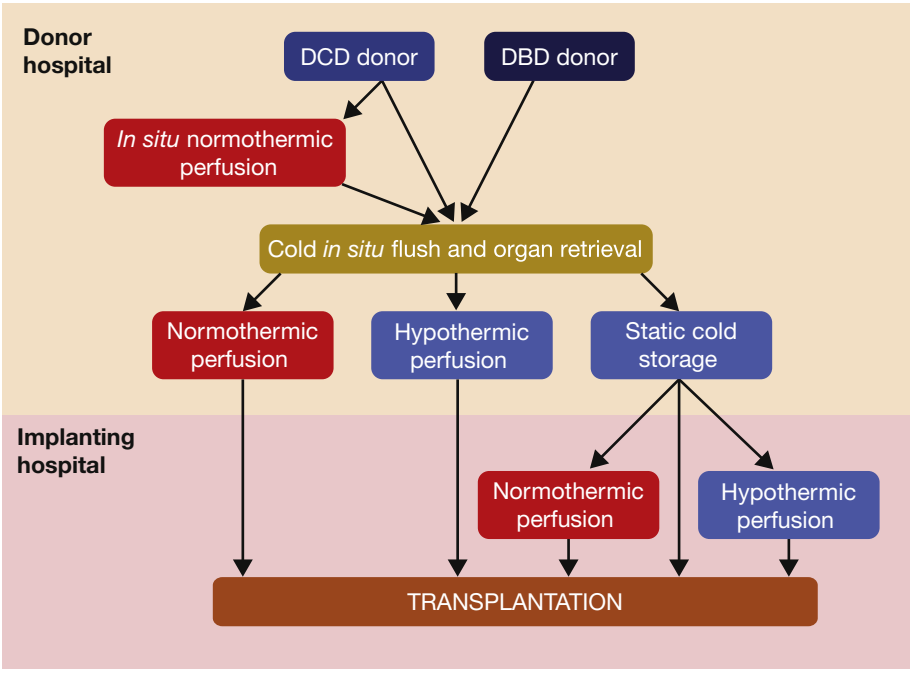

Figure 2 Possible interventions in the retrieval of cadaveric donor organs

safety of donation, and includes radiological imaging of the renal vessels to determine the operative anatomy. Living donor nephrectomy is usually performed laparoscopically, which is associated with less wound pain, a shorter hospital stay and faster recovery. Nevertheless, donation is not without risk, and evidence suggests that, in the long term, donors can have marginally increased rates of death, cardiovascular disease and gout. There is good evidence that live donors have 5–10 times the risk of developing ESRF in their lifetime, although absolute risk remains low (<1%).[3]

The Human Tissue Acts in the UK have also facilitated novel approaches to living donation. In addition to both related and unrelated donation, non-directed altruistic donation and paired donor exchanges have now been carried out in the UK (Figure 3). Although a positive cross-match test is a contraindication to deceased donor transplantation, such transplants can proceed from living donors with good results, using a combination of HLA-antibody removal (by plasmapheresis or immunoadsorption), potent immunosuppression and careful postoperative antibody monitoring. An alternative is 'paired donation', in which two (or more) incompatible living donor–recipient pairs donate kidneys to each other's recipient with whom they are compatible. The latter system is gaining in popularity because it offers the recipient a lower immunological risk transplant with better outcome and less immunosuppression (Figure 4).

The transplant operation

Most kidney transplants are placed in the extraperitoneal space in an operation that has changed little since its description by French surgeons in the 1950s. With kidneys removed from deceased donors, a 'Carrel' patch of donor aorta, surrounding the renal artery ostium, is left in place to facilitate the arterial anastomosis. The renal artery is usually anastomosed to the external iliac artery, although where a Carrel patch is not present, as with kidneys from living donors, it can be joined end to end to the internal iliac artery. The venous anastomosis is to the external iliac vein, with the ureter usually implanted directly on to the bladder (Figure 5), with an intraluminal stent placed to aid healing; the stent is usually removed 6 weeks later. Over the last decade there has been increasing interest in using marginal organs to increase donation rates. This has created surgical challenges including the separate implantation of both kidneys from a marginal donor into one recipient (a dual or double transplant) and 'en-bloc' transplantation of both kidneys from very young donors (typically <5 years of age) (Figure 6).

In addition to routine postoperative monitoring, particular attention should be paid to the fluid balance of kidney transplant recipients (KTRs) in the immediate post-transplant period; the recipient may be anuric or oliguric because of DGF, or can produce large volumes of urine (up to 1 litre/h) characteristic of the polyuria that results from recovering acute tubular injury. Electrolyte disturbances (hyper- or hypokalaemia) are common and require careful and frequent monitoring and management. The recipient may require urgent dialysis to correct hyperkalaemia in the early postoperative period, particularly if it required treatment intraoperatively.

Complications

The complications of kidney transplantation can be broadly related to the surgical procedure (Table 2) or the immunosuppression and related co-morbidities (Table 3). Surgical complications can occur early or late after transplantation and relate to the artery (thrombosis, stenosis), vein (thrombosis), ureter (stenosis, leak) or surgical bed (bleeding, infection, lymphocoele). Immunosuppression predisposes to neoplasia

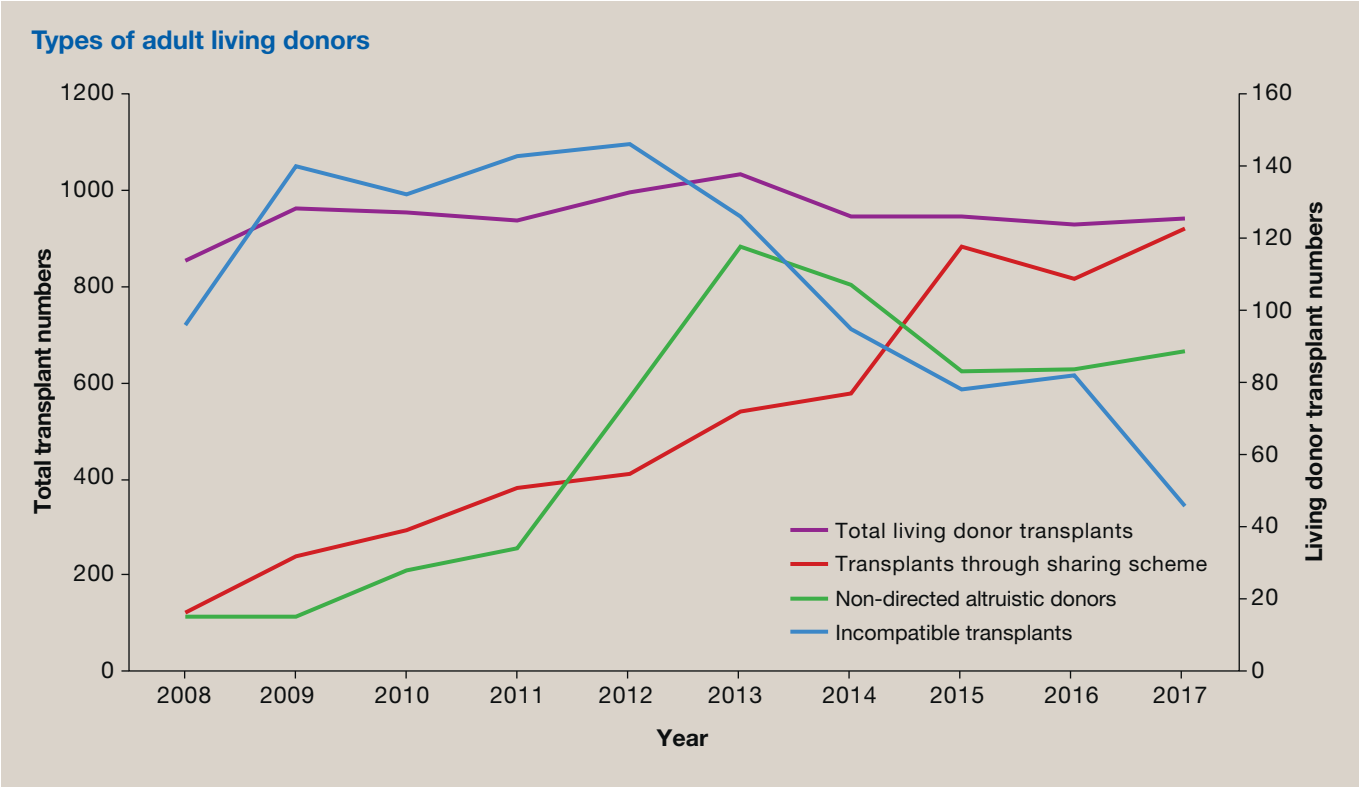

Figure 3

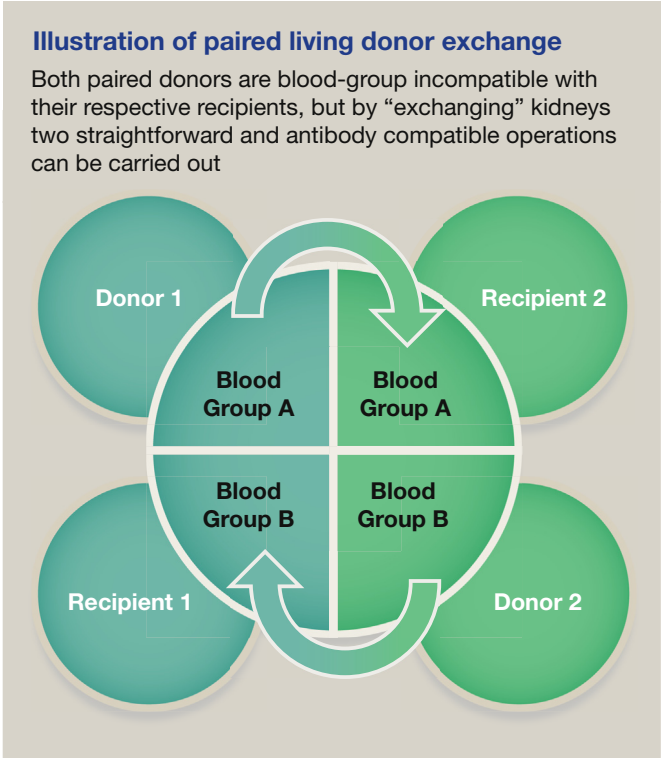

Figure 4

The standard surgical procedure implantation of the donor kidney extraperitoneally in the recipient's pelvis

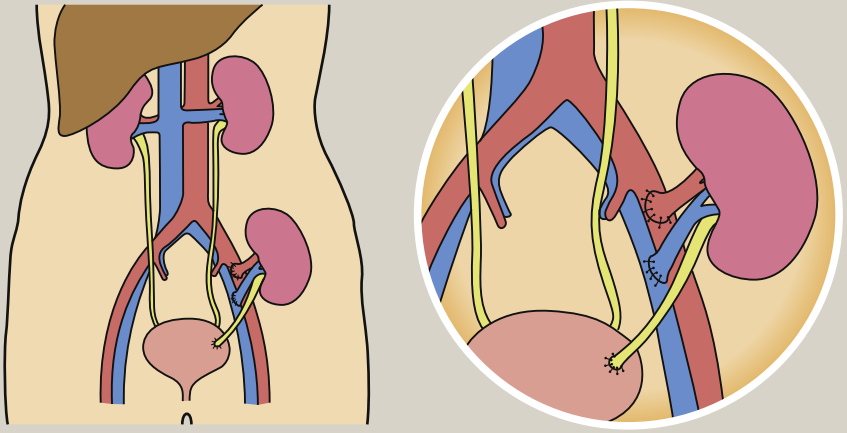

Illustration courtesy of Niaz Ahmad

Figure 5

and infections, particularly viral (e.g. cytomegalovirus (CMV), Epstein–Barr virus (EBV)) and fungal (e.g. *Candida*) infections.

Delayed graft function and primary non-function

After donor death, the kidney suffers ischaemic damage. This occurs from the time the donor circulation fails to perfuse the kidney adequately until the recipient circulation restores adequate perfusion. This damage is often compounded by the proinflammatory effects of donor brain death. The injury that follows reperfusion (IRI) often results in the kidney not working initially, such that dialysis support is required until normal function returns. In such cases, the kidney is said to have suffered from DGF. This occurs in <5% of living donor grafts, approximately 25% of DBD grafts and over 50% of DCD grafts. About 3% of deceased donor kidney transplants never function and this is called primary non-function. Despite the increased IRI experienced by DCD kidneys, evidence in the UK suggests that long-term outcomes are similar to those of DBD donors.[2]

Dual kidney transplantation (a) and 'en-bloc' renal transplantation (b)

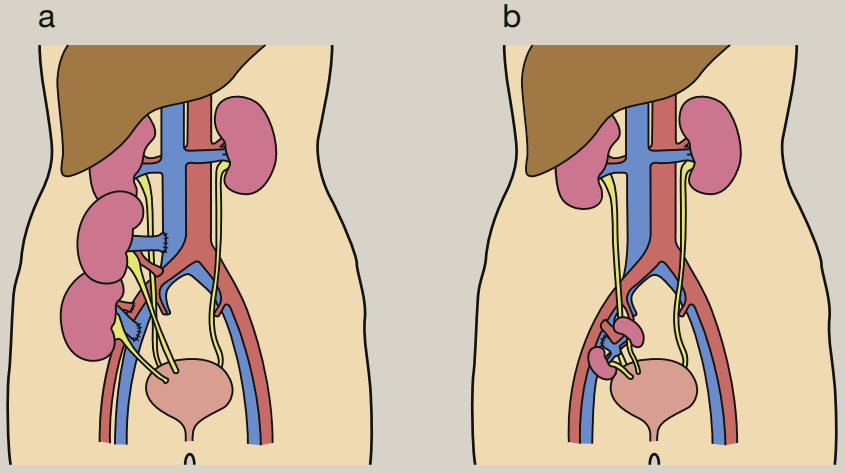

Illustration courtesy of Niaz Ahmad

Figure 6

Surgical complications of kidney transplantation

Complication	Description and incidence	Treatment
Early		
Bleeding	Usually within 48 hours	Conservative or surgical re-exploration
Wound infection	5–10%; can be superficial or deep	Antibiotics ± surgical debridement
Graft thrombosis	Occurs early. Caused by renal artery (1%) or vein (5%) thrombosis	Surgical re-exploration is usually unsuccessful; usually requires graft nephrectomy
Urine leak	<4%; incidence reduced by the use of ureteric stents	Radiological (drainage and stenting) or surgical reconstruction
Lymphocoele	5–20%; incidence can be reduced by careful ligation of lymphatic vessels	Radiological or surgical drainage
Late		
Ureteric stenosis	2–4%; usually caused by ureteric ischaemia or BK infection	Radiological (dilatation ± stenting) or surgical reconstruction
Renal artery stenosis	1–10%; usually presents at approximately 6 months	Radiological (angioplasty ± stent) or surgical reconstruction

Table 2

Immunosuppression

Because the principal components of the anti-donor response are the recipient lymphocytes, drugs that prevent rejection reduce the capabilities of these cells. Unfortunately, these are the same cells that patrol the body looking for foreign microbial and neoplastic antigens. As a result, all immunosuppressive agents currently available reduce the ability of the host to fight infection and cancer. The general principles governing choice of immunosuppression are to:

- use drugs in synergistic combinations to reduce the adverse effects of individual drugs that would otherwise need to be given at high doses
- tailor combinations to individual patients (e.g. avoid corticosteroids if the body mass index is high)
- expect the burden of immunosuppression to be highest during the first 6 months when the graft is most immunogenic
- give an intravenous induction agent at the time of transplantation to counteract the overwhelming initial stimulus to the host immune system
- avoid long-term adverse effects resulting from over-immunosuppression.

Immunosuppressive drugs are shown in Table 3 and important transplant drug interactions in Table 4.

Types of graft rejection

Hyperacute rejection occurs within 24 hours of the transplant operation and is caused by pre-formed antibodies against antigens on the graft endothelial cells. The most common clinical examples are pre-formed HLA-specific antibodies (resulting from previous transplantation, pregnancy or blood transfusion) and naturally occurring blood group antibodies. This form of rejection can be almost entirely avoided by ensuring blood group compatibility and a negative pre-transplant lymphocytotoxic cross-match. Hyperacute rejection usually results in rapid graft loss.

Acute cellular rejection is thought to be mediated by recipient T cells that recognize allogeneic HLA molecules on the surface of donor cells in the kidney. In milder forms, these T cells are limited to the interstitial spaces and tubules, but more severe forms can involve the endothelium of the blood vessels, leading to endarteritis. Acute cellular rejection typically occurs in the first month after transplantation but can occur later, particularly with low immunosuppression levels. Milder forms are usually treated with pulsed high-dose intravenous corticosteroid (e.g. methylprednisolone 500 mg daily for 3 days), while more severe grades can require lymphocyte-depleting antibodies (Table 3).

Acute antibody-mediated rejection has been increasingly recognized with advances in the technology for detecting donor-specific HLA antibodies (solid-phase assays based on flow cytometry) and the damage that they cause (covalently bound complement fragments – C4d). Graft damage occurs through the development of *de novo* antibodies to donor HLA molecules leading to acute graft dysfunction, which can be severe.[4] Treatment usually involves high-dose intravenous corticosteroids and antibody removal by plasma exchange or immunoadsorption. Intravenous immunoglobulins can also be used as adjunctive therapy.

Chronic antibody-mediated rejection (CAMR) has been increasingly recognized with the improved detection of antibody-mediated processes. There is a clear correlation between the development of anti-HLA antibodies and poor graft outcomes, although whether the relationship is causal remains uncertain. There is also a link between the development of CAMR and poor adherence to immunosuppressive medications. There is an urgent need to find treatments for CAMR. Most clinicians currently intensify immunosuppressive treatment, but the benefit of this approach remains unproven.

Graft dysfunction

Graft dysfunction is usually monitored as in other renal diseases by:

- serum creatinine concentration
- urine protein excretion

Characteristics of commonly used immunosuppressive agents

Class of drug	Examples	Description	Mechanism of action	Uses			Adverse effects and comments
				Induction	Maintenance	Rejection	
Biological agents							
Co-stimulation blockade	Belatacept	Fusion protein of human IgG_1 and CTLA4	Blocks co-stimulation of T cells through CD28 by binding its ligands		√		Not nephrotoxic, regular IV Infusions and increased PTLD
Non-depleting antibodies	Basiliximab	mAb against CD25 (IL-2 receptor α chain)	Inhibition of IL-2-induced T cell activation	√			Hypersensitivity and adverse effects are rare
Depleting antibodies	Alemtuzumab (Campath 1H)	mAb against CD52 on all lymphocytes	Prolonged depletion of B and T lymphocytes	√			Cause moderate cytokine release syndrome. Not formally licensed for use in transplantation
	Anti-thymocyte globulin	Polyclonal IgG from rabbits immunized with human thymocytes	Prolonged depletion of T lymphocytes	√		√	Cytokine release syndrome is common
	Rituximab	mAb against CD20 on B lymphocytes	Depletion of B lymphocytes			√	Not formally licensed for use in transplantation. Used in treating antibody-mediated rejection
Non-biological drugs							
Calcineurin inhibitors	Ciclosporin	Binds to cyclophilin	Inhibition of calcineurin phosphatase, blocks T cell activation		√		Nephrotoxicity is a significant adverse effect
	Tacrolimus (FK506)	Binds to FK binding protein (FKBP12)			√		
mTOR Inhibitors	Sirolimus (rapamycin)	Macrolide antibiotics, also bind to FKBP12	Inhibits mTOR and IL-2-induced T cell proliferation		√		Cause impaired wound healing, potentiate CNI nephrotoxicity
	Everolimus				√		
Anti-metabolites	Mycophenolate mofetil	Pro-drugs of mycophenolic acid; inhibit purine synthesis	Suppression of B and T cell proliferation		√		Myelotoxicity (pancytopenia) and gastrointestinal disturbance common
	Mycophenolate sodium				√		
	Azathioprine	Pro-drug of 6-mercaptopurine	Inhibition of DNA synthesis in lymphocytes		√		Occasional hepatotoxicity and marrow suppression
Corticosteroids	Prednisolone (oral)	Bind to cytosolic glucocorticoid receptors	Suppression of cytokine production, T cell activation and migration		√		Cause the full spectrum of Cushing's syndrome adverse effects
	Methylprednisolone (IV)						

CNI, calcineurin inhibitor; CTLA4; cytotoxic T-lymphocyte-associated antigen 4; FKBP12, FKBP prolyl isomerase 1A (also known as FKBP1A); IL, interleukin; IV, intravenous; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; PTLD, post-transplant lymphoproliferative disease.

Table 3

Important drug interactions in KTRs

Allopurinol and febuxostat with azathioprine
- Potentially fatal bone marrow suppression

Antivirals (valaciclovir, valganciclovir) with mycophenolate mofetil
- Competition for tubular secretion
- Approximate doubling of plasma concentrations of both

CNI and sirolimus

CYP450 enzyme inhibition (potentially toxic drug concentrations)
- Macrolide antibiotics (e.g. erythromycin but not azithromycin)
- Imidazole antifungals (e.g. fluconazole)
- Calcium channel blockers (e.g. diltiazem)
- Grapefruit juice

CYP450 enzyme induction (potentially subtherapeutic drug concentrations)
- Rifampicin
- Barbiturates
- Phenytoin
- Carbamazepine

Statins and CNI
- Risk of rhabdomyolysis increased

Colchicine and CNI
- Risk of rhabdomyolysis

CNI, Calcineurin inhibitor.

Table 4

- blood pressure
- urine output.

Early (first few days): during this period, urine output is of paramount importance and should be considered in the context of the pre-transplant output. Management is more complicated where there is DGF or a normal pre-transplant output. Causes of dysfunction are shown in Table 2; management involves regular and thorough clinical evaluation. If urine output drops, ultrasound examination with Doppler studies forms the cornerstone of management because it can detect vascular abnormalities and ureteric obstruction. If arterial and venous flows are normal and there are no other abnormal features, it is likely that the kidney has developed DGF secondary to a significant tubular injury caused by IRI. There is rarely a need to biopsy the kidney at this early stage unless there is a very high likelihood of hyperacute rejection.

Risk factors for the development of post-transplant diabetes mellitus

Recipient factors	Medications
• Obesity	• Corticosteroids
• Ethnicity	• Tacrolimus
• Age	• Ciclosporin
• Family history of diabetes mellitus	• Sirolimus
• Hepatitis C infection	
• Polycystic kidney disease	

Table 5

Intermediate (weeks to months): graft dysfunction in the first few weeks after transplantation is relatively common, and most units have a well-rehearsed algorithm for management. The dysfunction is usually detected by a rise in serum creatinine, and the patient typically has no symptoms. If there is no obvious cause, such as urinary tract infection, recent nephrotoxic drug usage or a toxic concentration of calcineurin inhibitor, an ultrasound and Doppler examination should be carried out, looking for vascular or obstructive abnormalities. If the cause is still not manifest, a renal biopsy is required to scrutinize the renal parenchyma for the cause of graft dysfunction.

Late (months to years): late graft dysfunction is usually detected by an insidious yet inexorable rise in serum creatinine, often accompanied by rising proteinuria and hypertension. Investigation is similar to that recommended in intermediate graft rejection, but the ultrasound examination is usually normal and diagnosis depends on obtaining a renal biopsy. About a half of all KTRs lose their grafts with a median graft life of about 15 years for deceased donor and 25 years for living donor grafts. As a result, failing grafts contribute a significant proportion of patients to the transplant waiting list.

Long-term care

Although the transplant fails in about 50% of KTRs, the other half die with a functioning transplant. The principal causes of

Relative risk of neoplasia after kidney transplantation

Relative risk	Cancer type
High (relative risk >5×)	Lip
	Kaposi's sarcoma
	Non-melanoma skin
	Lymphoma
	Kidney
	Thyroid
Medium (relative risk 1–5×)	Melanoma
	Cervix
	Vulvovagina
	Bladder
	Colon
	Lung
	Stomach
	Oesophagus
	Oropharynx and larynx
	Myeloma
	Anus
	Leukaemia
	Liver
No increase	Breast
	Prostate
	Ovary
	Uterus
	Pancreas
	Brain
	Testis

Table 6

Timetable for infections in the post-transplant period

Type of infection	< 1 month	1–6 months	> 6 months
Bacterial	Chest infection	Relapsed *Clostridium difficile* colitis	Urinary tract infection
	Catheter or stent infection	Urinary tract infection	Community-acquired pneumonia
	Wound infection	*Mycobacterium tuberculosis*	*Rhodococcus* species
	Anastomotic leaks	*Listeria monocytogenes*	*Mycobacterium tuberculosis*
	Fluid collections	*Mycobacterium tuberculosis*	
	Donor-derived (uncommon)		
Viral	Adenovirus	BK viral nephropathy	Tissue-invasive CMV infection
	Influenza viruses	CMV infection	HSV encephalitis
		Other herpes viruses (HSV, VZV, EBV)	HBV and HCV
		HBV and HCV	Polyomavirus (PML)
			Viral neoplasia (HPV, EBV, etc.)
Other	Donor derived (HCV, HBV, HIV)	*Pneumocystis jirovecii*	*Aspergillus*
	Recipient colonization (e.g. *Aspergillus*)	*Cryptococcus*	Atypical fungi (e.g. *Mucor*)
		Nocardia	*Nocardia*

HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

Table 7

death are vascular disease, neoplasia and infection. For this reason, it is essential to provide life-long follow-up in clinics that specialize in both preventing and treating these complaints.[5]

Hypertension

Higher blood pressures are linked to poor long-term outcomes and increased rates of vascular events. Clinic readings are often high, and it is essential to develop methods for regular and accurate

Haematological problems after transplantation

Clinical problem	Common cause	Treatment
Anaemia	Azathioprine	Drug withdrawal
	Mycophenolic acid derivatives	Iron supplements
	Sirolimus	Erythropoietin
	Angiotensin-converting enzyme inhibitors	Endoscopy
	Angiotensin receptor antagonists	
	Parvovirus (erythrovirus) infection	
	Dapsone	
	Poor renal function	
	Gastrointestinal blood loss	
Polycythaemia	Hypersensitivity to erythropoietin with improved renal function	Angiotensin-converting enzyme inhibitors
		Angiotensin receptor antagonists
		Aminophylline
		Venesection
Thrombotic microangiopathy	Ciclosporin	Drug withdrawal
	Tacrolimus	
	Sirolimus	
	Disease recurrence	
Leucopenia and thrombocytopenia	Anti-thymocyte globulin	Drug withdrawal
	Alemtuzumab	Colony-stimulating factors
	Azathioprine	CMV treatment
	Mycophenolic acid derivatives	
	Sirolimus	
	Valganciclovir	
	Co-trimoxazole	
	Cytomegalovirus (CMV) infection	

Table 8

blood measurement. Treatment consists of lifestyle modification and drug treatment. Choice of agent is relatively unimportant and the priority is to achieve the target (<135/85 mmHg).

Post-transplant diabetes mellitus

The development of post-transplant diabetes mellitus is a significant problem and is associated with significantly increased morbidity and mortality. Risk factors are shown in Table 5.

Lipids

Hyperlipidaemia is associated with poor outcomes after transplantation and immunosuppressive drugs often worsen the lipid profile. There is some evidence that outcomes can be improved with aggressive treatment with drugs such as statins and ezetimibe. These drugs must be used judiciously as there are significant interactions with immunosuppressive drugs.

Lifestyle

Cigarette smoking is strongly linked to adverse outcomes after renal transplantation, and patients should be strongly encouraged to quit. Drugs such as varenicline and bupropion may be necessary and can be used safely. Regular exercise, weight loss and healthy eating should also be encouraged.

Cancer

The risk of cancer after renal transplantation is approximately twice that of the normal age-matched population. Some cancers, particularly those that are virally driven, can be increased more than a 100-fold (Table 6). Central to this phenomenon is impaired immunosurveillance by lymphocytes under the influence of immunosuppressive drugs. Primary prevention is important and KTRs should be encouraged to follow the national cancer screening guidelines (http://www.cancerscreening.nhs.uk/).

Neoplasia related to human papillomavirus (HPV) is a particular problem and leads to markedly increased rates of squamous cell carcinoma of the skin, anus, cervix, lip, penis, vulvovagina, oropharynx and eye. Rates of non-melanoma skin cancer approach 200 times that of the normal population, such that in certain parts of the world more than half of all KTRs have developed skin cancer 10 years after transplantation. Ultraviolet radiation is an important co-factor, and KTRs must be advised to minimize their exposure to sunlight, wear appropriate clothing and use total sunblock (SPF $\geq$50).

In general, there is no evidence that any particular immunosuppressant is more likely to cause cancer, and the overall risk is related to the total burden of immunosuppression. The principal treatment of an established lesion is therefore reduction in immunosuppressive drugs. An exception is sirolimus, which is associated with a lower risk of neoplasia and probably reduces the incidence of non-melanoma skin cancer; everolimus probably has the same benefits.

Infection

Avoidance of infection involves the use of prophylactic antimicrobials in the early period when the organisms involved are similar to those causing postoperative infections in non-transplant patients. With increasing duration of immunosuppressive treatment, opportunistic infections become more problematic (Table 7).

CMV and EBV infections are particularly common in individuals who have not previously been infected (e.g. CMV or EBV immunoglobulin G-negative). When such individuals are given organs from positive donors, they usually develop a primary infection. In the case of CMV, this can cause a glandular fever-like syndrome associated with leucopenia, thrombocytopenia and hepatitis. Some patients develop tissue-invasive disease with retinitis, colitis, oesophagitis or pneumonitis. Primary infections with EBV are linked with a nearly 10-fold risk of developing post-transplant lymphoproliferative disease.

BK virus resides in the renal epithelial cells of most adults and does not usually cause disease. However, the virus can replicate under the influence of immunosuppression. At this stage, it starts to cause damage to renal tissue and eventually destroys the graft. Patients should be screened and immunosuppression reduced if infection occurs. A specific antiviral treatment for this agent remains a clinical priority.

KTRs can be given vaccinations but only killed vaccines are safe. Examples of safe vaccines include vaccination against hepatitis B, influenza and pneumococcus. Live vaccines (e.g. varicella-zoster in vaccine-naive patients) should be given before transplantation and the initiation of immunosuppression.

Bone disease

Renal bone disease is a complex entity in KTRs and represents the sum of pre-transplant disease and post-transplant factors such as corticosteroid usage. Post-transplant tertiary hyperparathyroidism is common and usually settles with time, but treatment can be required. Gout is also common and it is important to avoid allopurinol in patients who are taking azathioprine; non-steroidal anti-inflammatory drugs should generally be avoided and short courses of corticosteroids or colchicine used for symptomatic treatment.

Haematological

Haematological problems are common after transplantation (Table 8).

Adherence

Poor adherence to medication is thought to contribute to a significant proportion of graft loss and is specifically linked to the development of CAMR. Associations include poor clinic attendance, age <25 years and transitioning from paediatric to adult care; poor adherence to immunosuppression is suggested by low or highly variable immunosuppressive drug concentrations. ◆

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