Assessment and management of a patient with a renal transplant

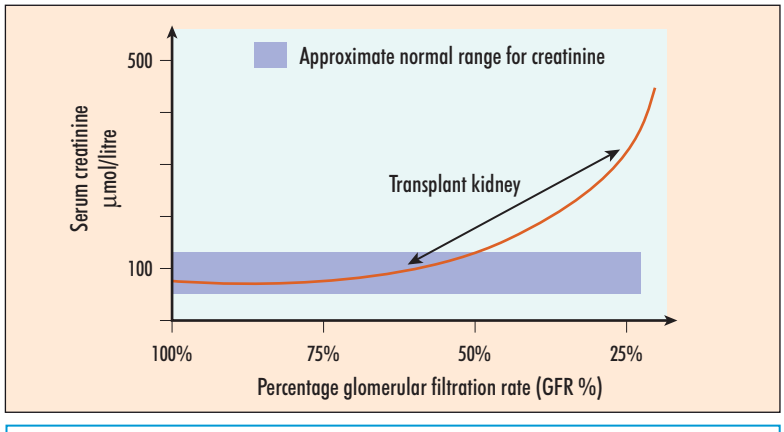
Renal transplant recipients admitted on the medical take can be challenging for the clinician. Immunosuppressant medications, reduced renal functional reserve, increased vascular risk, and propensity to uncommon infections and malignancies all contribute to make management more complex than in other patients. This article reviews salient points in the management of such patients by the non-specialist.

Assessing a patient with a functioning renal transplant as the admitting doctor can be intimidating, but if some fundamental points are appreciated then management is straightforward. This article provides pointers to help clarify the management of such patients.

Certain basic principles apply to all transplant recipients:

- Renal transplant recipients have a substantially increased risk of all forms of vascular disease which is often exacerbated by immunosuppressive drugs
- Immunosuppressive drugs increase the risk of infections by both common organisms and also opportunistic pathogens
- Reduced immunosurveillance increases the relative risk of many forms of cancer
- Immunosuppression dampens the inflammatory response, potentially masking symptoms and signs
- Patients with apparently stable renal transplant function are actually in a state of dynamic immunological equilibrium, the maintenance of which depends on their immunosuppression. This means that even missing a few doses may lead to a rejection episode
- Renal transplant patients have a reduced functional renal reserve, such that small changes in function (for example, those brought on by a urinary tract infection) affect creatinine more markedly than in the rest of the population. This is a result of the non-linear relationship between glomerular filtration rate (GFR) and creatinine, illustrated in *Figure 1*
- Advice is always available from the patient's transplant centre and should be sought if required.

Figure 1. Changes in creatinine in renal transplant patients. Small changes in renal function affect creatinine more markedly in renal transplant patients since they operate at a lower glomerular filtration rate to start with and the relationship of glomerular filtration rate to creatinine is non-linear.



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History and examination

The complex medical history of many renal patients means they can often give detailed background information. Particular note should be made of the patient's original renal disease and date of transplantation. An accurate medication history on admission is also important.

The significance of fluid status assessment in the examination cannot be overstated. As well as the jugular venous pressure, mucus membranes and skin turgor, valuable information can be obtained by performing lying and standing blood pressures at the bedside, and by ensuring daily charting of the patient's weight, and accurate monitoring of fluid intake and urine output. Previous dialysis access and whether it is functional should be noted (e.g. fistulae, peritoneal dialysis catheter). Intravenous cannulae should not be sited in a limb containing a fistula, and should be placed as distally as possible in the hands to avoid reducing potential fistula formation sites in the future.

Pain over the graft

Pain over the renal transplant can cause great concern for both the patient and clinician. Acute pyelonephritis is the most common cause, and reaching that diagnosis allows a degree of reassurance for the patient that the pain is not a sign of the transplant 'failing'. However, other diagnoses need to be considered, as detailed in *Table 1*. Rejection is discussed later.

Initial investigations

Standard biochemical and haematological parameters are essential. Urinalysis can quickly give useful information,

as it may indicate infection, and any proteinuria. Formal quantification of proteinuria may be helpful, depending on the presentation. Mid-stream urine for culture is often indicated. Immediately obtaining blood cultures in a pyrexial or septic patient, and noting on the request form that the patient is immunosuppressed is advisable.

Ultrasound of the renal transplant should be performed whenever reduced function is noted. This can detect structural abnormalities such as obstruction or renal stones, and Doppler studies of the main renal artery and vein are usually performed to assess perfusion.

Medications

Drug prescription should take account of both potential interactions and degree of renal dysfunction. It is important to calculate creatinine clearance to inform correct dosing of any medication used. The most straightforward method is the Cockcroft and Gault equation:

$$\text{Creatinine clearance} = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{\text{Creatinine (}\mu\text{mol/litre)}} \times 1.23 \text{ (m) or } 1.04 \text{ (f)}$$

An extremely useful reference text is *The Renal Drug Handbook* (Ashley and Currie, 2004). If not available, then the renal section (appendix 3) of the British National Formulary is also useful. During the course of a patient's illness the creatinine clearance is likely to fluctuate, so drug doses need to be recalculated as renal function changes. Common medications and what dose alterations they require at different levels of GFR can be found in *The Renal Drug Handbook*.

Analgesia can present a particularly difficult problem where renal function is reduced, since non-steroidal anti-inflammatory drugs should be avoided, and opiates and related substances must be used with caution because of the accumulation of toxic metabolites. Regular paracetamol should be prescribed as background analgesia. A short-acting opiate such as fentanyl may be appropriate and is available in lozenge as well as patch form. Naloxone can be used for opiate narcosis.

Low molecular weight heparins are not cleared normally in patients with significant renal dysfunction. If facilities for timely factor Xa level measurements are available, low doses can be used and adjusted according Xa levels. If not, unfractionated intravenous heparin with 6-hourly activated partial thromboplastin time monitoring is preferable to avoid complications.

Immunosuppression

Most renal transplant recipients take at least two immunosuppressants, and triple therapy, e.g. with a calcineurin inhibitor, antiproliferative and corticosteroid, is common.

- The calcineurin inhibitors ciclosporin and tacrolimus block the specific signal transduction pathways involved in lymphocyte activation
- Antiproliferative agents (azathioprine, mycophenolate) interfere with nucleotide synthesis, inhibiting DNA synthesis

Table 1. Possible causes of pain over the renal allograft

Early (days to weeks post transplant)	Surgical emergencies, all relatively rare:	Arterial or venous thrombosis or bleeding
		Graft rupture
		Large volume urine collection, e.g. from ureteral anastomotic dehiscence
Late (months post transplant)	Renal stones	
	Deliberate withdrawal of immunosuppression where a graft is failing can lead to pain from rejection	
At any time	Acute transplant pyelonephritis (most common)	
	Acute rejection (usually early, but less common overall because of calcineurin inhibitors)	
	Any fluid collection (e.g. urinoma, lymphocoele)	
	Pathology of nearby systems: bowel (appendicitis, herniae, diverticular disease), bones (e.g. pain from avascular necrosis), skin (e.g. cellulites, pain preceding shingles)	

- Corticosteroids have many actions, but their immunosuppressant effect largely derives from inhibition of lymphocyte functions
- Sirolimus is a macrolide inhibitor of the mammalian target of rapamycin. It disrupts interleukin-2-mediated signal transduction, reducing cell proliferation.

Table 2 summarizes considerations regarding the common immunosuppressants, including levels, interactions, adverse effects and conversion to intravenous dosing.

Rejection

In the era before calcineurin inhibitors, fever, oliguria and graft tenderness were classically described signs of acute rejection. These signs are less commonly seen today, with more than half of renal transplant recipients with acute rejection having neither fever nor reduced urine output (Schroeder and Moore, 1998).

Transplant biopsy is needed to diagnose rejection. While the possibility should always be considered when graft dysfunction occurs, transplant pyelonephritis is more likely to cause fever and graft tenderness. Nonetheless, recently transplanted patients with graft dysfunction should always be discussed with their transplant centre.

Vascular disease

The annual risk of a fatal or non-fatal cardiovascular event is 3.5–5% in renal transplant recipients, 50-fold higher than the general population (Ojo, 2006). At 15 years post-transplantation, 23% of patients have symptomatic coronary heart disease, 15% have cerebrovascular disease and 15% have peripheral vascular disease (Kasiske et al, 2000). Immunosuppressive drugs exacerbate this risk as shown in *Table 3*.

Diabetes and new onset diabetes after transplantation

Diabetes is a very common cause of end-stage renal disease in the UK and it accounts for 26.9% of the trans-

Table 2. Immunosuppressants

Pharmacological category	Immunosuppressant (trade names)	Use	Monitoring	Common adverse and toxic effects	Conversion to intravenous form	Interactions
Corticosteroids	Prednisolone	Long-term immunosuppression	None	Skin: thinning, easy bruising, striae; gastrointestinal: oral *Candida*, oesophagitis, ulceration; musculoskeletal: proximal myopathy, osteoporosis, avascular necrosis; endocrine: adrenal suppression, diabetes, weight gain, hirsutism, menstrual irregularities; other: cataracts, hypertension, mood changes	Prednisolone 5 mg = hydrocortisone 20 mg. Increase doses in severe illness; hydrocortisone may be used temporarily to cover other immunosuppressants	Mutual level increases with CyA; levels decreased by most enzyme inducers, enhanced effects of anticoagulants. Increased hypokalaemia with digoxin, diuretics, amphotericin. Antagonise most antihypertensives
	Methylprednisolone	Treatment of rejection episodes				
	Hydrocortisone	Intravenous therapy when PO not possible				
Calcineurin inhibitors	Ciclosporin (CyA) (Neoral, Sandimmun)	Long-term immunosuppression	CyA: At 0–3 months *C0: 2–300 ng/ml C2: 1–1.5 mg/ml; At 3–6 months C0: 1–200 ng/ml C2: 1–1.5 mg/ml; >6 months C0: 50–100 ng/ml C2: 8–900 ng/ml	CyA: hypertension, hirsutism, hyperlipidaemia, gum hyperplasia, hyperkalaemia (less neurotoxic and diabetogenic than Tac) Both CyA and TAC nephrotoxic in the longer term	CyA: Give 40% usual dose, in two divided doses	CyA: Increased levels with amiodarone; increased myopathy with statins; increased toxicity with methotrexate Levels of CyA and TAC increased by: macrolides, most antifungals and calcium-channel blockers, grapefruit juice. Levels of CyA and TAC decreased by: enzyme inducers. Increased hyperkalaemic effects and nephrotoxicity of other medications, e.g. ACEIs, NSAIDs
	Tacrolimus (TAC) (Prograf)	Long-term immunosuppression	TAC: Trough levels At 0–3 months 9–14 ng/ml; >3 months 5–9 ng/ml	TAC: Diabetogenic; headaches, fine tremor and altered mental state at toxic levels (less hypertension, skin changes and gum hyperplasia than CyA)	TAC: Incompatible with polyvinyl chloride lines. Give 1/5th of usual daily dose, as 24-hour infusion	TAC: Potentiates oral anticoagulants and antidiabetics
Antiproliferatives (purine synthesis inhibitors)	Azathioprine (Aza) (Imuran)	Long-term immunosuppression	None	Bone marrow suppression: leucopenia, anaemia, thrombocytopenia	1 mg PO = 1 mg intravenous very irritant to veins, cytotoxic – do not handle	Allopurinol – dramatic bone marrow suppression; if concomitant use essential, ↓ Aza dose by 50–75%. Leucopenia also increased with trimethoprim, cotrimoxazole, aminosalicylates, clozapine, captopril. Reduced effect of warfarin; reduced absorption of phenytoin
	Mycophenolate mofetil (MMF) (CellCept) Mycophenolate sodium (Myfortic)	Long-term immunosuppression	Controversial; area under curve of mycophenolic acid can be used (Holt, 2002)	Diarrhoea; reported to be less with Myfortic formulation Bone marrow suppression: leucopenia, anaemia	1 g PO = 1 g intravenous, 1 g bd MMF = 720 mg bd Myfortic, Exposure to active metabolite higher with TAC than CyA	Mutual level increases with aciclovir and ganciclovir; decreased oral bioavailability with (1) antacids containing magnesium or aluminium, and (2) colestyramine. Reduced absorption of phenytoin
mTOR inhibitors (mammalian target of rapamycin)	Sirolimus (Rapamune) (also Everolimus (Certican))	Long-term immunosuppression	Trough levels of 4–12 ng/ml (higher if CyA not used) for 1 year, then reduced levels	Hyperlipidaemia, proteinuria, thrombocytopenia, acneiform rashes, leucopenia, mucosal ulceration, pneumonitis	No intravenous equivalent	Levels increased by CyA, macrolides, most antifungals, most calcium-channel blockers, grapefruit juice, decreased by enzyme inducers

ACEI = angiotensin-converting enzyme inhibitor; bd = twice daily; NSAID = non-steroidal anti-inflammatory drug; PO = by mouth. *CO = 12-hour trough levels; C2 = 2-hour peak levels

plant population across the UK (Ansell et al, 2002). Calcineurin inhibitors and corticosteroids not only predispose to worsening of pre-existing diabetes but also to de novo diabetes. Azathioprine, mycophenolate mofetil and sirolimus are not thought to be diabetogenic.

New onset diabetes after transplantation occurs in between 4 and 20% of renal transplant recipients, and around 40% of those go on to require insulin. The diagnosis is most often made in the first year, and can be made as early as the first few weeks post-transplant (Jindal, 1994). It carries a poor long-term prognosis.

Infections

It is important to inform the microbiology laboratory that samples are from an immunocompromised individual. The main risk factor for opportunistic infections is the accumulated total dose of immunosuppression. Thus risk is increased in patients who have had treatment of rejection episodes, especially with antibody therapies, prolonged high doses or levels of immunosuppressants, multiple renal transplants or previous immunosuppression for autoimmune disease (e.g. systemic lupus erythematosus).

Other host factors such as diabetes, liver disease, malnutrition, cytomegalovirus (CMV) disease, splenectomy, and leucopenia (e.g. azathioprine or mycophenolate related) are also important. The timing of an infective episode post-transplantation can help derive likely causes (*Table 4*). As with any infection, a detailed food, drink, travel and contact history is essential. Infections may occur in less common anatomical sites (e.g. vertebral discs, heart valves or deep-seated bony sites). Specific infective complications are discussed by pathogen category below. Reducing immunosuppression is advised during significant or recurrent infections.

Bacterial

In the immediate postoperative period wound, respiratory and urinary infections are seen, caused by the usual local bacteria. Bacteraemia is more common than in the general population. Nosocomial infections such as methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile* may be particularly severe in the recently transplanted patient. Later, less typical bacterial infections such as listeria, legionella and nocardia can occur.

Tuberculosis

Patients at risk of tuberculosis are usually prescribed isoniazid prophylaxis, with pyridoxine to prevent peripheral neuropathy. Tuberculosis or other mycobacterial infection occurs in around 1.7% of the UK renal transplant population (Higgins et al, 1991). Disseminated tuberculosis occurs in around 30%, a higher proportion than non-immunosuppressed patients. The anatomical site of the tuberculosis infection may be unusual, delaying diagnosis and treatment. Mortality is high at approximately 30% (Singh and Paterson, 1998) – around ten times that seen in the general population.

The efficacy of anti-tuberculous treatment in renal transplant recipients is good, comparable to non-immunosuppressed persons with tuberculosis. Rifampicin is an inducer of the cytochrome c P450 3A4 enzyme system and

Table 3. Immunosuppressants with relevance to vascular risk

Medications	Relevance to vascular risk
Calcineurin inhibitors	Hypertension (ciclosporin > tacrolimus)
	Hyperlipidaemia (ciclosporin)
	Impaired glucose tolerance (tacrolimus > ciclosporin)
	Allograft dysfunction
	Hyperuricaemia
Corticosteroids	Hypertension
	Hyperlipidaemia
	Impaired glucose tolerance
	Weight gain
Sirolimus	Hyperlipidaemia

Table 4. Timing of infections post-transplantation

	1st month	Months 1–6	After 6 months
Bacterial	Postoperative infections (wound, respiratory, urinary, line-related) Other nosocomial infections – *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*	Uncommon bacterial pathogens: listeria, nocardia, legionella, *Mycobacterium* spp., including tuberculosis	Community-acquired pathogens, e.g. respiratory, urinary tract, *Mycobacterium* spp., including tuberculosis
Viral	Herpes simplex virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus	Cytomegalovirus, Epstein–Barr virus, varicella zoster virus, human herpes virus 6 or 7, influenza viruses, respiratory syncytial virus, adenoviruses	Cytomegalovirus, parvovirus B-19, varicella zoster virus, polyoma viruses, hepatitis B virus, hepatitis C virus, malignancy-associated viruses: Epstein–Barr virus, human herpes virus-8, papillomavirus
Fungal	Oesophageal candidiasis; disseminated candidiasis may also occur	*Aspergillus* spp., cryptococcus, candida	Cryptococcus
Parasitic	Rare at < 1 month	*Pneumocystis carinii* pneumonia, toxoplasma In patients from the tropics: strongyloides, leishmaniasis (both uncommon)	Uncommon unless relevant foreign travel occurs or patient in contact with others carrying parasites

reduces blood levels of calcineurin inhibitors, sirolimus and steroids. Unless serious disseminated infection requiring reduction in immunosuppression is present, doses should be maintained, with close monitoring of levels.

Viral

Cytomegalovirus

In a seronegative person, primary infection with CMV usually occurs between 6 weeks and 6 months post-transplantation. Symptoms include fever, night sweats and myalgia, and the treating clinician is often alerted by the combination of these non-specific symptoms with leucopenia, a transaminitis and moderate graft dysfunction. Respiratory symptoms should be taken seriously. Gastrointestinal involvement may present as bloody diarrhoea, nausea, and abdominal pain or dysphagia. CMV retinitis is well recognized, but relatively rare. If a seropositive recipient receives an organ from a seropositive donor with a different CMV strain, the clinical syndrome is less severe, and may be delayed until around 3 months (Grundy et al, 1988). Reactivation also produces this milder clinical picture. In some individuals it only delays the onset of primary CMV, which can then present 2–3 months after the end of prophylactic treatment.

Valganciclovir, now established as the mainstay of prophylaxis against CMV, is given orally and has good bioavailability (comparable to intravenous ganciclovir, superior to oral ganciclovir). Polymerase chain reaction (PCR) detection of CMV DNA is now widely used, and can help make the difficult distinction between CMV disease requiring treatment and latent CMV infection. IgM and IgG directed against CMV are used for determining prior exposure in both donors and recipients rather than as diagnostic tests. Treatment of CMV disease involves reduction in immunosuppression. The antiproliferative agent is withheld first, and this may be all that is required in milder cases. However, in the presence of marrow suppression, hepatitis, pneumonitis or gastrointestinal disease, calcineurin inhibitors should be reduced to approximately half their previous dose, and treatment with intravenous ganciclovir (through a central vein) commenced. Length of treatment can be difficult to decide, but is increasingly influenced by serial measurement of CMV DNA PCR viral load. Often 2–4 weeks intravenous therapy is needed. Relapse with recurrent CMV disease is possible (Humar et al, 1999). Both ganciclovir and valganciclovir require careful dose adjustment depending on the patient's level of renal dysfunction.

Epstein–Barr virus

Discussed under post-transplant lymphoproliferative disorder (PTLD) below.

Hepatitis viruses

Hepatitis B surface antigen positive renal transplant recipients are treated with lamivudine for 1–2 years after transplantation. Immunosuppression favours viral replication of both hepatitis B and C. Allograft survival is lower for both hepatitis C virus and hepatitis B surface antigen positive recipients. Hepatocellular carcinoma may occur in recipients positive for either hepatitis virus and can occur well after transplantation (e.g. >20 years).

Polyomaviruses

Around 60–80% of immunocompetent adults are serologically positive for polyomaviruses. BK virus normally remains in the renal tubular cells in a latent state, without apparent functional consequence. However, in the renal transplant recipient, BK virus may cause an interstitial nephritis which can be mistaken for acute rejection. Extensive replication of the virus can also cause tubular necrosis and thus allograft dysfunction. The presence of 'decoy cells' in the urine (containing viral inclusions) suggests infection but PCR for BK DNA can be performed on blood and is more specific. Treatment consists of careful reduction in immunosuppression. No specific agent has been proven to be effective although leflunomide, cidofir and ciprofloxacin have been used.

Fungal and parasitic infections

Fungal infections are commonest between 2 and 6 months post-transplantation. Fungal infections occur most commonly in the oesophagus, but are also seen in the lungs, meninges and urinary tract (Abbott et al, 2001).

Pneumocystis carinii pneumonia is a serious infection with nearly 50% mortality in renal transplant recipients. Prophylaxis (trimethoprim/sulfamethoxazole at low dose for 6 months) provides some protection against urinary tract infections as well, but the trimethoprim competes with creatinine for secretion into the tubules, raising serum creatinine without a fall in true GFR. Without prophylaxis, around 5% of renal transplant recipients will develop *P. carinii* pneumonia. It occurs between 3 and 6 months post-transplantation, but is rare after 1 year (Gordon et al, 1999). Classically oxygen saturations are normal at rest, but fall precipitously on exercise. Diagnosis is made on bronchoalveolar lavage, but serious clinical suspicion is sufficient grounds to instigate treatment as large numbers of *P. carinii* are detectable in bronchoalveolar lavage samples for weeks after treatment has commenced. High dose trimethoprim/sulfamethoxazole is used, parenterally in severe cases, in combination with steroids, which have been shown to reduce mortality (Bozzette et al, 1990).

Malignancy

Immunosuppression increases the risk of malignancy, so patients diagnosed with malignancy before transplantation must be disease free for between 2 and 5 years, depending on the type, before they can be listed for transplantation. The risk of recurrent malignancy varies with the type of malignancy. Particularly high risk of recurrence is seen with pre-transplant melanoma, multiple myeloma, invasive bladder cancer, sarcomas and non-melanomatous skin cancer. Around half of the recurrences occur in the

first 2 years post-transplantation, and recurrence rates fall off as time post-transplant lengthens (Penn, 1993).

De novo malignancy risk is also increased (Kasiske et al, 2004) (*Table 5*). Risk factors for the development of de novo post-transplant malignancy include:

- Intensive or long duration of immunosuppression
- History of cancer before transplantation
- Older age
- Solar exposure.

Skin cancers account for more than 33% of de novo malignancies in organ transplant recipients, with squamous cell carcinomas most common. Incidence ranges from 10 to 40% (Hartevelt et al, 1990). High levels of sun exposure increase the risk, as does use of azathioprine. Compared to the non-transplant population, these skin malignancies occur at a younger age, are more likely to be disseminated, more aggressive and to result in death.

Post-transplant lymphoproliferative disorder and Epstein–Barr virus

PTLD occurs in around 1.4% of renal transplant recipients (Caillard et al, 2005). It has a variable clinical presentation including classical lymphoma symptoms like night sweats, fevers and weight loss. CNS involvement occurs in around 1 in 4 PTLD patients, and extranodal involvement is common (70%, compared to 35% in non-transplant lymphoma patients). Allograft infiltration occurs in around 20%, and can be confused clinically with rejection. Around 85% of PTLD is derived from B lymphocyte lineages, and is Epstein–Barr virus (EBV) related. In the developed world, around 50% of young adults are seronegative for EBV, and are then commonly infected when they become sexually active.

PTLD may occur anywhere between 1 and 254 months post transplantation. Average onset of PTLD is around 2.5–3 years. Treatment involves reduction or elimination of antiproliferatives and calcineurin inhibitors in the first place. Further treatments include surgical excision, chemotherapy, radiotherapy, monoclonal antibodies or antivirals.

Musculoskeletal disorders

Osteoporosis

Persistent use of corticosteroids leads to loss of bone mineral density in many renal transplant recipients, although a number of steroid-free immunosuppression protocols are now in use (Hricik, 2002). Lower doses of prednisolone (e.g. ≤7.5 mg/24 hours) may not be associated with bone loss greater than expected for age and gender over time. Treatment with bisphosphonates (if creatinine clearance permits), and calcium and vitamin D supplements are used in a similar fashion to other populations. Common osteoporotic problems like pain from vertebral collapse may present to the acute medical take.

Gout

Renal transplant recipients often have a number of risk factors for gout: diuretic use, renal insufficiency and ciclosporin all cause hyperuricaemia. As well as the usual sites, gout occurs more frequently in proximal joints in renal transplant recipients, and may present less dramatically if corticosteroids are being used for immunosuppression (Clive, 2000). Colchicine, with appropriate dose reductions for the level of renal dysfunction, can be used, combined with an increased short-term corticosteroid dose. Long-term prophylaxis can be given as allopurinol (possibly with dose reduction), although the dramatic interaction of allopurinol with azathioprine, which causes profound leucopenia, should be avoided. Allopurinol is safe in combination with mycophenolate, however. Reduction or elimination of diuretics may be appropriate.

Hyperparathyroidism

Persistent tertiary hyperparathyroidism, with high calcium and inappropriately high parathyroid hormone levels, is seen in around 17% of patients at 4 years post-transplantation (Evenepoel et al, 2004). Parathyroidectomy may be required, but is often delayed until >1 year in case spontaneous resolution occurs. An increasing number of patients are taking the novel calcimimetic cinecalcet post-transplantation. Abrupt discontinuation can lead to striking rebound hypercalcaemia and should be avoided.

Avascular necrosis

Intensive use of corticosteroids, especially in the pre-ciclosporin era, resulted in high rates of avascular necrosis. It still occurs, mostly in patients who have had high dose steroids for acute rejection. Hip joints are commonly affected, but avascular necrosis is also seen in knees, shoulders, ankles, elbows and even wrists. Magnetic resonance imaging is most sensitive for detection. A sharp decline in dose, or discontinuation, of corticosteroids is not thought to help the lesion, and may jeopardize the allograft.

Neurological disease

A number of renal diseases also have neurological aspects. Polycystic kidney disease is associated with subarachnoid haemorrhage from berry aneurysms in the circle of Willis. Other examples are Von–Hippel–Lindau disease and Fabry's disease.

Table 5. Approximate relative risk of malignancies in renal transplant recipients

Risk	Type of malignancy	Approx. relative risk
Increased risk	Colon, lung, prostate, gastric, oesophagus, pancreas, ovarian and breast	2
	Testes and urinary bladder	3
Moderately increased risk	Cutaneous melanoma, leukaemia, liver and gynaecological tumours	5
	Renal	15
Greatly increased risk	Kaposi's sarcoma, skin cancer, post-transplant lymphoproliferative disorder, hepatocellular carcinoma	>20

Phosphate and magnesium disturbances

Hypophosphataemia and hypomagnesaemia are usually asymptomatic. The former can impact on bone mineral density in the long term, and contribute to insulin resistance. The latter may be related to calcineurin inhibitors or sirolimus. Intravenous supplementation is appropriate in the rare emergency situations, along with concurrent checking of other electrolytes. Longer term oral supplementation is sometimes necessary.

Post-transplantation erythrocytosis

Approximately 5–20% of renal transplant patients develop post-transplant erythrocytosis, defined as a haematocrit of >51%. This is thought to result from angiotensin II mediated stimulation of erythroid precursors. Around one fifth of patients with post-transplant erythrocytosis develop thromboembolic complications. Treatment involves blockage of the renin–angiotensin system, and venesection in appropriate cases.

Recurrent and de novo glomerulonephritis

The probability of recurrence of a patient's previous glomerulonephritis in a transplant depends on the original disease. Even where such recurrence occurs, the incidence of graft loss is similar to that for other causes of renal failure (Briganti et al, 2002). Less commonly, renal transplant recipients develop de novo glomerulonephritis. Membranous glomerulonephritis is most common, occuring in 1–2% of transplant patients.

Failing allografts

As a renal allograft reaches the end of its life, the patient may present with any of the well-known manifestations of worsening chronic kidney disease, such as hyperkalaemia, uraemic symptoms or fluid overload.

Conclusions

The increased propensity to vascular disease, infective complications and malignancy mean that renal transplant recipients are frequently admitted on the acute medical take. Immunosuppressant medications and reduced renal functional reserve contribute to make management more complex than in other patients. Hopefully this article provides some assistance in this regard but if in doubt advice can be sought at any time from the renal team in the transplant centre. BJHM

KEY POINTS

- Renal transplant recipients have a substantially increased risk of all forms of vascular disease.
- Immunosuppressive drugs increase the risk of infections by both common organisms and also opportunistic pathogens.
- Reduced immunosurveillance increases the relative risk of many forms of cancer.
- Immunosuppression dampens the inflammatory response, potentially masking symptoms and signs.
- Immunosuppressive drugs should not be omitted without clear clinical indication to do so.
- Renal transplant patients have a reduced functional renal reserve, so their serum creatinine rises notably in many acute illnesses.
- Advice is always available from the patient's transplant centre and should be sought if required.

Conflict of interest: none.

Abbott KC, Hypolite I, Poropatich RK et al (2001) Hospitalizations for fungal infections after renal transplantation in the United States. *Transpl Infect Dis* **3**: 203–11

Ansell D, Ansell D, Feest T, Byrne C (2002) *The UK Renal Registry: the fifth annual report.* UK Renal Registry, Bristol

Ashley C, Currie A (2004) *The Renal Drug Handbook.* Radcliffe Medical, Oxford

Bozzette SA, Sattler FR, Chiu J et al (1990) A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med* **323**: 1451–7

Briganti EM, Russ GR, Mcneil JJ, Atkins RC, Chadban SJ (2002) Risk of renal allograft loss from recurrent glomerulonephritis. *N Engl J Med* **347**: 103–9

Caillard S, Dharnidharka V, Agodoa L, Bohen E, Abbott K (2005) Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. *Transplantation* **80**: 1233–43

Clive DM (2000) Renal transplant-associated hyperuricemia and gout. *J Am Soc Nephrol* **11**: 974–9

Evenepoel P, Claes K, Kuypers D, Maes B, Bammens B, Vanrenterghem Y (2004) Natural history of parathyroid function and calcium metabolism after kidney transplantation: a single-centre study. *Nephrol Dial Transplant* **19**: 1281–7

Gordon SM, Larosa SP, Kalmadi S, Arroliga AC, Avery RK, Truesdell-larosa L, Longworth DL (1999) Should prophylaxis for *Pneumocystis carinii* pneumonia in solid organ transplant recipients ever be discontinued? *Clin Infect Dis* **28:** 240–6

Grundy JE, Lui SF, Super M et al (1988) Symptomatic cytomegalovirus infection in seropositive kidney recipients: reinfection with donor virus rather than reactivation of recipient virus. *Lancet* **ii**: 132–5

Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP (1990) Incidence of skin cancer after renal transplantation in The Netherlands. *Transplantation* **49**: 506–9

Higgins RM, Cahn AP, Porter D, Richardson AJ, Mitchell RG, Hopkin JM, Morris PJ (1991) Mycobacterial infections after renal transplantation. *Q J Med* **78**: 145–53

Hricik DE (2002) Steroid-free immunosuppression in kidney transplantation: an editorial review. *Am J Transplant* **2**: 19–24

Holt DW (2002) Monitoring mycophenolic acid. *Ann Clin Biochem* **39**: 173–83

Humar A, Uknis M, Carlone-Jambor C, Gruessner RW, Dunn DL, Matas A (1999) Cytomegalovirus disease recurrence after ganciclovir treatment in kidney and kidney-pancreas transplant recipients. *Transplantation* **67**: 94–7

Jindal RM (1994) Posttransplant diabetes mellitus--a review. *Transplantation* **58**: 1289–98

Kasiske BL, Vazquez MA, Harmon WE et al (2000) Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. *J Am Soc Nephrol* **11** (Suppl 15): S1–86

Kasiske BL, Snyder JJ, Gilbertson DT, Wang C (2004) Cancer after kidney transplantation in the United States. *Am J Transplant* **4**: 905–13

Ojo AO (2006) Cardiovascular complications after renal transplantation and their prevention. *Transplantation* **82**: 603–11

Penn I (1993) The effect of immunosuppression on pre-existing cancers. *Transplantation* **55**: 742–7

Schroeder TJ, Moore LW (1998) Efficacy Endpoints Conference on Acute Rejection in Kidney Transplantation: summary report of the database. *Am J Kidney Dis* **31**: S31–9

Singh N, Paterson DL (1998) *Mycobacterium tuberculosis* infection in solid-organ transplant recipients: impact and implications for management. *Clin Infect Dis* **27**: 1266–77