Update on the long-term complications of renal transplantation

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Introduction: Powerful immunosuppressive regimens have reduced rejection risk, leading to an expanding cohort of long-term kidney transplant recipients who are likely to encounter practitioners in other specialties.

Sources of data: Key review papers and primary literature identified through searches of PubMed, Google Scholar and Medline.

Areas of agreement: Death from cardiovascular disease and malignancy remain the chief causes of transplant loss. Risk factors and phenotypes for these differ from the general population.

Areas of controversy: Many guidelines for renal transplant recipients are based on extrapolation from studies on non-transplant cohorts and may not be appropriate. Emerging studies demonstrate that established interventions in the general population are less efficacious in transplant recipients.

Growing points: The influence of immunosuppression on the development of complications.

Areas timely for developing research: Markers to guide individualized optimal immunosuppression and predict the development of complications would allow for targeted early intervention.

Keywords: kidney/renal/transplantation/long-term/cancer/malignancy/transplant dysfunction/cardiovascular/complications

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Background

Transplantation has brought improved survival and quality of life to patients with end-stage renal disease. Since 1960, there has been a steady increase in short-term patient and transplanted kidney (termed ‘graft’) survival; deceased donor one-year graft survival in the UK was 94% for the period 2007–2010.¹ Recent American registry data demonstrate diverging survival of recipients of organs from deceased and living donors, respectively: greater than 96% for both at one year,
87 versus 93% at five years and 74 versus 83% at 10 years. Despite advances in preventing the main causes of short-term graft and patient loss (antimicrobial prophylaxis, early diagnosis of post-operative complications and increasing potency of immunosuppression reducing acute rejection), long-term patient survival rates in the USA appear to have plateaued or even decreased since 1991. However, mean donor and recipient age have increased, and there is increasing utilization of suboptimal kidneys from deceased donors. It remains contentious whether these groups negatively impact on long-term survival statistics. Early factors that have been suggested to predict long-term transplant outcome are shown in Figure 1.

Death with a functioning graft (DWFG) accounts for 47% of all transplant loss after 10 years. Retrospective analyses of long-term outcome from randomized trials, and registry data have highlighted cardiovascular disease followed by malignancy as the top causes of morbidity and DWFG. However, while death from cardiovascular disease in renal transplant recipients (RTRs) appears to be declining, mortality from malignancy is increasing.

The increasing number of transplants worldwide is resulting in a growing cohort of long-term transplant recipients (179,361 RTR in the USA in 2010); due to the limited number of transplant nephrologists, these patients are increasingly likely to encounter practitioners in other...
specialties. This review will focus predominantly on current issues regarding the two complications mentioned earlier as they are the main influence on long-term outcomes relevant to generalists.

Cardiovascular disease

Introduction

Mortality from cardiovascular disease accounts for 40–50% of deaths after the first-year post-transplant.\(^8\) Cardiovascular mortality is up to 20 times higher than age- and sex-matched members of the general population, but is significantly less than that of the dialysis population, even accounting for selection bias.\(^8\) The Patient Outcomes in Renal Transplantation (PORT) study retrospectively analysed cardiovascular events in over 23,000 RTR and demonstrated a cumulative incidence of fatal or non-fatal MI, coronary revascularization and sudden cardiac death of 7.6% by 5 years post-transplant.\(^10\)

Predicting risk

The Framingham Risk Score has consistently demonstrated an underestimation of cardiovascular risk when applied to transplant recipients, even with insertion of putative new factors, such as uric acid and highly sensitive C-reactive protein.\(^10,11\) While the majority of cardiovascular disease in the general population is due to atherosclerosis, patients with impaired renal function display an altered phenotype. Post-mortem studies of patients with end-stage renal failure demonstrate medial calcification in vessels and left ventricular hypertrophy, likely accumulated over a number of years as renal function declines. Registry data indicate that sudden cardiac death in those on dialysis has an annual incidence of 5–6%\(^9\); compared with <1% in the general U.S. population, whereas acute MI accounted for less than 5% of deaths in the same group. There is a poor correlation between traditional modifiable risk factors and cardiovascular events in RTR, suggesting a reduced relative contribution in the transplant cohort. Factors that have been found to be predictive of cardiovascular events include increasing age, male sex, transplant function, proteinuria, pre-transplant diabetes or cardiovascular disease and duration of dialysis. Preserving transplant function is a key intervention in preventing cardiovascular disease in this cohort; a recent post-hoc study analysis suggested a 16% increased risk of cardiovascular death for every 5 ml/min/1.73 m\(^2\) decrease in eGFR below 45 ml/min/1.73 m\(^2\).\(^12\)
An additional risk factor in this population is immunosuppression, which has been associated with an adverse risk profile (shown in Table 3). Calcineurin inhibitors and corticosteroids increase blood pressure, whereas corticosteroids, calcineurin inhibitors and mTOR inhibitors are associated with dyslipidaemia. The relative contribution of individual immunosuppressive agents to cardiovascular risk cannot be easily assessed in clinical studies due to combination therapy. Belatacept, a selective co-stimulation blocker, shows promise in being associated with lower non-HDL cholesterol and triglyceride levels and a lower systolic and diastolic blood pressure compared with ciclosporin therapy. However, higher secondary rates of post-transplant lymphoproliferative disorder (PTLD) and acute rejection may reduce the benefit due to an increased cardiovascular risk.

The cardiovascular disease exhibited by RTR represents an amalgamation of ‘traditional’ risk factors, risk factors related to chronic kidney disease and dialysis and those acquired post-transplantation. Risk factors that may contribute to the cardiovascular risk are summarized in Figure 2 and demonstrate a number of potentially modifiable elements at all stages of kidney disease. A full review that addressed the evidence for post-transplant risk factors was published recently. A full review that addressed the evidence for post-transplant risk factors was published recently. There is an overlap between these, for example, most RTRs are left with a degree of impaired transplant function that may deteriorate and ultimately require dialysis.

![Fig. 2](image-url)
**Intervention**

Few algorithms exist for accurately identifying RTR at particularly high risk of events, in order to guide primary prevention. Risk calculators based on retrospective analysis of two studies have been published, but neither externally validated, thus it is difficult to assess the impact of different immunosuppressive regimes and regional genetic variation and thus its applicability to other renal transplant populations, including those excluded from the trials.\(^{10,14}\) Prospective development and validation of a predictive cardiovascular risk score in RTR is ongoing.\(^{15}\)

The use of cardioprotective therapy in RTR is diminished compared with the general population, though this is improving.\(^{16}\) Following myocardial infarction (MI), transplant recipients are significantly less likely to receive revascularization using percutaneous coronary intervention (PCI) and a trend towards decreased likelihood of bypass grafting.\(^{17}\) Retrospective analysis of the PORT study suggests a reluctance to use angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockade with use in only a quarter of RTR in the four months post-transplant (representing a decrease in use compared with pre-transplant) and a low incidence of use in diabetics.\(^{16}\) Only 75 and 60% of RTR with a history of previous MI were prescribed aspirin and a statin, respectively. Despite a 70% prevalence of hypertension in the study, and meta-analysis evidence suggesting a reduction in risk of transplant loss,\(^{18}\) only 42% were taking a dihydropyridine calcium channel blocker. With the exception of statins, prescribing of these therapies did not significantly change with increasing time post-transplant. Suboptimal primary and secondary prevention in RTR may reflect the reluctance of the treating physician to instigate therapy for fear of transplant dysfunction (ACE inhibitors- or contrast-based interventions), adverse reactions or drug interactions.

Managing cardiovascular disease in the transplant recipient is limited by the paucity of specific evidence regarding interventions; guidelines are extrapolated from general or chronic kidney disease population studies. RTR represents a unique cohort and it is likely that pooled endpoints of cardiovascular disease, based on a predominance of coronary arterial disease, in trials involving other populations fail to take into account the altered pattern of cardiovascular morbidity and mortality in this group. Data from the ALERT study exemplify this; the clinical impact of lowered LDL-cholesterol in the arm receiving fluvastatin was less than that seen in the general population. Study extension was required, with an increase in statin dose and post-hoc analysis, to demonstrate a reduced rate of cardiovascular events. Key guidelines for the management of cardiovascular risk factors are summarized in Table 1. ACE inhibitors or angiotensin II receptor blockers (ARBs) are of particular
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Target</th>
<th>Therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>&lt;130 mmHg systolic, &lt;80 mmHg diastolic</td>
<td>Any antihypertensive (typically dhCCB or ACEi first) ACEi/ARB as first-line therapy if proteinuria (with monitoring of renal function, see main text) Avoid non-dihydropyridine CCB (such as verapamil and diltiazem) if on calcineurin inhibitor</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>Fasting triglycerides ≤ 1.65 mmol/l LDL-C &lt; 2.59 mmol/l Non-HDL-C &lt; 3.36 mmol/l</td>
<td>Dietary modification Ezetimibe Statin (low dose if on CnI) Fibrates (low dose if on CnI)</td>
</tr>
<tr>
<td>Diabetes and NODAT</td>
<td>HbA1c 7.0–7.5%</td>
<td>No guidelines for NODAT specifically—options given are as for type 2 diabetes and should be individualized to each patient. First line: dietary advice and weight reduction. Liaise with the transplant team to wean steroids and/or switch away from CnI Second line: oral therapy (individual then in combination): metformin (if eGFR &gt; 30 ml/min/1.73 m²) Sulphonylureas can be used cautiously (potential CnI interaction and danger of hypoglycaemia with falling eGFR) DDP4 inhibitors (e.g. sitagliptin) generally considered safe GLP-1 agonists safe generally if eGFR &gt; 30 ml/min/1.73 m² Third line: insulin therapy</td>
</tr>
<tr>
<td>Obesity</td>
<td>BMI &lt; 30 Abdominal circumference &lt; 88 cm (women) or &lt; 102 cm (men)</td>
<td>Lifestyle advice Orlistat Bariatric surgery</td>
</tr>
<tr>
<td>Smoking</td>
<td>Screen annually for tobacco use</td>
<td>Counselling Nicotine replacement therapy</td>
</tr>
<tr>
<td>Gout</td>
<td>Hyperuricaemia defined as &gt; 0.36 mmol (women), &gt; 0.42 mmol (men)</td>
<td>Avoid allopurinol if on azathioprine Avoid NSAIDS generally Colchicine or short-course prednisolone for acute attack</td>
</tr>
<tr>
<td>General</td>
<td>Risk assessment annually</td>
<td>Aspirin 75 mg daily if diabetic, previous CVD. Consider aspirin if CVD risk factors (&gt; 40 years old, albuminuria, smoking, dyslipidaemia or family history)</td>
</tr>
</tbody>
</table>

‘Therapeutic options’ indicate pharmacological interventions that are generally considered safe in RTR without any other contraindication. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker (dhCCB, dihydropyridine calcium channel blocker, such as amlodipine or nifedipine); CnI, calcineurin inhibitor. Proteinuria is defined in this instance as > 1g/day urinary protein loss.
value in the treatment of hypertension, proteinuria and in established impaired left ventricular function. Caution must be taken in high-risk patients (such as those with diabetes) where transplant renal artery stenosis may rarely cause a rapid decline in transplant function. Current guidelines recommend that renal function should generally be checked within a month of ACE of ARB commencement\textsuperscript{19}—we would suggest in transplant patients 7–10 days: a rapid decline in graft function (>15\%) would mandate cessation and investigation of renal vasculature.

Registry data suggest death rates from cardiovascular disease are decreasing.\textsuperscript{8} This may be due to increased use of primary and secondary prevention and increased cardiovascular screening and intervention in potential transplant recipients.

More prospective studies with cardiovascular endpoints to assess the impact of interventions specifically in RTR are needed; however, it is difficult to see this in the near future given the length of follow-up and cohort sizes required to achieve power. Elucidation and validation of surrogate markers predictive of future cardiovascular disease are perhaps more realistic and would make further studies more practical.

## Malignancy

### Introduction

Rates of malignancy now compete with cardiovascular disease as the leading cause of DWFG; accounting for 27\% of deaths in RTR.\textsuperscript{8} This reflects increasingly powerful induction and immunosuppressive regimes along with increasing duration of immunosuppression due to improved survival beyond one year. Immunosuppression potentiates tumour development through a number of pathways including decreased immunosurveillance, direct oncogenic effects and impaired tumour- and virus-specific immune responses. The only randomized trial to look at cancer as an outcome compared two trough ciclosporin targets and found about a 20\% reduction in cancer incidence in those maintained at a lower level at 5.5 years post-transplant.\textsuperscript{20} Retrospective analysis of an Australian study suggested no difference in malignancy risk between various immunosuppressive regimes incorporating azathioprine, steroids and/or ciclosporin at 20 years follow-up.\textsuperscript{21}

Some cancers are significantly overrepresented in the post-transplant cohort, some due to their association with renal failure, whereas others have a similar incidence in the general population (Table 2). Renal cell carcinoma (RCC) is an unusual cause of end-stage renal failure, but malignant cystic change is often seen in native non-functioning kidneys. Cutaneous malignancy represents the majority of all cancer seen post-
transplant, of which 95% is non-melanoma skin cancer (NMSC). Other overrepresented malignancies include lymphoma (encompassing PTLD) and Kaposi’s sarcoma, with oncogenic viral aetiologies. While NMSC is a major cause of morbidity and mortality in the post-transplant cohort and relatively common in the general population, PTLD is limited to the transplant population, and therefore, the general physician may be unlikely to consider it in a differential diagnosis; for this reason, PTLD and NMSC will be the focus of this section.

An excess burden of cancers associated with oncogenic viruses in patients with HIV offers some clues into the specific role of immunosuppression. An excess burden of skin, colorectal, lip and thyroid cancer in transplant recipients compared with those immunosuppressed through HIV/AIDS may relate specifically to immunosuppressive carcinogenicity and metabolic DNA damage.

The effectiveness of intensified screening strategies for cancer in the RTR population is not clear. It is generally presumed that screening is
<table>
<thead>
<tr>
<th>Complication</th>
<th>Calcineurin Inhibitors</th>
<th>Anti-metabolites</th>
<th>mTOR inhibitors</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclosporin</td>
<td></td>
<td>Azathiaprine</td>
<td>Sirolimus</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td>Mycophenolate</td>
<td>Everolimus</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased: blood pressure, lipid concentrations, risk of NODAT</td>
<td>No effect</td>
<td>Markedly increased lipid concentrations</td>
<td>Increased: blood pressure, lipid concentrations, risk of NODAT</td>
</tr>
<tr>
<td>Carcinogenesis</td>
<td>Widely accepted carcinogen</td>
<td>No definite mutagenic or carcinogenic effects demonstrated in oral form in humans</td>
<td>Widely accepted carcinogen</td>
<td>Animal and in vitro studies suggest anti-tumour effects. Some evidence in humans.</td>
</tr>
<tr>
<td>Other</td>
<td>Pancreatitis Gingival hyperplasia</td>
<td>GI effects Insomnia Headache</td>
<td>Diarrhoea Teratogenic</td>
<td>Oedema rash pneumonitis Proteinuria GI effects</td>
</tr>
<tr>
<td>Transplant toxicity</td>
<td>Sulphonylureas ndhCCB Amiodarone</td>
<td>Proton-pump inhibitors</td>
<td>Allopurinol</td>
<td>Oral iron Antacids (if taken simultaneously)</td>
</tr>
<tr>
<td>Common Interactions</td>
<td>Macrolides</td>
<td>Agranulocytosis</td>
<td>Macrolides</td>
<td>Nil</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>A major contributor to non-adherence. Transplant recipients are usually on at least five different medications. Avoid unnecessary medication and regularly reinforce the importance of compliance.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>All transplants have impaired function (even if biochemically normal). Avoid NSAIDS and aminoglycosides.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The list of interactions is not exhaustive and appropriate literature should be consulted before commencing any new therapy in a patient on immunosuppression. ndhCCB, non-dihydropyridine calcium channel blocker. Carcinogenicity refers to the direct carcinogenic effects of the drug, rather than carcinogenicity due to immunosuppressive effects.
beneficial in RTR where it has been shown to be of benefit for the general population, though little randomized controlled evidence exists for the benefit of screening for any malignancy in RTR specifically.

**Non-melanoma skin cancer**

Squamous cell (SCC), basal cell (BCC) and rarer malignancies such as cutaneous neuroendocrine (Merkel cell) carcinoma are increased in frequency in RTR. The disproportionate increase in SCC causes a reversal of the SCC: BCC pattern seen in the general population. SCC has a wide global variation in incidence, which is unsurprising given that UV exposure and sunburn are strong risk factors for SCC development. UV radiation is thought to directly damage DNA and reduce local tissue tumour surveillance. Cumulative incidence ranges from 20–30% in the UK to over 70% in Australia by 10 years after transplantation, representing a 65- to 200-fold increased risk compared with the general population. Ethnic differences, beyond that of skin type, also play a role, as Japanese RTR experience a markedly lower incidence of NMSC. Other risk factors are similar to that in the general population, such as increasing age and fair skin. Human papilloma virus (HPV) is often found within NMSC in both the general population and RTR, and is thought to play a role in oncogenesis, though the specific mechanisms have not been elucidated.

NMSC in transplant recipients occurs at a younger age and is more aggressive, with a 5–8% rate of SCC metastasis (<5% in the general population). Both the incidence of NMSC and risk of SCC metastasis are proportional to immunosuppression duration and dosage; the annual NMSC incidence in a UK cohort rose from 3% in those less than 5 years post-transplant to 11% in those over 10 years post-transplant. Due to the generalized pre-malignant changes found throughout the dermis in RTR (termed ‘field cancerization’), previous SCC is a predictor for the development of further multifocal NMSC; up to 88% of Western European RTR may develop a second tumour within 5 years, with a median interval of 10 months. SCC has also been demonstrated to be a predictor of non-cutaneous cancer. There should be a low threshold of suspicion for malignancy when a transplant recipient reports the development of a new skin lesion and RTR considered to be high-risk should undergo regular dermatological screening. RTR should be educated and encouraged to self-examine frequently. Attempts to identify those at risk have led to studies exploring objective immunological and clinical markers of future SCC development to guide screening. A predictive index for time to first NMSC post-transplant based on clinical markers such as skin type was
developed in an Australian cohort, whereas low NK-cell and high regulatory T-cell numbers following SCC diagnosis were found to be predictive of earlier tumour recurrence in RTR.\textsuperscript{29,30}

The immunosuppressive mTOR inhibitors have anti-tumourigenic and anti-angiogenic effects \textit{in vitro}.\textsuperscript{31} Two recent clinical trials, comparing sirolimus conversion versus calcineurin inhibition continuation in RTR with cutaneous SCC, found a lower number of subsequent SCC in the conversion arm.\textsuperscript{32,33} However, delayed time to recurrent SCC was significant only in those with a history of a single SCC and not those with multiple previous tumours. mTOR inhibitors were associated with a high rate of adverse effects in both studies, including oedema, dyslipidaemia and pneumonitis, leading to a significant discontinuation rate that may restrict uptake. There may be a role for mTOR inhibitor conversion earlier in RTR with single cutaneous SCC lesions.

Transplant recipients are often poorly compliant with measures such as sunscreen due to lack of education, and practical reasons such as the time required for application. A recent study analysed factors in self-reported use of sunscreen in transplant recipients without a history of skin cancer and provided a simple clinical counselling model to aid provision of tailored education to high- and low-risk groups.\textsuperscript{34} RTR should be strongly discouraged from smoking, as this is a risk factor for NMSC and many other malignancies.

Recent guidelines from the American Academy of Dermatology have reviewed treatment options for NMSC.\textsuperscript{35} Mohs micrographic surgery aiming for clear margins is the treatment of choice in biopsy-proven malignancy. Topical therapies include 5-fluorouracil, NSAIDs (such as diclofenac), imiquimod, cryosurgery or photodynamic therapy in areas of pre- or early-malignant change. Adjuvant radiotherapy may play a role in selected cases. This is usually undertaken in conjunction with a reduction in immunosuppression if NMSC are recurrent or metastatic, coordinated by the transplant team.

Systemic retinoids have been demonstrated in small short-term prospective and retrospective long-term studies to play a role in the secondary prevention of NMSC, but are teratogenic and can be poorly tolerated at higher doses.\textsuperscript{36,37} Rebound NMSC development may occur if retinoids are stopped.

\textit{Post-transplant lymphoproliferative disorder}

PTLD is a heterogeneous disorder that covers a spectrum of lymphoproliferation. The incidence of PTLD in the USA is 1–5% following adult renal transplant; this is lower compared with other solid organ
transplantation due to the lower cumulative dosage of immunosuppression. PTLD in RTR frequently develops later than other solid organ transplants (where it is predominantly an early complication); this may also relate to burden of immunosuppression.\textsuperscript{38} RTR at specifically increased risk are those who are Epstein–Barr virus (EBV) naive at transplant (especially if the donor is seropositive, with up to a 30-fold increased risk) and those who receive T-cell depleting therapy. PTLD (80\%) is associated with EBV and usually arises from B-cells; 15\% derive from T-cell lineages and the remainder NK-cell.\textsuperscript{38} EBV-negative and non-B-cell-derived PTLD usually are monomorphic and have a poor prognosis.

Up to 95\% of adolescents and young adults in the developed world are seropositive for EBV. Following primary B-cell infection, the viral genome remains as an episome in host DNA. In immunocompetent individuals, subsequent viral proliferation is inhibited by virus-specific T-cell-mediated responses. Subsequent depletion of T-cell populations (depleting antibodies) or inhibition of T-cell responses (calcineurin inhibitors) following solid organ transplantation allows polymorphic expansion of infected B-cells, which may progress to a monomorphic lymphoma-like malignancy. A case–control study found use of EBV viral prophylaxis was associated with an 83\% decreased incidence of PTLD;\textsuperscript{39} use of antivirals following the development of PTLD has not been as convincing.

Initial symptoms may be vague and therefore present through primary care or the emergency department; there should therefore be a high index of suspicion for this disease in those at high risk. Frequent extranodal sites are the GI tract, lung, skin and CNS. Presentations can include pyrexia of unknown origin, weight loss, dyspnoea, lymphadenopathy or abdominal symptoms such as non-specific pain, diarrhoea or intestinal obstruction; neurological involvement (in 30\%) may manifest in behavioural changes or focal neurology. If suspected, assessment of extent of disease radiologically, EBV viral load quantification and tissue diagnosis are key.

PTLD progression is classified according to WHO criteria (early-lesion, polymorphic, monomorphic and Hodgkin lymphoma-like disease); histology guides both treatment and prognosis. In high-grade lymphoma, one-year survival is about 50\%, whereas the prognosis is significantly better in early-lesion or polymorphic disease; regression often occurs simply with reduction of immunosuppression. Poor prognostic factors in retrospective studies include multifocal disease, CNS involvement, increasing age and male sex.

The heterogeneity of PTLD and paucity of prospective studies means no consensus exists regarding treatment protocols. Gradual reduction of immunosuppression (while monitoring transplant function) forms the mainstay of treatment in all disease; adjuvants to this in more
aggressive subtypes include use of rituximab, surgery and chemoradiotherapy; these are discussed in more detail elsewhere.  

Other complications

While malignancy and cardiovascular disease represent the main causes of DWFG, other complications impact upon quality of life and morbidity.

Infection

The greatest risk for infection in RTR is in the immediate post-transplant period due to the high level of immunosuppression, although incidence of this has fallen significantly with improvements in antimicrobial prophylaxis. Vigilance for opportunistic infection is required following treatment for acute rejection, when immunosuppression is usually sharply increased. The main sources of infection in RTR are community acquired respiratory and urinary infections. Atypical infections such as mycobacteria and fungal infections remain chronically overrepresented. Mycobacterial infection has a 1% incidence in Western Europe; generally, this is reactivation of latent TB (from either donor or recipient) though the risk of this appears to be reduced by the prophylactic use of isoniazid post-transplant in those considered high-risk. The treatment of infection generally requires a longer course, and is more likely to result in admission to hospital for intravenous therapy, compared with non-transplant cohorts.

Renal Association guidelines recommend that RTRs are vaccinated against pneumococcus (5 yearly), influenza (annually) and hepatitis B in addition to the usual schedule of vaccination (http://www.renal.org/Clinical/GuidelinesSection/Post-operative-Care-Kidney-Transplant-Recipient.aspx, 18 April 2013, date last accessed). Live vaccines should be absolutely avoided post-transplant. Ideally, vaccination should be administered in anticipation of transplant, as the immune response while on immunosuppression is likely to be suboptimal. Varicella vaccination is given to those who are seronegative pre-transplant to reduce the risk of subsequent viraemic complications with immunosuppression.

Infective endocarditis is more common in RTR, though is still relatively infrequent. Current UK guidelines do not recommend routine prophylaxis against endocarditis during invasive procedures in transplant recipients. However, it should be on the differential diagnosis list in transplant recipients presenting with suggestive signs or symptoms.
Transplant failure

The causes and investigation of the chronically failing transplant is beyond this review, falling primarily under the remit of the transplant physician, and has been recently reviewed elsewhere. However, the preservation of transplant function is a paramount aspect of long-term care of these patients as failure of the graft and a return to dialysis is associated with severe emotional and physical sequelae, resulting in reduced patient survival.

RTR with failing or failed transplant (TF) demonstrate impaired quality of life and more depressive symptoms compared with patients on dialysis who were never transplanted (TN); TF also have a 50 and 150% increased risk of mortality from cardiovascular and infectious disease, respectively. The same study highlighted poorer achievement of serological targets, such as haemoglobin and parathyroid hormone levels, and increased likelihood of dialysing through a line rather than arteriovenous fistula or graft in TF compared with TN. Previous studies have demonstrated a lack of benefit from starting dialysis early in CKD and while there is guidance about the timing of dialysis in patients with CKD, no guidelines exist for RTR with a failing transplant. Similarly, no evidence exists to guide optimal reduction or cessation of immunosuppression in these patients.

Bone disease

All patients receiving a renal transplant will have accumulated bone damage due to mineral bone disease (MBD) pre-transplant, and this may become relevant again with progressive transplant dysfunction. Bone disease contributes to the risk of cardiovascular disease and transplant loss. Although transplantation may stabilize MBD progression, RTR have a 15–44% incidence of post-transplant osteoporosis and a 34% increased fracture risk compared with the dialysis population in the first six months; the risk declining by 1% per month thereafter. It is likely that steroids and calcineurin inhibitors make a significant contribution.

There is a lack of good quality trial data to inform guidelines regarding post-transplant bone therapy. While both vitamin D supplementation and bisphosphonates have been suggested to preserve bone density in various studies, an effect on clinical outcomes has not been demonstrated. In the absence of clear evidence to support pharmacological intervention post-transplant, optimal management of MBD prior to transplantation remains the main evidence-based intervention to reduce morbidity.
Mental health

Depression and anxiety is endemic within the RTR cohort with an estimated incidence of 22% and is associated with poorer transplant outcomes, risk of death and higher rates of medication non-adherence. Depression is underdiagnosed and poorly treated in RTR. While selective serotonin reuptake inhibitors are not contraindicated in RTR, some (such as fluoxetine) may increase plasma ciclosporin levels. Citalopram is generally considered safe to use. Psychotherapy may play a role, with lower Beck Depression Inventory scores following both group and individual psychotherapy in an RCT. There is no increase in the rate of hospitalization for psychosis in RTR compared with the general population.

Conclusion

The combination of comorbidity related to chronic kidney disease and the influence of chronic immunosuppression post-transplantation result in a tendency towards atypical presentations of cardiovascular and neoplastic disease, requiring a high index of suspicion amongst the managing clinical team.

Immunosuppression is a complex issue as patients are on multiple agents. Typically, management of the immunosuppressive regimen is primarily the remit of nephrologists; however, complications of therapy often leads these patients to present to other practitioners (Table 3). The complex therapeutic regimen frequently results in polypharmacy and there is a substantial risk of drug toxicity. It is essential to carefully consider drug interactions when commencing new medication in transplant recipients.

Optimal management of the transplant patient reflects a delicate balance between over-immunosuppression (manifesting in the development of infection, cancer or cardiovascular disease) and the development of rejection through inadequate dosage. Frequently, the impact of over- or under-immunosuppression is subclinical initially, and by the time that biochemical or clinical changes are seen, and immunosuppression reduced, the damage may be irreversible. A key objective to guide dosing of immunosuppression is the need to establish independent markers of immunosuppressive effect, which may enable minimization prior to the development of complications. Unfortunately, no current immunological or clinical marker is sufficiently robust to be used in clinical practice.

Transplantation is a major success of modern medicine and revolutionizes the lives of patients with end-stage renal disease. Despite the risk
of long-term complications, RTR with functioning transplants can expect to live longer than their counterparts on dialysis. Clinicians from a wide range of specialties can consequently expect to see an increasing number of kidney transplant recipients, and should be prepared to deal with complications of their immunosuppressed state, underlying kidney disease and immunosuppression itself.

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**Conflict of Interest**

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**References**