Medical Complications After Kidney Transplantation: Late

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Abstract

Over the years, the length of stay post-kidney transplantation (post-KT) has significantly reduced, leading to most of the post-KT care in an outpatient setting. With introduction of current immunosuppression rate of early rejection has declined, but inherent side effects in the long term have escalated. Hence, the long-term graft dysfunction and graft loss among post-KT patients have not changed significantly. Furthermore, the new kidney allocation policies and increased use of high kidney donor profile index (KDPI) kidneys have pushed the boundaries further, leading to new challenges in the management of post-KT recipients. These KT recipients, who have already been dealing with problems related to comorbidities prior to KT, now have to face new challenges resulting from the effects of immunosuppression. The type of comorbid illnesses post-KT determines the morbidity, as well as their short- and long-term patient and graft survival outcomes. This chapter summarizes late post-KT medical complications, focusing on the importance of early diagnosis and efficient management of these complications in the outpatient setting in improving outcomes. The goal is to identify causes of graft dysfunction, graft loss, and patient mortality post-KT and to devise strategies to improve patient and graft survival.

Keywords

dev- novo DSA · Surgical complications ·
Aretial thrombosis · Mortality ·
Hyperlipidemia · Hypertension ·
Cytomegalovirus · Post transplant ·
Lymphoproliferative disease · Post transplant
diabetes mellitus · Tertiary
hyperparathyroidism · Post transplant
erthrocytosis · Recurrent and dev novo
glomerular disease · CKDT · Allograft
nephrectomy

Introduction

Renal transplantation is the most successful and frequently performed form of organ replacement and has improved quality and survival in chronic kidney disease (CKD) and/or end stage renal disease (ESRD) population. The short- and long-term graft and patient survival rates of renal transplantation are superior to those for liver, heart, and lung transplantation (Rana et al. 2015). Earlier in the history of renal transplantation, length of hospital stay for recipients was approximately 1 month for postsurgical care and immunosuppression administration. Improvements in surgical technique, immunosuppressive drugs, and medical management led to progressive reductions in morbidity and mortality, which allowed a steady decline in hospital stay. Average length of stay for uncomplicated renal transplantation patients now is less than a week after surgery. Transplant teams now have a detailed understanding of potential medical or surgical problems encountered during the early postoperative period (Ronco, Critical care nephrology textbook, 2nd edition).

Improvements in short-term patient and graft outcomes using better surgical techniques and more potent immunosuppressive drugs do not translate to better long-term outcomes, though. The following factors may play a role in the lack of improvement in long-term outcomes post-KT: the use of kidney allografts from high KDPI donors, occurrence of polyoma virus nephropathy, goals of immunosuppression, incomplete functional recovery after rejection episodes, and chronic inflammatory changes in the kidney allograft. Other factors such as cardiovascular disease, infections, and malignancies may also shorten patient survival and, therefore, may reduce the functional life of a kidney allograft (Meier-Kriesche et al. 2004a, b; Mannon 2004).
Short-Term Complications and Management

Medical Complications

Early graft dysfunction occurring during the first few weeks post-KT is more commonly related to delayed allograft function secondary to ischemic acute tubular necrosis. Rejection typically does not develop before 7–10 days after surgery unless there are preformed antibodies against donor antigens that have been present prior to KT. The following are predisposing factors to development of early acute rejection: presence of preformed donor-specific antibodies (DSA), ABO mismatches, and prior sensitization. Rarely, patients with unacceptable antigens (e.g., de novo DSA), which were not defined preoperatively, may be at risk for early acute rejection. Other causes of early allograft dysfunction include: volume depletion due to overzealous use of diuretics or ultrafiltration with hemodialysis. Furthermore, the use of kidney allografts from high kidney donor profile index (KDPI) or recurrent kidney disease in the allograft, i.e., atypical hemolytic uremic syndrome (aHUS) and recurrent focal segmental glomerulosclerosis (FSGS), may increase the risk of allograft dysfunction. Calcineurin inhibitor (CNI) toxicity, thrombotic microangiopathy (TMA), or nephrotoxic agents should be sought when renal dysfunction cannot be explained. Angiotensin-converting enzymes inhibitors (ACE-I)/angiotensin receptor blockers (ARBs) should be delayed in early posttransplantation period particularly in volume-depleted patients. BK viremia, hypertension, noncompliance, ongoing humoral injury, new renal disease, and post-transplant diabetes can also lead to early and delayed graft dysfunction (Djamali et al. 2006).

Causes of short- and long-term graft dysfunction

Pre-renal
- Decreased effective circulating volume
- Volume contraction
- Congestive heart failure
- Liver failure
- Renal transplant artery stenosis

Renal
- Urinary tract infection and/or pyelonephritis
- Acute rejection (prior sensitization/histocompatibility mismatch)
- Acute interstitial nephritis
- Acute tubular necrosis
- Recurrent/de novo glomerular disease

Postrenal
- Hydronephrosis
- Late allograft loss
- Chronic allograft nephropathy (CAN)
- CNI nephrotoxicity
- Polyoma (BKA) virus nephropathy
- Recurrent/de novo glomerular disease
- Chronic rejection (immunologic)
- Acute rejection
- Patient death with functioning graft
- Cardiovascular disease
- Infectious complications
- Malignancies
- Others

Surgical Complications

Most surgical complications may be encountered after discharge from hospital but seldom are seen 1 month after transplantation. Potential surgical complications post-KT are listed below:

Short- and long-term surgical and urological complications after renal transplantation

Hematomas
- Renal artery or vein thrombosis
- Deep vein thrombosis
- Arteriovenous fistulas and pseudoaneurysms
- Urinary obstruction
- Urinary leaks
- Ureteral strictures
- Lymphocele
- Infection and abscess
- Renal artery stenosis
- Infarction
- Renal calculi
- Renal cancer
- Wound infection

Drugs: CNI, ACE-I, ARB, NSAIDs
Gastrointestinal complications (like Ogilvie Syndrome or pseudo-obstruction)

Localized hematomas can be common and may arise within days after surgery or may develop at any time due to allograft biopsy or trauma. Large hematomas (requiring four or more units of blood transfusion within 48 h) that are rapidly expanding or causing obstruction of vessels or the ureter should be evacuated immediately along with repair of bleeding vessel. Late profound hematomas can result from rupture of mycotic aneurysm. Old hematomas found during an evaluation of fever may require aspiration to rule out infection. The diagnosis is typically made with ultrasound or computed tomography. Pre-transplantation coagulation parameters and medications should be paid special attention.

Arterial thrombosis often occurs within 2–3 days posttransplantation, mostly in patients with thrombotic tendencies, multiple renal arteries, or significant atherosclerosis. Venous thromboses typically develop in the early post-KT period as well as may develop from renal vein kinking, anastomosis stenosis, hypotension, hypercoagulable state, and acute rejection. These usually present with loss of allograft function, acute kidney injury, hematuria, or pain over the allograft. It is best diagnosed with Doppler ultrasound. If there is no flow, urgent surgery should be performed and patients with tendency for thrombosis should be anticoagulated in the perioperative KT period. For venous thrombosis, urgent thrombectomy with revision of anastomosis should be attempted. Renal transplant patients are at moderate risk for developing deep vein thromboses. If present, patient may require 3–6 months of anticoagulation, starting with heparin and later bridged to coumadin.

Arteriovenous fistulas or pseudo-aneurysms are usually complications of allograft biopsy or caused by partial disruption of an arterial anastomosis. These problems may develop at any time after first postoperative week. Most centers delay renal biopsies until after the first week, because the risk of complications is greater and rejection is seldom seen before the first week. These lesions are usually asymptomatic but may cause mild to severe hematuria and hypotension. The diagnosis can be made with Doppler ultrasound, but magnetic resonance imaging may be needed in technically difficult cases. Most arteriovenous fistulas and pseudo-aneurysms can be managed conservatively, but progressively expanding pseudo-aneurysms may require embolic therapy such as absorbable gelatin sponges (gel foam) or steel coils.

Urinary leaks may be result of distal ureteric ischemia as allograft ureter receives blood supply solely from renal artery. Stented ureteric anastomosis to bladder has low incidence of urinary leaks.

**Patient Mortality**

The causes of death after transplantation are listed in Table 1 (Morales et al. 2012). During the first year, the risk of death due to infection or hemorrhage is greater; the late mortality risk is greater for malignancy and other causes. Cardiovascular and cerebrovascular disease is more common in patients older than 60 years of age and is rare in those 25 years of age or younger. During the early or late periods, mortality is strongly associated with number and type of comorbid illnesses. The greatest mortality occurs in older patients with significant comorbidity who receive higher KDPI organs.

**Long-Term Complications and Management: 1 year Posttransplantation**

The long-term follow-up of post-KT recipients entails continued management of comorbid illnesses, disease progression, and KT associated medical problems. This would require a collaborative effort between the transplant center, community nephrologist, and primary care physicians. The suboptimal long-term outcomes post-KT may be attributed to the use of kidney allografts from high KDPI donors, BK viremia, under immunosuppression, and chronic allograft nephropathy (CAN). In recent years, there were several
Medical Complications After Kidney Transplantation: Late

Table 1 Causes of death after transplantation based on age group (5 year mortality)

<table>
<thead>
<tr>
<th>Causes</th>
<th>&lt;40% (%)</th>
<th>40–60 (%)</th>
<th>&gt;60 (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>25.0</td>
<td>20.8</td>
<td>24.5</td>
<td>22.9</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>33.9</td>
<td>35.6</td>
<td>31.0</td>
<td>33.9</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>18.8</td>
<td>8.9</td>
<td>7.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6.3</td>
<td>7.9</td>
<td>8.2</td>
<td>7.9</td>
</tr>
<tr>
<td>Other heart causes</td>
<td>12.5</td>
<td>11.9</td>
<td>8.2</td>
<td>10.1</td>
</tr>
<tr>
<td>Sudden death</td>
<td>6.3</td>
<td>6.9</td>
<td>7.3</td>
<td>7.0</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0.0</td>
<td>1.0</td>
<td>4.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Cancers</td>
<td>12.5</td>
<td>13.9</td>
<td>11.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Accidental</td>
<td>0</td>
<td>1.0</td>
<td>0.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Uncertain</td>
<td>0</td>
<td>5.0</td>
<td>4.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Other</td>
<td>12.5</td>
<td>16.8</td>
<td>17.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.3</td>
<td>5.9</td>
<td>6.4</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Table 2 Timing and frequency of posttransplantation laboratory and clinical evaluations after 1 year

<table>
<thead>
<tr>
<th>Years after transplantation</th>
<th>Basic (mo)</th>
<th>Desired (mo)</th>
<th>Potentially advantageous (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical</td>
<td>Laboratory</td>
<td>Clinical</td>
</tr>
<tr>
<td>Year 2</td>
<td>Every 3</td>
<td>Every 3</td>
<td>Every 2</td>
</tr>
<tr>
<td>Year 3–5</td>
<td>Every 6</td>
<td>Every 3</td>
<td>Every 4</td>
</tr>
<tr>
<td>Year 6+</td>
<td>Every 12</td>
<td>Every 6</td>
<td>Every 6</td>
</tr>
</tbody>
</table>

Hypertension

Hypertension is common in dialysis patients and in renal transplant patients. Table 3 lists potential causes of hypertension after transplantation. Patients with systolic blood pressure (SBP) >140 mmHg at 1 year posttransplantation but controlled to ≤140 mmHg clearly had significantly improved long-term graft outcome compared with patients with sustained high-SBP (Opelz and Dohler 2005). The American Society of Transplantation (AST) recommends target blood pressure levels of <140/90 mmHg (Kasiske et al. 2000). Kidney Disease Outcomes Quality Initiative (K/DOQI) recommends blood pressure targets of <130/80 mm Hg in KT patients (KDOQI clinical practice guidelines 2004; Midvedt and Hartmann 2002).

Mailloux 1998, National Kidney Foundation (NKF) task force on cardiovascular disease recommends that the goal for antihypertensive therapy should probably be ≤135/85 mmHg for KT recipients without proteinuria and should possibly be ≤125/75 mmHg for patients with proteinuria.

European best practice guidelines (EBPG), published in 2002, recommend blood pressure...
goal of <130/85 mmHg without proteinuria and <125/75 mmHg with proteinuria. Lifestyle modifications are necessary and should include weight reduction, a DASH (dietary approaches to stop hypertension) eating plan, dietary sodium reduction, and physical activity (Chobanian et al. 2003). No preferred agent is offered by any of the guidelines for blood pressure control. Initially efficacy suggested that calcium channel blockers might have greater benefit in achieving BP control and limiting graft loss (Midvedt and Hartmann 2002; EBPG 2002), but it has not been shown to have a clear benefit over ACE-I on long-term kidney allograft function and survival (Midvedt et al. 2001). ACE-I have potential advantage of delaying progression of renal disease and proteinuria. The routine side effects of hyperkalemia, anemia, and increased creatinine should be expected, and these drugs should not be used in patients with hyperkalemia, severe anemia, renal artery stenosis, or unstable renal function. Diltiazem and verapamil may increase calcineurin inhibitor blood levels. They have been used to lower the dosage of these agents by approximately 50%.

### Cardiovascular Morbidity

Cardiovascular morbidity post-KT can be attributed to modifiable and nonmodifiable risk factors. The nonmodifiable risk factors can be used to identify high-risk population who can be targeted for screening purposes and possible intervention. The risk factors are: pre-KT cardiovascular disease, diabetes, smoking, hyperlipidemia (mostly high LDL), hypertension, platelet and coagulation abnormalities, allograft dysfunction or rejection, low albumin, erythrocytosis, presence of oxygen free radicals, infectious complications like CMV, and increased homocysteine.

The following are the American Heart Association (AHA) and American College of Cardiology (ACC) recommendations for primary prevention of coronary heart disease: cessation of smoking, blood pressure control (<130/80 mmHg), dietary reduction of trans-fats and saturated fats, low dose aspirin, increase physical activity (30 min per day for at least 5 days/week), weight management (BMI goal of 18.5–24.9 kg/m²), maintenance of waist circumference (<35 inches in women and <40 inches in men), blood sugar control (HbA1c <7%), lipid management (LDL-C < 100 mg/dl; secondary goal, if triglyceride ≥200 mg/dl, HDL ≤40 mg/dl), and maintenance on ACE-I and beta blockers indefinitely for all post-MI patients.

### Hyperlipidemia

High level of LDL and low level of HDL contribute to high cardiovascular disease risk in post-transplantation patients. Hypertriglyceridemia as a risk factor is less convincing in post-transplantation patients. The main reason to reduce triglycerides is to reduce incidence of pancreatitis. Most important cause of hyperlipidemia posttransplantation is immunosuppressive medications like rapamycin, cyclosporine, and tacrolimus (in order of severity). Other causes are steroid dose, diet, genetic predisposition, proteinuria, and possibly decreased renal function.

**Table 3** Causes of hypertension in renal transplant recipients

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting hypertension</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive therapies</td>
<td>Steroids</td>
</tr>
<tr>
<td></td>
<td>Calcineurin inhibitors (acute vascular effect)</td>
</tr>
<tr>
<td>Disease in the renal allograft</td>
<td>Chronic allograft nephropathy</td>
</tr>
<tr>
<td></td>
<td>Chronic calcineurin toxicity</td>
</tr>
<tr>
<td></td>
<td>Recurrent diabetic nephropathy</td>
</tr>
<tr>
<td>High renin output in native kidneys</td>
<td>Renal artery stenosis of native kidneys</td>
</tr>
<tr>
<td>Recurrent essential hypertension</td>
<td>Recurrent/persistent systemic disease</td>
</tr>
<tr>
<td></td>
<td>Transplantation of a predisposed graft</td>
</tr>
</tbody>
</table>

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Transplant patients with LDL >130 mg/dl should be considered for pharmacologic treatment, especially if they have preexisting cardiovascular disease, diabetes, or other risk factors. Recognizing patients with metabolic syndrome is important early after transplantation so that patients can be targeted for lifestyle modifications and drug therapy. Reduction in urine protein excretion with an ACE-I or ARB may help to reduce lipid levels for patients with nephrotic range proteinuria. Diet modification and physical activity can help reduce lipid levels.

Studies have shown that HMG-CoA reductase inhibitors (statins) are safe and effective in lowering LDL cholesterol after renal transplantation. In the ALERT (Assessment of Lescol in Renal Transplantation) trial, fluvastatin lowered LDL levels by 32%, and although there was no significant reduction in rate of coronary intervention or mortality, the incidence of cardiac deaths and nonfatal myocardial infarction appeared to be reduced (Fellstrom et al. 2004; Jardine et al. 2004). However, another study showed that HMG-CoA reductase inhibitors in KT recipients, who are on maintenance tacrolimus, were not associated with improvement in graft or patient survival. Another study analyzing the effects of statins in KT recipients reported a 24% improvement in survival in KT recipients on statins (Cosio et al. 2002).

Plasma level of HMG-CoA reductase inhibitors is increased in cyclosporine-treated renal transplant recipients, and therefore, it is generally prudent to use half of the prescribed dose. KT recipients on statins should have lipid panel at baseline, 2–3 months after a change in treatment dose, and at least annually, thereafter.

Patients who would require LDL-C lowering agent may be treated with atorvastatin or simvastatin. Patients with low HDL-C levels may benefit from simvastatin use, while patients with elevated TGL may benefit from high dose atorvastatin. In patients with high TGL-C secondary to rapamycin, gemfibrozil may be the drug of choice and is better tolerated than nicotinic acid. Bile acid sequestrants may alter the bioavailability of immunosuppressive medications and may also increase TGL levels. Statins and fibrates interact with calcineurin inhibitors and may result in hepatitis, myositis, and rhabdomyolysis.

**Reproduction and Pregnancy**

By the end of the first year after a successful transplantation, fertility may be restored rapidly, menstrual function and ovulation typically return, and prolactin fall to normal levels in most women. Contraceptive counseling should begin immediately after transplantation because menstrual cycles may begin within 1–2 months of transplantation in women with well-functioning graft. It has been estimated that 2% of women of childbearing age can conceive after transplantation. The incidence of spontaneous abortion and ectopic pregnancy is reported to be 13% and 0.5%, respectively, which is similar to the general population. The criteria that should ideally be met before contraception (Danovitch, Handbook of transplantation 5th edition) are listed below:

**Criteria for the reduction of posttransplantation pregnancy risk**
1. At least 1 year after transplantation
2. Serum creatinine <2.0 mg/dL, preferably <1.5 mg/dL
3. No recent episodes of acute rejection
4. Normotensive or minimal antihypertensive regimen
5. Minimal or no proteinuria
6. Normal allograft ultrasound
7. Pregnancy safe drug regimen

Kidney Disease Improving Global Outcomes (KDIGO) recommendation is to wait for 1 year after transplantation when kidney function is stable with <1 gm/d proteinuria. It is recommended that mycophenolate mofetil (MMF) and enteric coated-mycophenolate sodium (EC-MPS) should be discontinued and/or replaced with azathioprine before pregnancy is attempted. Similar recommendations are for mammalian target of rapamycin inhibitors (mTOR-I) as well.

Male infertility may improve after kidney transplantation as well. Pregnancies fathered by a kidney transplant recipients appear to have no
more complications than those in general population. Male kidney transplant recipient who wished to maintain fertility should consider avoiding mTOR inhibitors.

The Lisbon Conference reviewed the recommendations by the AST and KDIGO; the most important features are summarized in Table 4.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommendation</th>
<th>AST 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval after transplantation and before pregnancy</td>
<td>1–2 years</td>
<td>1 year</td>
</tr>
<tr>
<td>Kidney function</td>
<td>Creatinine &lt;133 μmol/L</td>
<td>Same</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>None or minimal</td>
<td>&lt;500 mg/day</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Allograft ultrasound only</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rejection history</td>
<td>None within first year</td>
<td>No recent rejections</td>
</tr>
<tr>
<td>Immunosuppression dosing</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>Care providers</td>
<td>High risk obstetrician and transplant physician</td>
<td>High risk obstetrician and transplant physician</td>
</tr>
<tr>
<td>Initial visit frequency</td>
<td>N/A</td>
<td>Every 4 weeks</td>
</tr>
<tr>
<td>Third trimester frequency</td>
<td>N/A</td>
<td>Every 1–2 weeks; weekly after 34 weeks</td>
</tr>
<tr>
<td>Postpartum frequency</td>
<td>N/A</td>
<td>To 3 months postdelivery</td>
</tr>
<tr>
<td>Laboratory frequency</td>
<td>N/A</td>
<td>Every 2–4 weeks</td>
</tr>
<tr>
<td>Blood pressure checks</td>
<td>N/A</td>
<td>At each visit</td>
</tr>
<tr>
<td>Blood pressure target</td>
<td>N/A</td>
<td>Not above baseline</td>
</tr>
<tr>
<td>Fetal monitoring</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Infection

Infection is one of the most common and serious complications after transplantation. It is also the second most common cause of death in transplant recipients (Djamali et al. 2006; Danovitch, Handbook of transplantation 5th edition). Figure 1 illustrates timing of common infections (Abbud-Filho et al. 2007; Fishman and Rubin 1998). Patients who receive increased immunosuppression for acute rejection are more at risk for severe opportunistic infections like Pneumocystis carinii, Listeria monocytogenes, Nocardia asteroides, Cryptococcus neoformans, and Aspergillus.

Cytomegalovirus (CMV) is one of the most common infections after renal transplantation. CMV and Pneumocystis carinii pneumonia (PCP) prophylaxis with valganciclovir and sulfamethoxazole/trimethoprim, respectively, for 3–6 months is needed and is based on transplant center preference. BK virus is another emerging infection that can cause graft dysfunction and ultimately graft failure.

During the first month, bacterial infections such as wound infections and pneumonia are common. Fungal infections are frequent in programs using high-dose steroids but uncommon in steroid-free programs. Patients with preexisting viral hepatitis may develop increased viral replication and clinical liver disease. Immunization for viral hepatitis (hepatitis B) in nonimmunized patients is done at several transplant institutes prior to transplantation.

Epstein-Barr virus (EBV) may predate transplantation, or patients may acquire it as a primary infection from donor. It is associated with post-transplantation lympho-proliferative disease (PTLD). This usually develops in a setting of aggressive immunosuppression in patients at risk (new or preexisting exposure). Reduction of cessation in immunosuppression may be sufficient to cure many patients, although others may require chemotherapy. Patients with prior papillomavirus
Fig. 1 Timeline of infection after organ transplantation (Fishman and Rubin 2007)
infection (HPV) may develop rapid growth in venereal warts or malignant cervical lesions. Herpes simplex virus (HSV) prophylaxis is also instituted at several transplantation centers.

Avoiding excessive immunosuppression can reduce the risk of serious posttransplantation infections. Prophylaxis and vaccination can prevent many infectious complications. Appropriate long-term tapering of immunosuppression and avoidance of repeated rejection treatment in poorly functioning grafts are important in reducing the risk of infectious complications. Periodontal infections are common in posttransplantation patients. These patients should maintain dental hygiene and have access to dental care.

**Bone Disease**

Clinically evident bone disease is a common complication after renal transplantation (Saifu et al. 2005). Maximum bone loss occurs within the first 3–6 months post-KT and continues at a slower rate in the long term.

Immunotherapy and secondary hyperparathyroidism are most important pathogenic factors leading to bone disease and fracture after transplantation. In addition to steroids, cyclosporine has been associated with decreased bone marrow density (BMD). Other implicated factors are pre-existing uremic osteodystrophy, metabolic acidosis, smoking, beta-2 microglobulin-associated amyloidosis, and diabetic osteodystrophy (Djamali et al. 2006; Heaf 2003; Rodino et al. 1998; NKF-K/DOQI 2003). Screening for decreased BMD with DEXA scan can be done at baseline, 6 months, and 12 months (if results of DEXA scan are abnormal) post-KT. Intact parathyroid hormone (iPTH) should be checked at 6 months and 12 months and then annually, at least during the first 3 years post-KT. Guidelines are based on extrapolation of CKD studies for iPTH goal. Patient with decreased BMD (>2.5 SD below adult mean value) may be candidate for oral calcium and vitamin-D supplementation. Management should begin with early ambulation, encouragement of physical exercise, and routine weight bearing exercise program. Phosphate binders, correction of metabolic acidosis, and/or Bisphosphonates have been used to manage these complications. But there are no data showing any benefit with the use of these agents in preventing fractures in KT patients. Bisphosphonate should be used with caution, as there is a risk for adynamic bone disease and should always be dose adjusted for impaired kidney function.

Corticosteroids cause bone disease by decreasing intestinal calcium absorption, increasing calcium excretion, decreasing production of insulin-like growth factor 1, suppressing gonadal hormone secretion, and inhibiting transformation of protoblasts to osteoblasts. They also cause avascular necrosis (AVN) or osteonecrosis, most commonly in the femoral head. The incidence of AVN is close to 1% per year in the 2nd and 3rd post-transplantation years, while the overall incidence is reported to be 5.5%.

Hypophosphatemia is common early after transplantation but less common in the late posttransplant period. It is usually caused by tertiary hyperparathyroidism that remains unresolved in late posttransplantation period. Hyperphosphatemia is encountered usually in transplant patient with renal insufficiency and can be managed with dietary restrictions and binders.

Persistent hyperparathyroidism is observed in approximately 50% of patients during the first year posttransplantation (Djamali et al. 2006). Patients may be treated with Cinacalcet (calcimimetics) with close monitoring of calcium and phosphorus levels. Parathyroidectomy may be required if calcium and PTH levels remain elevated. Bisphosphonates may be effective in reducing steroid-induced bone disease and bone fractures in kidney, liver, and lung transplants recipients. There is limited experience in the use of calcitonin in posttransplantation bone disease. Therefore, this should not be considered the first-line therapy in this setting.

Hypomagnesemia is seen in about 10% of KT recipients who are on maintenance CNI immunosuppressive medications. This is typically managed with oral magnesium replacement.
Posttransplantation Diabetes Mellitus (PTDM)

Posttransplant diabetes mellitus is diagnosed when plasma fasting glucose level is ≥126 mg/dl or the 2-hour plasma glucose level is ≥200 mg per/dl during an oral glucose tolerance test. About 20% of nondiabetic KT patients may develop hyperglycemia post-KT, of which approximately 5–10% would require oral hypoglycemic medications or insulin treatment. Immunosuppressive therapy with tacrolimus, older recipients, deceased donor status, hepatitis C sero-positivity, acute rejection episodes, black race, and high body weight are independent risk factor for PTDM. Patients with strong family history of diabetes are also at increased risk for PTDM. The effect of PTDM in mortality and morbidity and graft survival is similar to pretransplantation diabetes. Steroids and CNI contribute in varying degrees to glucose intolerance and can significantly decrease patient and graft survival. Patients who develop PTDM should be referred to an endocrinologist for blood sugar monitoring and blood sugar control. It is also recommended to consider modifying immunosuppressive drug regimen to reverse progression of diabetes after weighing the risk for rejection and other potential adverse events.

Posttransplantation Anemia

It has been estimated that 25% of post-KT patients are anemic (defined as hemoglobin <13 g/dl for males and <12 g/dl for females), and 13% are iron deficient at 12 months post-KT. In the late post-transplantation period, anemia is most commonly caused by immunosuppression or decreased renal function. Immunosuppressive drugs, i.e., azathioprine, mycophenolate mofetil (MMF), and sirolimus, can cause anemia, thrombocytopenia, and leukopenia, which can be managed by dose reduction or discontinuation of these medications. ACE-Is and ARBs may also cause anemia. Parvovirus and CMV infection may cause refractory anemia for which treatment with intravenous immunoglobulin (IVIG) may be effective. Acute rejection, thrombotic microangiopathy anemia along with malignancies may also contribute to anemia. Comprehensive work-up to assess the etiology of anemia is warranted, and this should include the following: infectious work-up, monitoring iron stores, reticulocyte count, vitamin B12 and folate levels, and fecal occult blood. Appropriate therapy based on the work-up results should be instituted to manage anemia. When no underlying cause is found, erythrocyte stimulating agents may be indicated.

Posttransplantation Erythrocytosis (PTE)

Posttransplant erythrocytosis is seen in 20% of patients after transplantation and most commonly during the first 2 years post-KT. It is rarely seen in patients who have had a native nephrectomy. It is attributed to elevated levels of insulin-like growth factor 1 (IGF-1), which increases sensitivity of erythroid precursor to erythropoietin. Other conditions such as renal artery stenosis, malignancy, and obstructive sleep apnea should also be ruled out. Treatment of erythrocytosis should commence when hematocrit level reaches a level of >55%. Low-dose ACE-Is and ARBs are generally effective treatment for PTE. Phlebotomy may be indicated in refractory cases of PTE.

Posttransplantation Vaccination

All kidney transplant-approved patients should receive inactivated vaccines, according to recommended schedule for the general population, except for Hepatitis-B vaccination (HBV). KDIGO suggests HBV vaccination prior to transplantation. HBsAb titers should be checked 6–12 weeks after completing the vaccination series. Revaccination may be indicated if antibody titer falls below 10 mIU/mL. Live vaccines should be avoided in all KT recipients. Vaccinations should be avoided in the first 6 months following KT except influenza vaccination. KDIGO also suggests giving vaccination for rabies, tick borne meningoencephalitis, inactivated Japanese B
encephalitis vaccine, meningococcus, pneumococcus, and Salmonella typhi-inactivated vaccination. This is because post-KT patients are at increased risk for these specific diseases, due to age, direct exposure, residency, or travel to endemic areas or other epidemiological risk factors.

**Malignancies Posttransplantation**

Age, smoking, immunosuppression, and chronic viral infections contribute to increased incidence of malignancies in the posttransplantation patient population. There is 2–3 fold increase in common malignancies such as lung, prostate, breast, colon, in situ carcinoma of uterine cervix, carcinomas of vulva and perineum, renal carcinomas, and sarcomas, and up to 100 fold increase for entity such as Kaposi sarcoma, posttransplantation lymphoproliferative disease (PTLD), and nonmelanoma skin cancer (Kasiske et al. 2004; Morath et al. 2004). Nonmelanotic skin and lip cancers (basal or squamous cell) are the most common malignancies posttransplantation and develop more frequently in azathioprine-treated patients. After the first posttransplantation year, the KT recipient should undergo annual or biannual skin examination. Age-appropriate annual prostate-specific screening/measurements, fecal occult blood testing, digital rectal examination, breast examination, mammography, and colonoscopy are indicated as in nontransplant patients. If the patient has a history of hepatitis B or Hepatitis C, hepatobiliary ultrasound examination and serum alphafetoprotein measurements are warranted. Patients with a history of cyclophosphamide use should undergo a cystoscopy to check for bladder malignancy. The use of sirolimus has been associated with decreased incidence of cancer, including skin cancer, in the first 2 years posttransplantation.

The reported incidence of PTLD in solid organ transplant recipients ranges between 0.8% and 15% depending on the type of transplantation, age, and immunosuppressive regimen. The incidence in the KT population is reported to be 1–2%. PTLD is 12-fold higher in the transplant compared to the nontransplant population. Most cases develop within 1 year of transplantation. Most cases are the non-Hodgkin’s lymphoma type in age-matched control. They usually are of B cell origin and are CD20 positive. PTLD can be confused with acute rejection as they often present as graft dysfunction. There can be extra nodal involvement and multiple sites are often involved. Mortality is higher with PTLD compared to other lymphomas. Prolonged or repeated lymphocyte depleting agents and high risk for EBV (donor serology positive and recipient negative for EBV) are significant risk factors for development of PTLD. Although typically it is considered to be due to EBV infection of recipient B cells, PTLD may be of donor origin in some patients.

PTLD can be monomorphic/monoclonal or polyclonal B cell lesions. Polyclonal B cell lesions are likely to be benign and respond to withdrawal of immunosuppression and acyclovir, whereas monoclonal lesions are believed to be malignant. Polyclonal lesions might represent the early stages in the spectrum of disease progression.

The mainstay of treatment for PTLD is withdrawal or reduction of immunosuppression. Anti-CD20 monoclonal antibody (rituximab) with rapamycin has shown to be of benefit. Recently, a novel treatment has been reported using an infusion of EBV specific cytotoxic T cells.

**Recurrent or De Novo Glomerular Renal Disease**

The risk of recurrent disease varies by native disease. MPGN, oxalosis, and diabetic nephropathy have the highest risk of recurrence ranging from 80% to 100%. These are followed by focal segmental glomerulosclerosis, IgA nephropathy (by histology), HUS/TTP/TMA (recurrence rate of 30–70%), and membranous nephropathy (recurrence rate of 10–30%). Rare recurrent diseases post-KT include: ANCA vasculitis, Fabry disease, and lupus nephritis. In patients with little or no pre-ESRD care or follow-up, and who lack native kidney disease diagnostic biopsy, it is often difficult to assess whether the disease is recurrent or de novo. There is a significant increase in the
incidence of graft failure among the recurrent and de novo disease groups (55%) when compared to others (25%, \( p < 0.001 \)).

The true prevalence of recurrent glomerulonephritis also depends on counting both patients who have lost their allograft as a result of recurrence and those who have recurrence with a functioning graft. A retrospective analysis of the ANZDATA database revealed that 8.4% of patients lost their grafts as a result of recurrent glomerulonephritis by 10 years after transplantation. However, this analysis did not include those with a functioning graft. A more recent analysis of the ANZDATA database from 2001 through 2004, including those with a functioning graft, revealed recurrence in 93 (4.2%) of 3502 KT recipients (Table 5). The lower prevalence in the cohort of patients from 2001 through 2004 is possibly related to shorter duration of follow-up (Golgert et al. 2008; Danovitch, Handbook of transplantation).

Dense deposit disease recurs in 100% of patients and often leads to graft failure. Idiopathic MPGN recurs in 20–30% of patients and leads to graft failure in 50% of patients. Membranous nephropathy recurs in 5–10% of patients after KT, and about 25% of patients develop graft failure. Histologic recurrence is higher in IgA nephropathy and graft loss can be up to 25%. Antiglomerular basement membrane disease recurs in 10–25% of patients but rarely causes graft failure.

**Table 5** Epidemiology of recurrent glomerulonephritis reported through various registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>Prevalence of recurrent GN posttransplantation (%)</th>
<th>FSGS (%)</th>
<th>IgAN (%)</th>
<th>MPGN (%)</th>
<th>MN (%)</th>
<th>SLE (%)</th>
<th>HUS/ TTP (%)</th>
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<td>NAPRTCS 2006</td>
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<td>5.5</td>
<td>–</td>
<td>0.8</td>
<td>–</td>
<td>–</td>
<td>1.1</td>
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<tr>
<td>ANZDATA 1996–2005</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RADR 1998–2001</td>
<td>2.9</td>
<td>1.0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

NAPRTCS: North American pediatric renal trials and collaborative studies
ANZDATA: Australia and New Zealand dialysis and Transplantation registry
RADR: Renal allograft Disease Registry

**Chronic Kidney Dysfunction in Transplant**

Although renal transplantation is a highly effective treatment for end stage renal disease, a few patients have normal renal function and should be classified as having chronic kidney disease (CKD), similar to patients before dialysis. Causes of CKD in transplant recipients include, among others, chronic allograft nephropathy, acute/sub-acute/chronic rejection, calcineurin nephrotoxicity, recurrent or de novo glomerular disease, polyoma (BK) nephropathy, and with aging donors, preexisting donor renal insufficiency or high KDPI organs.

All renal transplant recipients should have measures instituted aimed at delaying progression of renal disease regardless of stage (Table 6). These include excellent blood pressure control, minimization of nephrotoxic agents (including calcineurin inhibitors), and the use of ACE inhibitors (Abbud-Filho et al. 2007). Control of comorbid illnesses such as hyperlipidemia is particularly important in all stages. Avoiding nonadherence to medications is vital especially in young patients and in those with low socioeconomic status who may not be able to afford expensive immunosuppressive medications. Despite these measures, many patients progress to CKD stage 4 or 5. Such patients should be prepared for dialysis or preferably, re-transplantation (if deemed a candidate).
The Failing Allograft

Once a patient has developed advanced chronic kidney disease posttransplantation (CKD-T) and returned to dialysis, immunosuppression should be reduced or discontinued. If the transplantation was performed within the previous year, most centers proceed to an allograft nephrectomy, because 50% of these patients will require nephrectomy due to rejection after weaning off immunosuppression.

Patients with longer surviving grafts can undergo slow weaning. Once patients have started dialysis, the general approach to weaning off immunosuppression, includes the following: prednisone doses are slowly tapered by approximately 2.5–5 mg/month depending on starting dose; mycophenolic acid, rapamycin, and azathioprine can be stopped immediately; and calcineurin inhibitors are reduced by 50%. All agents should be progressively reduced so that most patients are off all immunosuppressive medications by 6–8 months. Patients losing their allograft to severe refractory rejection may benefit from nephrectomy regardless of the time posttransplantation.

Nephrectomy

Indications for allograft nephrectomy are listed in Table 7. Some patients develop graft intolerance syndrome and present with refractory anemia, pain over allograft, hematuria, fever, while being weaned off immunosuppression. Treatment usually involves a short course of steroids and nephrectomy, if steroid resistant.

Patients with recurrent severe nephrotic syndrome due to recurrence of glomerulonephritis may obtain pain relief from the symptoms of nephrotic syndrome after nephrectomy. Patients with persistent urinary tract infections involving the allograft should undergo nephrectomy, as should any other patients for whom rapid withdrawal of immunosuppression would be beneficial.

Conclusion

The incidence and prevalence of renal transplantation late complications depends on their long-term management and early recognition of modifiable risk factors. The vast majority of successful renal transplant recipients has CKD and should be
managed similarly to patients who have CKD before progression to ESRD.

Avoiding excessive immunosuppression during the short- and long-term period can minimize complications. A great transplant team with multidisciplinary team approach can improve and target these risk factors and improve overall outcomes. Nonadherence with recommendations and medications, secondary to personal or social issues, remains a major barrier and needs to be identified early on.

Timely management of these late complications and management issues can significantly affect short- and long-term patient and graft survival outcomes.

Cross-References

▶ History and Future Direction of Renal Transplantation
▶ Infection in Kidney Transplantation
▶ Kidney Transplantation: Surgical Complications
▶ Pregnancy After Kidney Transplantation
▶ Psychosocial and Financial Aspect of Transplantation
▶ Transplantation Immunosuppression

References

Meier-Kriesche HU, Schold JD, Kaplan B et al (2004b) Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and