Kidney Transplant Management

A Guide to Evaluation and Comorbidities

Sandesh Parajuli
Fahad Aziz
Editors

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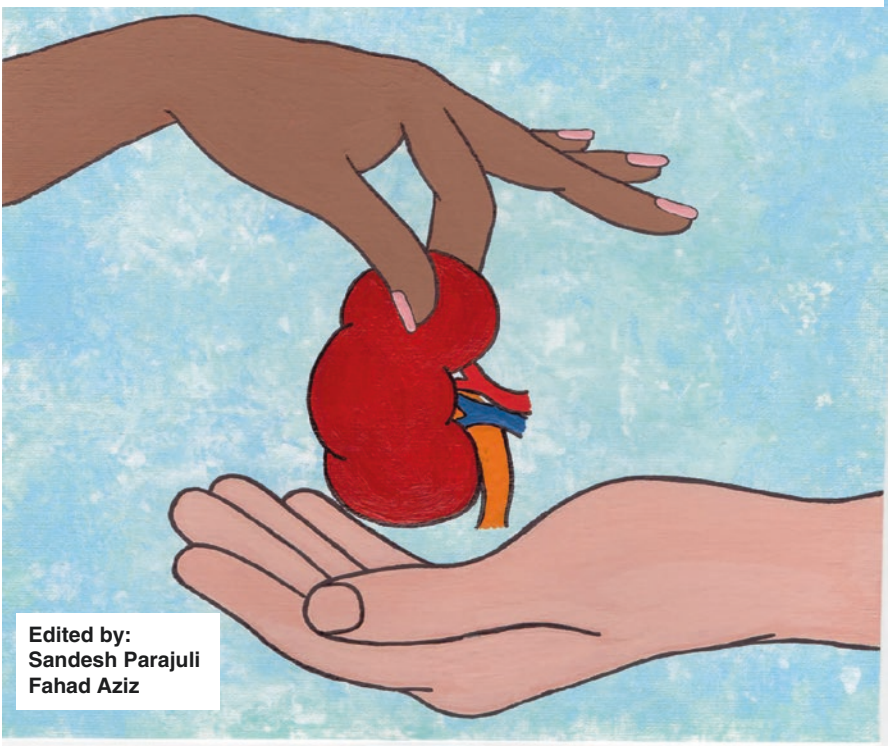

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Preface

Transplant medicine is both science and art. A kidney transplant is a unique modality of treatment with a clear advantage to the patient in terms of survival and quality of life despite being cheaper than dialysis in patients with the end-stage renal disease. Chronic medical conditions are common in transplant recipients. Immunosuppression-related side effects could also play a significant role in overall patients' medical condition.

This book provides an overview of the different problems we face daily while treating our transplant patients. It will discuss the different aspects of transplant nephrology as well as provide a brief look at life after transplant. It will also highlight the importance of proper immunosuppressant adjustment to improve the graft half-life.

We believe various chapters included in this book will provide some knowledge to the health-care providers at the beginning level in their career or anyone who is interested in the transplant medicine or takes care of the kidney transplant recipients. Chapters included in this book were inspired by our patients who we take care and see routinely.

Madison, WI, USA — Sandesh Parajuli
Madison, WI, USA — Fahad Aziz

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Chapter 1
Introduction to Kidney Transplantation

Fahad Aziz and Dana F. Clark

According to the United States Renal Data System (USRDS) 2017 annual report, 124,111 new cases of end stage renal disease (ESRD) were reported in 2015 [1]. The incidence of ESRD rose sharply in the 1980s and 1990s before plateauing in the early 2000's and peaking again in 2006 [1]. In 2003, the Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that the crude 1-year mortality rate was 21.7% in the United States for patients on dialysis [2]. Depression, sexual dysfunction, and sleep related problems are common among this patient population [3] and medical professionals recognize that dialysis is associated with both poor quality and quantity of life [4–6].

The idea of replacing diseased or non-functional body organs has existed for centuries. Although attempts at transplantation began in earnest towards the nineteenth century, the first successful kidney transplant was performed by Dr. Joseph E. Murray in 1954 at Brigham Hospital in Boston between two identical twins [7]. With the improvement in the surgical techniques and immunosuppression over last few decades, kidney transplantation has become the preferred treatment option for patients with ESRD. Kidney transplant recipients enjoy freedom from dialysis with improvement in both quality and quantity of life, and indeed multiple studies have shown that kidney transplant is a superior option in all age groups as compared to being on maintenance dialysis [8–11].

As of the end of 2017, 114,958 patients were waiting for life-saving organ transplants in the United States; of these, 87% are waiting for a kidney transplant [1]. The median wait list for an individual's first kidney transplant is 3.6 years and varies depending on factors such as blood group, geographic location, and organ availability [1]. Generally, there are two types of kidney transplant, living donor transplants and deceased donor transplant. Living donation can be directly from the relatives or

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friends. Living donation can also be part of paired kidney exchange program. Deceased donation occurs after the donor has died.

In 2015, 18,805 kidney transplants took place in US; of these 13,132 (69.8%) came from deceased donors and 5672 (30.2%) came from living donors [1]. Due to organ deficiency, more than 13 people die each day while waiting for a kidney transplant in the United States. Unfortunately, approximately 5000 patients died while waiting for a kidney transplant in 2014 and another 4000 patients became too sick to receive a kidney transplant [1]. The number of patients placed on the transplant waiting list continues to grow, but they still represent only a small fraction of the patients living with ESRD. As per the United Network of Organ Sharing (UNOS) transplant registry of 2014, over the last 10 years, despite increasing efforts by the transplant community, organ shortage remained the biggest hurdle in increasing the number of transplant recipients [12]. Since living donor transplants have a shorter waiting time and longer half-life than deceased donor transplants, they are preferred over deceased donor transplants. It is imperative that we increase awareness regarding the live donation process to increase the organ pool and decrease the number of people on the waiting list.

Although many comorbidities, including anemia and bone and mineral disease. Improve after transplant, kidney transplant recipients continue to have higher a cardiovascular mortality risk and an increased risk of malignancies and infections [13]. Because of this combination of overall improved outcome but increased risk, kidney transplant recipients are unique subset of patients with multiple traditional and transplant-specific risk factors. Appropriate preventive health measures and the monitoring and appropriate adjustment of the immunosuppressants are essential for prolonged allograft and patient survival. Kidney transplant recipients require appropriate, regular adjustment of their immunosuppression to maintain the fine balance between preventing rejection on one hand (if immunosuppression is too low), or infections or malignancies on the other (if too high). With all these considerations, transplant nephrology continues to be an interesting and challenging branch of nephrology. The effective treatment of the different aspects of the transplant population remains a hallmark of this specialty. With increasing number of transplant recipients every year, more transplant nephrologists are needed.

This book provides an overview of the different problems we face daily while treating our transplant patients. It will discuss the different aspects of transplant nephrology as well as provide a brief look at life after transplant. It will also highlight the importance of proper immunosuppressants adjustment to improve the graft half-life.

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Chapter 2
End Stage Renal Disease – Treatment Options: Dialysis Versus Transplant

Sandesh Parajuli and Patrick K. Reville

There are limited treatment options for a patient with end-stage renal disease (ESRD). Options include initiation of dialysis, kidney transplantation or palliative care (Fig. 2.1). Based on the medical conditions and patient's wish, patients opt to choose one or more of the above-mentioned treatment modalities. In patients deemed to be suitable candidates for transplantation, kidney transplantation is usually the preferred treatment modality. There are clear advantages to the patient in terms of survival, cost, and quality of life with transplant compared to dialysis.

Dialysis

Dialysis is one form of treatment option for patients suffering from ESRD. There are two main types of dialysis: Hemodialysis (HD) and peritoneal dialysis (PD) (Fig. 2.2). In the United States of America HD is the most common form of dialysis utilized while in other countries, for example, Mexico, PD is utilized more frequently.

The majority of hemodialysis is performed in a dialysis center, where patients spend 3–5 h on the machine 2–4 times a week. For dialysis, patients need good vascular access with arteriovenous (AV) fistulas being the preferred method of vascular access. Unfortunately, in certain circumstances and patients, an AV fistula may not be possible. These patients will require another form of vascular access in the form of an AV graft or less preferred, a centrally placed dialysis catheter. Home

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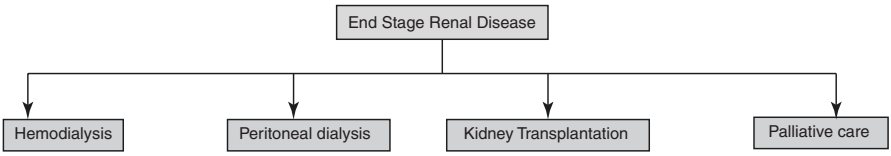

Fig. 2.1 Options for patient with End stage renal disease

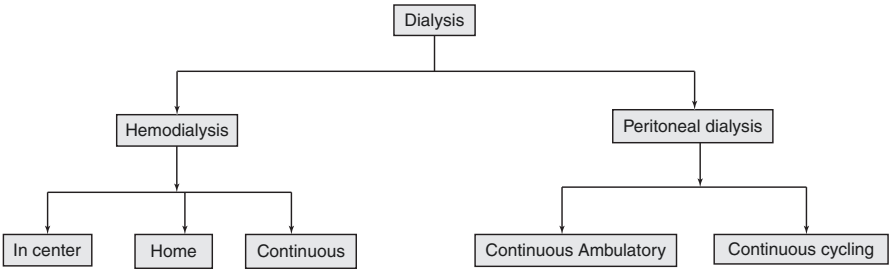

Fig. 2.2 Different types of dialysis

hemodialysis is also becoming more popular, where a patient can perform dialysis at home 4–5 times a week generally at night after work. For patients in hemodynamic shock that require dialysis treatment, continuous veno-venous hemodialysis (CVVHD) is performed with slower blood and dialysate flow rates for prolonged periods of days or weeks.

Peritoneal dialysis is another form of treatment for patients with ESRD. Peritoneal dialysis consists of a highly concentrated glucose containing solution instilled in the peritoneal cavity which creates an osmotic gradient and convection to remove uremic toxins and fluid. A PD catheter is required to perform PD. There are two types of PD: continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD). In CAPD, the dialysate solution stays in the peritoneal cavity for about 4–6 h. After which, the solution is drained from the peritoneal cavity and recycled 4–5 times a day. In CCPD, a machine automatically fills and drains the dialysate for 10–12 h a day. Most of the patients that perform CCPD, do so at). night during sleep. Generally speaking, PD is cheaper and more convenient than HD for patients with ESRD.

Transplantation

Kidney transplantation is another form of treatment for patients with ESRD. Transplantation is generally a better treatment for ESRD than dialysis, but it is also no cure for ESRD. There are clear advantages to the patient in terms of survival, quality of life, and cost. Although it is the often-preferred method, there are adverse effects of transplantation including increased risk of cancer, infections,

obesity, to name a few. There are two general types of kidney transplants, one from a living donor and another from a deceased donor. A living donor transplant is preferred to the deceased donor because these tend to be better quality kidneys in that the waitlist times tend to be low and graft survival is longer than deceased donor kidneys. The half-life of living kidneys is around 12–14 years while that of the deceased donor is around 9 years. The longer people wait for transplantation while on dialysis, the more unfavorable their outcomes are after transplant. Ideally, patients would be transplanted before initiating dialysis, referred to as pre-emptive transplant, or as soon as possible after initiating dialysis. Patients can be listed for transplant when their glomerulus filtration rate is below 20 mL/min/m^2.

Comparison of Clinically-Relevant Outcomes of ESRD Treated with Dialysis Compared with Transplantation

Anemia

The prevalence of anemia is very high in chronic kidney disease (CKD) populations. As CKD progresses, the prevalence of anemia also increases affecting almost every patient with ESRD [1]. The kidney is the main source for erythropoietin production, the hormone most responsible for erythropoiesis. Anemia in CKD is multifactorial, but mainly due to a reduction in the erythropoietin production along with short lifespan of red blood cells [2]. Additionally, there is an increased iron loss of approximately 1–3 grams per year in a dialysis patient due to chronic blood loss from uremic platelet dysfunction, frequent phlebotomy, and/or blood trapping in the dialysis machine [3]. In ESRD patients, oral iron has been shown to be no better than placebo in treating anemia; intravenous iron is preferred in the ESRD patient with iron deficiency, which in turn reduces the need for erythrocyte stimulating agents [3]. However, intravenous iron supplementation is not without risk, it has been associated with increased atherosclerosis and risk of infections, which are the two major causes of mortality in ESRD patients [4]. Anemia in ESRD also poses a significant financial burden. In 2005, erythrocyte stimulating agents were the largest expenditure within the Medicare program approaching $2 billion, by 2007 they cost Medicare $3.9 billion and these costs continue to increase [5].

After a kidney transplant, anemia is not uncommon with the prevalence of 20–57%, with prevalence higher in patients with impaired or poor renal function after transplant [6]. In patients with well-functioning kidney allografts, anemia usually resolves by 3–6 months after transplantation [7]. However, some patients develop persistent anemia caused by immunosuppressive medications which can cause or exacerbate anemia [6]. In one study, post-transplant anemia was associated with poor patient and graft survival along with increased risk of rejections [8]. Although the prevalence of anemia is lower after kidney transplantation, it is still common and an important contributing factor in allograft function.

Cardiovascular Risk

Chronic kidney disease is a well-known risk factor for cardiovascular disease and has been confirmed in many epidemiological studies. After adjusting for traditional risk factors, impaired renal function and albuminuria increase the risk of cardiovascular disease by two to four-fold [9]. In a large cohort of 16,958 people and median follow up of 24 years, after adjusting for conventional risk factors, the hazard ratio for cardiovascular disease were 1.55 for CKD stage 1 and 1.72 for CKD stage 2 patients [10]. This indicates that even mild renal impairment is a risk for cardiovascular disease. The risk of cardiovascular mortality is even higher in ESRD with 10–100 fold increased risk compared to matched control population [11]. The majority of cardiovascular mortality in ESRD patient is due to sudden cardiac death [12]. Left ventricular hypertrophy, heart failure, rapid electrolyte shifts, hypervolemia, and hyperphosphatemia are common in ESRD patients, all of which are associated with sudden cardiac death [13].

Cardiovascular disease and mortality decrease after kidney transplantation but still remains higher than the general population. Risk of cardiovascular mortality is worse with renal transplant compared with dialysis in the early transplant period with a relative risk of 2.84, but the risk equals out by 3–4 months and after that, there is reduced risk and a long-term survival benefit [14]. In the long term, annual cardiovascular mortality drops to two times higher than the general population [15, 16]. It is estimated that by 3 years post-transplant approximately 40% of transplant recipients experience cardiovascular events- mainly related to congestive heart failure (CHF) which is the second most common cause of hospital admission after infection in this population [17]. Myocardial infarction is more common in elderly and diabetic transplant recipients [17]. Other risk factors for cardiovascular events in kidney transplant recipients are unique to immunosuppressive medications. Prevalence of hyperlipidemia in kidney transplant recipients is 40–60% [18]. Most of the commonly used immunosuppressive medications are known to cause hyperlipidemia. Corticosteroids, even at low maintenance doses are related to hyperlipidemia [19]. Tacrolimus, cyclosporine, and to the greatest extend sirolimus are all known to cause hyperlipidemia [20, 21]. Newer immunosuppressive agents such as belatacept appear to have improved cardiovascular and metabolic risks when compared to traditional calcineurin inhibitors [22]. Although cardiovascular risk and mortality are significantly higher in kidney transplant recipients compared to the general population, their risk is much lower related to the immunosuppressive medications, with novel immunosuppressive medications expected reduce this risk.

Vascular Calcification

Vascular calcification is a very common finding in a patient with CKD and has been linked with mortality [23]. It is the most common extra-osseous calcification in a patient with ESRD affecting both medial and intimal layers of arteries [24]. The greater the number of blood vessels that are calcified, the greater the risk for death in

patients with ESRD [25]. Vascular calcification is an independent predictor of all-cause and cardiovascular mortality after kidney transplant [26]. The exact mechanism of vascular calcification is poorly understood but multiple risk factors are involved. These include the high total burden of calcium and phosphorus, low levels of circulating and locally produced inhibitors, impaired renal excretion which can induce vascular smooth muscle cells to become a chondrocyte or osteoblast-like cell [27].

Vascular calcification improves after kidney transplantation. It was found that kidney transplantation leads to better control of calcium-phosphorus metabolism and control of uremia and progression of coronary artery calcification slows by 6–12 months post-transplantation [28]. Most of the studies have shown vascular calcification slows but does not stop altogether after transplantation [29]. In one study, after 1 year of follow-up, coronary artery calcification regressed in 14.5% of the patients after transplantation [30]. Vascular calcifications are common findings in ESRD patients and are related to both mortality and graft survival. Unfortunately, there is no effective therapy to consistently reverse calcifications but transplantation often leads to decelerating calcifications.

Quality of Life

Quality of life (QOL) is a crucial clinical outcome measure, with some claims that it is better than traditional clinical outcome measures [31]. ESRD patients on dialysis often are concerned with the poor quality of life from perpetual feelings of fatigue and increased rates of depression that can be debilitating [32]. In clinical practice, patients on hemodialysis often compare being on dialysis as having a part-time job, they spend 9–15 h per week on the machine excluding travel and preparation time. Moreover during and after dialysis patients often feel drained and quite awful. The prevalence of depression, sexual dysfunction, and sleep-related problems are very common and under-diagnosed in ESRD patient [33]. Sleep quality has been associated with decreased QOL and mortality in ESRD patients [34]. In one study, QOL scores were decreased overall but comparable between patients with advanced CKD and dialysis [35]. Dialysis patients are often unsatisfied with complex aspects of care such as information provided about dialysis and when choosing a dialysis modality, and accuracy of this information and instructions [36].

Health-related QOL measures improve after successful kidney transplantation [37]. After a kidney transplant, young recipients are well adapted socially and often satisfied with their current life situation; however, they report lower QOL on most scales than the general population [38]. In one survey among 200 successful kidney transplant recipients, patients were more satisfied with their health condition, were involved more in social and leisure activities, and were traveling more after kidney transplant compared to while on hemodialysis [39]. In clinical practice, patients oftentimes express their happiness and realize how unwell they felt and were while on dialysis only after kidney transplantation. Overall patients are more satisfied with the better quality of life after kidney transplantation compared to dialysis.

Cost

Medicare cost to manage CKD is rising. In 2013, Medicare spending for CKD in patients aged 65 and older was more than $50 billion, which represented about 20% of all Medicare spending in this age group [40]. Compared to the previous year, total Medicare fee for service declined by 0.2% in 2013, but spending for ESRD patients increased by 1.6% to $30.9 billion [41]. In 2013, per patient per year (PPPY) peritoneal dialysis was $69,919 and hemodialysis was $84,550 [41].

Transplant is a cost-effective ESRD treatment. After the first year of transplant, PPPY in 2013 was $29,920 [41]. The financial impact of other medical comorbidities after transplantation, especially cardiovascular events is less studied but presumably lowers than compared with dialysis given the lower event rates [42]. After adjusting for inflation, the annual cost of immunosuppressive drugs peaked in 2007 but then declined due to generic competition [43]. There are clear direct and indirect cost-effective benefits of kidney transplant compared to dialysis.

Infections

Patients with CKD are at increased risk for hospitalization due to infectious complications, pneumonia, or sepsis. Acute infection is one of the most common causes of hospitalization in ESRD patient [44]. Uremia has been associated with immunodeficiency in CKD patients and the immune system is chronically activated leading to immune dysfunction in uremia [45]. Mortality due to infections is very high in the ESRD patient ranging from 7% to 30% [46]. Risk factors for infections in CKD or ESRD include advanced age, multiple comorbid conditions, low albumin level, uremia, malnutrition, and anemia [44].

Risk of infection is significantly higher after kidney transplantation and is a common cause of morbidity and mortality. After cardiovascular disease, infection is a second most common cause of death in kidney transplant recipients [47]. Urinary tract infections are the most common bacterial infection requiring hospitalization in kidney transplant recipients [47]. Many viral infections in kidney transplant recipients are due to reactivation of a latent viral infection [48]. Recently with increased prophylactic strategies and early diagnosis, the negative impact of infection on transplant-related outcomes has been improving [47]. Although the risk of infection is high in kidney transplant recipients, with proper prophylaxis and early diagnosis most infections can be managed without significant morbidity.

Malignancy

Chronic kidney disease and malignancy are associated in different ways. ESRD patients carry a 10–80% increased risk of malignancy than the general population [49]. Although exact mechanisms of increased malignancy risk in CKD is not well

understood, uremia induced immune dysfunction and increased circulating toxins are commonly speculated to contribute [50]. A graded relationship between severity of CKD and malignancy mortality has been found with higher mortality risk for liver, kidney, and urinary tract cancers [51]. In a longitudinal population-based study, an association between elevated albumin-to-creatinine ratio and malignancy incidence has been shown [52].

The incidence of malignancy is significantly higher after kidney transplant than on dialysis. The overall incidence of malignancy is 3–5 times higher in kidney transplant recipients compared to the general population [53]. The risk of malignancy in kidney transplant recipients is higher than patients on dialysis or those on the waiting list for transplant [54]. Malignancy is the third leading cause of death in kidney transplant recipients. Death from cardiovascular disease and infections are decreasing in the frequency due to aggressive screening and prophylaxis while mortality from malignancy is rising [55]. It is speculated that malignancy will surpass cardiovascular disease as a leading cause of mortality in the near future [56]. Increased risk of malignancy is associated with more intense immunosuppressive medications and longer duration of immunosuppressive exposure [57]. There are multiple risk factors for malignancy in kidney transplant recipients including chronic uremia, immunosuppressive medications, and increased rates of oncogenic viral infections [58]. Risk of malignancy is significantly increased in kidney transplant recipients and incidence is on the rise making it one of the leading causes of the mortality in the post-transplant period.

CKD After Transplantation

Although after kidney transplant patients do better in many aspects of their clinical and personal life, allografts have limited lifespans. Patient death with a functional graft is a major cause of kidney allograft failure, occurring in approximately 40% of transplant recipients [59]. The majority, however, develops CKD and some return to the dialysis and/or get re-transplanted. It is estimated that 4–10% of all dialysis patients and 20–40% of patients listed for a kidney transplant were previous kidney transplant recipients [60].

Kidney transplant recipients are a unique subgroup of patients with CKD due to the presence of single functional kidney, immunosuppressive medications, and disease vintage. Patients receive kidney transplant when their eGFR is less than 20, either in CKD stage 4 (eGFR <30) or stage 5 (eGFR <15). After kidney transplantation, their CKD can regress to any CKD-T stage 1 through 5. After transplant surgery, the majority of the transplant recipients' renal function stabilizes between CKD-T stage 2 and 3 [61, 62]. These patients are always at risk for CKD progression due to unique transplant-related complications including clinical or subclinical rejections, infections, immunosuppressive medication induced damage, or due to traditional risk factors for CKD progression. There is an independent and graded association between rate of decline in GFR and risk for death in

CKD [63]. In one study the rate of creatinine clearance decline in CKD patients was higher than CKD-T patients, but there was no difference in mortality, likely because multiple comorbid conditions offset the potential benefits of slower CKD progression [64]. Similarly, in another study, progression from any given stage of CKD to another was prolonged in CKD-T with a half-life of 11.7 years compared to 5.44 years in CKD, yet patient survival was significantly lower in CKD-T compared with CKD [65].

In another study, among human leukocyte antigen (HLA) identical renal transplant recipients with a median follow up of 8 years, in the absence of rejection, the transplanted kidney maintained the same capacity for functional adaptation as its native partner donor. However, with rejection GFR was significantly lower in the recipients [66]. In another study comparing CKD and CKD-T (stage 4 and 5), there was no difference in prevalence of anemia, use of erythropoiesis-stimulating agents, mean blood pressure or intact parathyroid hormone level; however serum calcium was higher in CKD-T and higher percentage of CKD-T patients were on statin therapy with lower low-density lipoprotein level [67]. The incidence of hypertension, serum calcium, serum phosphorus, the incidence of anemia, and acidosis was higher in advancing stages of CKD-T with the number of complications per patient 1.1 in stage 1 CKD-T to 2.7 in stage 5 CKD-T [61]. In CKD-T patients, control of CKD related parameters was inferior compared to non-transplanted CKD patients [68, 69]. Similar to CKD, progressive renal dysfunction in CKD-T increases the risk of cardiovascular complications [70]. Additionally, transplant recipients are at high cardiovascular risk related to immunosuppressive medications side effects including hypertension, post-transplant diabetes, hyperlipidemia, anemia, hyperhomocysteinemia, micro-inflammatory states, abnormal coagulation, and oxidative stress [70, 71].

Graft failure and return to dialysis in CKD- T is an important risk factor related to increased mortality, mainly in the first month after restarting dialysis [60]. Compared with dialysis-naïve patients, initiation of dialysis after kidney allograft failure has inferior patient survival [72]. Cardiovascular and infections are the leading causes of mortality in patients with allograft failure and return to dialysis [73].

Summary

Kidney transplantation is one of the treatment options for a patient with ESRD but is not a “cure”. With every management, there are beneficial outcomes and many expected and unexpected adverse outcomes. As compared with patients on dialysis, after transplantation there are clear advantages posed to patients; where they live longer and they enjoy a better quality of life with less overall healthcare expenditures (Table 2.1). To our best knowledge, no other outside of transplantation offers patients improved survival, quality of life, and is still cheaper than the alternative treatment options. Other advantages of kidney transplantation not discussed above are improved ability to carry children to term, increased growth in children, and

Table 2.1 Summary of Kidney transplantation compared to dialysis, with reference to the CKD not on dialysis

	ESRD	Transplantation
Anemia	↑↑↑↑	↑↑
Cardiovascular disease	↑↑↑↑	↑↑↑
Mortality	↑↑↑↑	↑↑
Vascular calcification	↑↑↑	↑
Metabolic bone disease	↑↑↑	↑↑↑
Cost	↑↑↑↑	↑↑
Malignancy	↑↑	↑↑↑↑
Quality of life	↓↓↓↓	↓↓
Risk of infections	↑↑↑	↑↑↑↑
Progression from one stage to another	Not applicable	↑↑

fewer dietary restrictions [74, 75]. Adverse effects of transplantation are, increased risk of infections, malignancy, new onset diabetes, obesity, and specific side effects related to immunosuppressive medications [17].

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Chapter 3
Pre-kidney Transplant Evaluation

Anil Regmi

Introduction

Kidney transplantation is the treatment of choice for suitable patients with end-stage renal disease (ESRD). Successful transplantation increases survival and quality of the life in most ESRD patients in comparison to dialysis. Most ESRD patients have significant comorbidities. A thorough evaluation to detect and treat a coexisting illness that may affect perioperative risk and survival after transplantation is necessary. The pre-transplant evaluation of the potential recipient includes an initial assessment for transplantation suitability which includes medical, surgical, immunological and psychosocial assessment [1].

Referral for Transplantation

While a kidney transplantation referral does not imply immediate transplantation, an earlier referral can improve the chances of a patient receiving a preemptive transplantation [1, 2]. Renal transplantation should be discussed with all patients with advanced chronic kidney disease with no absolute contraindications. Interested patients without contraindications should be referred to a transplant program when the estimated glomerular filtration rate (eGFR) is <30 ml/min/1.73 m^2 [1, 3]. In the United States, candidates can accrue wait time on the deceased-donor list when the eGFR is ≤20 mL/min or when they start receiving chronic dialysis therapy.

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Patient Education

All potential transplant candidates are encouraged to attend a "patient education" session before the formal evaluation process. Patients are educated on the benefits and risks of renal transplantation, the necessity for frequent outpatient visits in the early postoperative period, the potential adverse effects of immunosuppression and the importance of compliance with immunosuppressive therapy during this meeting [1]. Differences between livings versus deceased donor renal transplantation are discussed. Candidates are advised on the adverse effects of wait time on graft and patient survival. Occasionally some patients have different specific concerns that can also be addressed during education.

Transplant Workup

The purpose of the evaluation is to identify contraindications to kidney transplantation and correct medical and psychological conditions that may affect transplant outcomes.

General Assessment

General assessment starts with a detailed history and physical examination. The history should focus on the etiology of the renal disease with a review of the native kidney biopsy if available. It may help to assess the risk of recurrence in the transplanted kidney [4]. A detailed history of coronary heart disease, cerebrovascular disease, peripheral vascular disease, and coagulation disorders should be obtained. Sensitization risks, including a history of blood or platelet transfusions, pregnancies, and previous transplants should be documented [1]. A detailed history of any prior transplant courses including the causes of graft loss, medication compliance, and previous transplant complications should be obtained in re-transplant candidates. For candidates with ESRD secondary to congenital and urological abnormalities, appropriate urological evaluation is required. Documentation of the patient's residual urine volume and daily urine production can provide information about the size and functionality of the urinary bladder. A thorough family history, with a focus on kidney disease, hypertension, and diabetes should be solicited. Financial and psychosocial evaluations are necessary to assess the candidate's ability to afford transplant medications as well as maintain an adequate support network to care for the transplant afterward. Everything is important to ensure a successful transplant outcome.

A complete physical examination should include careful assessment of peripheral vascular disease, carotid artery disease, and dental disease. Candidates' BMI

should be measured as obesity is associated with adverse outcome and poses technical challenges with surgery.

Contraindications for renal transplantation [3, 4]
Absolute Contraindications
Active malignancy
Active infection
Severe irreversible extrarenal disease
Life expectancy <2 years
Liver cirrhosis (unless combined liver and kidney transplant)
Primary oxalosis (unless combined liver and kidney transplant)
Limited, irremediable rehabilitative potential
Poorly controlled psychiatric illnesses
Active substance abuse
Relative Contraindications
Active peptic ulcer disease[a]
Medical noncompliance
Active hepatitis B virus infection[b]
Morbid obesity
Special Considerations
ABO incompatibility[c]
Positive T-cell crossmatch[c]

[a]Should be treated prior to transplantation.
[b]Liver biopsy and pre-transplant antiviral therapy recommended and Hepatology consult.
[c]Pretransplant desensitization protocols may allow successful transplantation across these barriers.

In addition to a thorough history and physical examination, patients should also undergo a number of routine laboratories testing and imaging as outlined below.

Assessment of renal transplant candidate [1, 3, 4]
Laboratory Evaluation
Serologies: HIV, hepatitis B, and C, CMV, EBV, HSV, RPR (FTAABS if positive)
Comprehensive metabolic panel, CBC with differential and platelet count, PT/INR, PTT
Urinalysis, urine culture
PSA in men >50 years of age[a]
Other Evaluation
ECG
Chest X-ray
Colonoscopy in patients older than 50 years
Native renal ultrasound to assess for acquired cystic disease or masses
Gynecological evaluation, including Papanicolaou smear in women of childbearing age
Mammogram for women>40 years of age[b] or with a family history of breast cancer
Purified protein derivative (PPD) test in those with a history of exposure to tuberculosis, prior residence in an endemic area, or chest X-ray suspicious of tuberculosis

Serum immunoelectrophoresis in patients older than 60 years and those with unexplained
Renal failure and anemia
Cardiac evaluation (see text)
Urologic evaluation if the history of bladder/voiding dysfunction, recurrent urinary tract infections (see text)
Immunologic studies
Blood group and HLA typing
HLA antibodies
Vascular study (see vascular section)
Detailed coagulation study in those with a history of deep venous thrombosis, spontaneous
Abortion, recurrent clotting of a dialysis fistula or graft, or bleeding tendency
Toxoplasmosis, coccidioidomycosis, and histoplasmosis titers in residents of endemic areas

CMV cytomegalovirus, *EBV* Epstein–Barr virus, *HSV* herpes simplex virus, *RPR* rapid plasmin reagin, *FTA-ABS* fluorescein treponemal antibodies, *PSA* prostate-specific antigen, *ECG* electrocardiogram

[a]High-risk patients should be screened at an earlier age (African- Americans, those with two or more first-degree relatives with prostate cancer)

[b]Part of routine health maintenance, not required for listing unless deemed necessary by the clinician at the time of evaluation

Targeted Evaluation of Individual Patients

Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death after renal transplantation [4, 5]. Therefore, an assessment of cardiovascular disease should be performed in all transplant candidates. Cardiovascular screening is an essential component of the transplant evaluation process. It includes a detailed cardiovascular history and physical examination to assess for cardiovascular symptoms, signs, and risk factors. ECG is recommended for all patients [7]. Then current guidelines for pre-transplant cardiovascular evaluation in an asymptomatic kidney transplant candidate are based on expert opinion. Noninvasive screening is recommended for asymptomatic patients at high risk [4, 6]. There is no consensus on the preferred myocardial perfusion scan (MPS) in the setting of patients with renal failure [5]. Since there is no clear optimal non-invasive screening test for the diagnosis of coronary artery disease in renal failure, the choice of MPS is best determined by the expertise of the individual center. Patients with symptomatic ischemic heart disease should undergo coronary angiography, which remains the gold standard for evaluation of the coronary arteries.

The Fig. 3.1 below is the proposed plan and management of coronary artery disease [4–6].

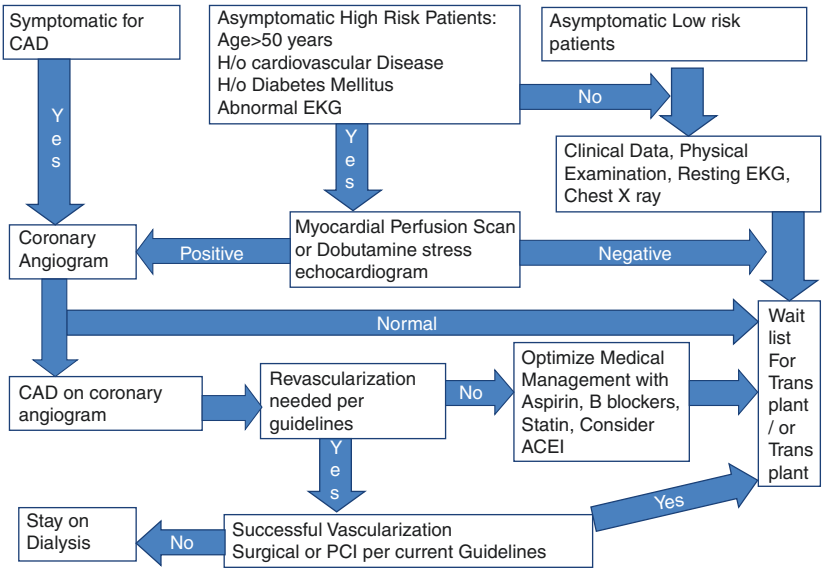

Fig. 3.1 Proposed algorithm for the pre- transplant screening and management of patients with coronary artery disease. CAD Coronary artery Disease, EKG Electrocardiogram, ACEI Angiotensin-converting enzyme inhibitors, PCI Percutaneous intervention

Heart Failure

Calcific aortic stenosis and valvular heart disease are common in transplant candidates. Patients with evidence of increased risk of left ventricular dysfunction or valvular disease should undergo echocardiography. Patients with EF <40% are considered moderate to the high-risk candidate and warrant a formal cardiology consultation [4]. Severe ischemic cardiomyopathy <30% is a relative contraindication to kidney transplantation and the patient may be considered fora combined heart and kidney transplantation [3].

Cerebrovascular Disease

Patients with a history of transient ischemic attacks or cerebrovascular accidents should undergo carotid Doppler studies [4]. Patients with a carotid bruit on physical exam also should be sent for carotid Doppler. Candidates with severe stenosis requiring carotid endarterectomy should have the procedure performed prior to transplantation and should be asymptomatic for at least 6 months prior to transplantation [4].

Peripheral Vascular Disease

The peripheral vascular disease is common in renal transplant candidate and is associated with increased morbidity and mortality. Doppler studies of iliacs and lower-extremity vessels or CT abdomen and pelvis should be performed in patients with diabetes, history of claudication or poor peripheral pulses on physical exam. CT will provide insight into the degree of iliac calcification and the feasibility of allograft placement. Angiography may be performed if noninvasive studies suggest the presence of large vessel disease. Severe bilateral iliac or lower-extremity arterial disease and large abdominal aneurysms that are not amenable to intervention are contraindications to transplantation [2].

Infections

The patient should be free of untreated and/or active infections before transplantation [2]. Candidates should be screened for exposure to mycobacteria with a careful clinical history, chest radiography and purified protein derivative (PPD) skin testing. Patients with latent tuberculosis without a history of adequate treatment or prophylaxis should be considered for prophylaxis pre- or post-transplant [7]. Dental infections should be treated prior to transplantation. HIV infected patients must demonstrate adherence to a highly active antiretroviral therapy (HAART) regimen. They should have a CD4 lymphocyte count above 200/μL for more than 6 months as well as an undetectable viral load for at least 3 months. The patient should be free of opportunistic infections during the previous 6 months [2, 7]. Transplant candidates also should complete recommended immunization at least 4–6 weeks before transplantation to achieve optimal immune response and to minimize the possibility of live vaccine derived infection in the post-transplant period [4].

Gastrointestinal Disease

Patients with active peptic ulcer disease should be adequately treated and have documented endoscopically confirmed resolution of their disease [2].

All transplant candidates should be screened for evidence of liver disease. Patients who are hepatitis B surface antigen (HBsAg) negative should be vaccinated against hepatitis B virus if they have not already been immunized. HBsAg positive patients are at greater risk of death after kidney transplantation. Patient with evidence of active viral replication should undergo liver biopsy and antiviral therapy should be started pre-transplantation. Mild cirrhosis on biopsy would not preclude transplantation but candidates with established liver cirrhosis should be considered for combined liver and kidney transplantation [4].

Hepatitis C positive patients should be referred to a hepatologist and would preferably undergo liver biopsy. Emerging therapies are very successful in clearing the virus pre-transplant. Deferring treatment until after transplant can in many instances shorten a patient wait time, as hepatitis C donor kidneys usually only get allocated to hepatitis C positive recipients. The presence of minimal to mild chronic hepatitis does not preclude transplantation. Patient with bridging fibrosis or cirrhosis should be considered for combined liver and kidney transplantation [4].

Malignancy

Transplant recipients are at higher risk of developing both de novo and recurrent malignancy due to the use of immunosuppression. Age-appropriate screening tests are performed early in the evaluation process [7]. Consultation with an oncologist may be advisable for those patients with a history of malignancy. Even though the optimal waiting time varies depending on the type, stage and location of the tumor, as well as response to therapy, the Table 3.1 below provides the general guidelines for minimum tumor free waiting period for common malignancies. In addition, further information can be obtained from the Israel Penn International Tumor Registry.

Pulmonary Disease

Preoperative pulmonary assessment for kidney transplantation should be the same as for the general population. In addition to a history and physical examination, candidates should undergo chest X-ray and appropriate further testing depending upon the indication. Uncontrolled asthma, severe cor-pulmonale, and severe chronic obstructive pulmonary disease are contraindications for kidney transplantation [2].

Hematological Disorders

Thrombophilia may require initiation of anticoagulation in the perioperative period to reduce thrombotic complications and early graft loss. Patients with recurrent miscarriage, arterial or venous thrombosis, hemodialysis graft or fistula thrombosis, lupus or abnormal prothrombin time or partial thromboplastin time in the absence of medications that interfere with these tests should be evaluated for the underlying hypercoagulable state [1, 4]. It includes screening for protein C or protein S deficiency, anti-thrombin III deficiency, antiphospholipid antibody, lupus anticoagulation, Factor V Leiden mutation, and homocysteine level.

Candidates with monoclonal gammopathy of undetermined significance (MGUS) require pre-transplant evaluation by a hematologist. Patients with unexplained

Table 3.1 Recommended wait time

Recommendations for minimum tumor-free waiting periods for common pre-transplantation malignancies [1, 2, 4]	
Tumor type	Minimal wait time
Renal	
Wilm's tumor	2 y
Renal cell carcinoma	
Incidental tumors	None
Symptomatic	2 y
Large invasive	5 y
Bladder	
In situ or noninvasive papilloma	None
Invasive	2 y
Prostate	
Localized	None
Invasive	2 y
Uterus	
Cervix (in situ)	None
Cervical invasive	2–5 y
Uterine body	2 y
Breast	
Stage 0–2(including early stage)	2y
Stage 3 and 4	5 y
Colorectal	2–5 y
Lymphoma/leukemia	2–5 y
Skin (local)	
Basal cell	None
Squamous cell	Surveillance
Melanoma	
In situ	2 y
Invasive	5 y
Testicular	2 y
Thyroid	2 y
Lung	2 y

ESRD in conjunction with hemolytic anemia, thrombocytopenia, or biopsy-proven thrombotic microangiopathy of unclear etiology should be evaluated for the atypical hemolytic uremic syndrome. Pre-transplant diagnosis and treatment with eculizumab may prevent disease recurrence post-transplant.

Hyperparathyroidism

Calcium, phosphorus and parathyroid hormone levels are measured as part of the pre-transplant evaluation. Candidates with severe, persistent complications of hyperparathyroidism and failed medical management should undergo a parathyroidectomy [2].

Urological Evaluation

Candidates with a history of recurrent urinary tract infections, pyelonephritis, vesicoureteral reflux, urinary retention, or other abnormal voiding patterns should undergo a urologic evaluation [4]. Renal ultrasound, fluoroscopy, computerized tomography, or magnetic resonance imaging may be indicated. Urodynamic studies are considered in patients with a suspected neurogenic bladder and may be indicated in young patients with unexplained chronic kidney disease. Patients with abnormal prostate examination findings, elevated PSA or obstructive voiding symptoms may require urologic procedures to resolve these issues before they can be considered for transplant [1]. Chronic pyelonephritis, vesicoureteric reflux and/or megaureter complicated by stone or infection, heavy proteinuria, refractory hypertension, polycystic kidney disease with massive nephromegaly, renal hemorrhage and suspicious renal masses are the most common conditions that require native nephrectomy before transplantation [1, 2].

Glomerular Disease Recurrence

Disease recurrence is the third most common cause of graft loss [4]. The clinical course and impact of graft survival vary among different types of glomerulonephritis. The reported incidence of recurrent renal disease after renal transplantation and the risk of graft loss from disease recurrence are shown in Table 3.2 below:

With the exception of primary focal segmental glomerulosclerosis (FSGS), the recurrent glomerular disease is usually a late complication after transplantation.

Table 3.2 Recurrence rate

Rates of recurrent Renal Disease after Transplant and Risk of Graft Loss from Disease Recurrence[a]		
	Recurrence rate (%)	Graft loss from disease recurrence (%)
FSGS	20–50	50
IgA nephropathy	20–60	10–30
MPGN I	20–50	30–35
MPGN II	80–100	10–20
Membranous GN	3–30	30
HUS[b]	10-40	10–40
Anti- GMB disease	15–50	<5
ANCA associated Vasculitis	7–25	<5
SLE	3–10	<5

FSGS focal segmental glomerulosclerosis, *MPGN* membranoproliferative glomerulonephritis, *GN* glomerulonephritis, *HUS* hemolytic uremic syndrome, *SLE* systemic lupus erythematosus

[a]Only selected renal diseases are listed

[b]Diarrhea (+) HUS usually does not recur; Diarrhea (−) or familial may recur in 21–28%; Factor H or I mutation may recur 80–100%; patients with mutation membrane cofactor protein do not have a recurrence

Patients should be made aware of the risk of recurrent disease during their pre-transplant education. Despite the risk, recurrence generally does not preclude transplantation.

Psychosocial Evaluation

All candidates should have a pre-transplant psychosocial evaluation to ensure adherence to therapy post-transplant. Issues to be assessed include cognitive impairment, mental illness, non-adherence to therapy and drug and alcohol use [4]. Non-adherence to therapy is a contraindication to transplantation. Care should be taken in candidates with cognitive impairment to ensure informed consent can be obtained and support system is in place to ensure adherence to therapy. Patients with mental illness should be evaluated by a psychiatrist and should be able to give informed consent and be capable of adhering to therapy.

Evaluation of Risk Factors Related to Specific Patients' Characteristics

Age and Functional Capacity

Transplant candidates should have a reasonable probability of surviving beyond current waiting times for transplant. Advanced age per se is not a contraindication to kidney transplantation [2]. Poorer functional status may limit the success of rehabilitation and may promote a return to premorbid activities. Careful evaluation of the potential for improvement in current functional status and participation in a rehabilitation program may be helpful adjuncts in the assessment process for some patients. Patients with active substance abuse should demonstrate abstention for at least 6 months [4].

Obesity

Obesity is considered a contraindication to transplantation by some centers as it is associated with increased risks of post-transplant complications including delayed graft function, deep vein thrombosis, and surgical wound infection. Although there has been no consensus on an acceptable upper limit of body mass index (BMI), it is strongly recommended candidates have a BMI of 30–35 kg m^2 or less prior to transplantation [4]. Determination of transplant candidacy in obese patients should be assessed on an individual basis rather than reliance on an absolute BMI index.

Table 3.3 Cardiac surveillance

Suggested cardiac surveillance for wait-listed transplant candidates [4]	
No known CAD or initial evaluation negative	
(A) Diabetic ESRD	Annually
(B) Nondiabetic + any of the following	Biannually
‡2 traditional risk factors	
Or ‡1 CAD risk equivalents	
(C) Lower risk[a]	Every 3 years
Established CAD	
Medical management per ACC/AHA guidelines	Annually
Successful prior PCI	Annually
History of successful CABG	3 years post-CABG then annually
Asymptomatic aortic stenosis[b]	
Mild	Echocardiogram every 3–5 yrs
Moderate[c]	Echocardiogram annually

ACC American College of Cardiology, *AHA* American Heart Association, *ESRD* end-stage renal disease, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft

[a]Lower risk: defined as not meeting criteria (A) or (B) above

[b]Clinical evaluation annually

[c]Cardiology consultation advisable

Managing the Waitlist Candidate

Periodic reassessment of transplant candidates on the waiting list is recommended. Most transplant programs follow up at least annually to update their listed patient's overall health status, demographics, changes in active medical diagnoses, blood transfusion history, routine health maintenance including age-appropriate cancer screening and cardiac surveillance. Significant changes may require temporary inactivation or even delisting. Although recommendations for cardiac surveillance of wait-listed patients vary among transplant centers, most transplant programs advocate annual cardiac screening in diabetic transplant candidates.

Suggested cardiac surveillance for wait-listed transplant candidates is shown in Table 3.3 above.

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Chapter 4
Kidney Transplant-Immunosuppression and Rejection

Joe Lockridge and Ali Olyaei

Immunosuppressive Therapies–Induction Therapy

Current immunosuppression agents can be divided into three clinical categories: Induction, Maintenance, and Rejection Treatment (Table 4.1).

Each of the detailed therapeutic agents can be understood scientifically in terms of their effect upon the T-cell receptor as a primary activator of the immune response (Fig. 4.1).

The goal of induction, or initial, immunosuppression therapy is a reduction in the incidence of early acute rejection episodes, which are known to be a risk factor for long-term allograft survival. Stronger induction agents are particularly useful in recipients with preformed antibodies, a history of previous transplants, multiple HLA mismatches, transplantation of kidneys with prolonged cold ischemia time, or from high risk donors with advanced age or medical comorbidities. Further, induction therapy can be used to prevent early onset calcineurin inhibitor-induced nephrotoxicity. Under the cover of induction agents, calcineurin inhibitor therapeutic targets can be temporarily reduced until the graft regains some degree of function [1, 2]. The three most commonly used antibodies for induction therapy are basiliximab, anti-thymocyte globulin, and alemtuzumab.

Basiliximab is a chimeric monoclonal antibody directed to the alpha chain of the IL-2 receptor on activated T cells, leading to a decrease in clonal expansion [3]. Basiliximab has demonstrated a significant reduction in rejection episodes compared to placebo in various clinical trials [4–6]. A major advantage of basiliximab is the low side effect profile - adverse reactions to basiliximab were shown to be similar to placebo in clinical trials.

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Table. 4.1 Classification of Immunosuppressive Agents

Immunosuppressive classifications		
Induction	Maintenance	Treatment of rejection
T cell depleting agents ATGAM Thymoglobulin Alemtuzumab	**Calcineurin inhibitors** Cyclosporine Tacrolimus	Mild ACR rejections **Corticosteroids** Prednisone Methylprednisolone
IL-2 receptor antagonist Basiliximab	**Antiproliferative agents** MPA Azathioprine Sirolimus Everolimus	**Moderate to severe ACR rejections** **T-cell depleting agents** ATGAM Thymoglobulin
	Corticosteroids Prednisone Methyprednisone	**AMR** IVIG/PP Rituximab Bortezomib Eculizumab
	Costimulatory pathway blocker Belatacept	

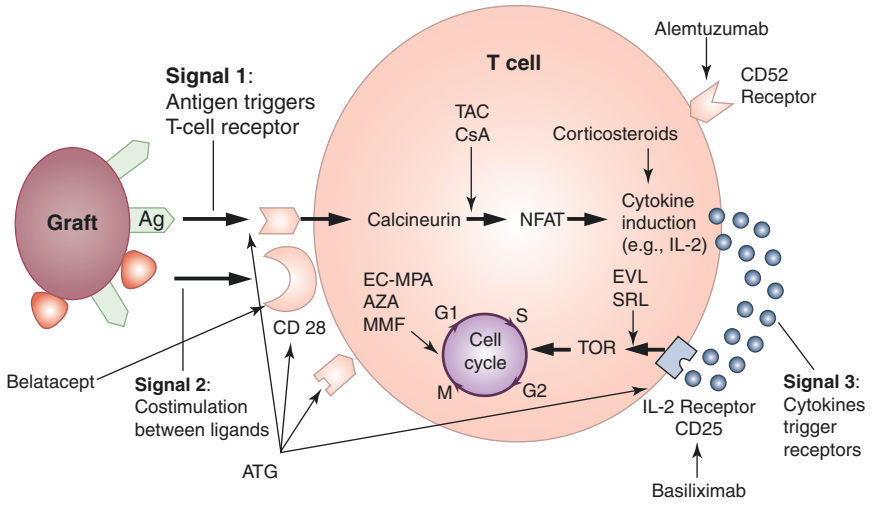

Fig. 4.1 Mechanism of action of immunosuppressive medications. T cell activation: adopted with permission from Olyaei AJ et al. Soild Organ Transplantation. Pharmacotherpay Principles and Practice Chisholm-Burns, Wells, Schwinghammer, Malone, Kolesar and Dipiro. McGram Hill Medcial. New York, 4rd edition, 2018)

Rabbit Antithymocyte Globulin (r-ATG) is a polyclonal antibody produced from the immunization of rabbits with human thymocytes. R-ATG induces T-cell clearance and alters T-cell activation, homing, and cytotoxic activities. It is believed that

r-ATG plays a role in inducing T-cell apoptosis. Adverse reactions are common and related predominantly to cytokine release related to cellular cytotoxicity. Reactions include fever, chills, headache, nausea, diarrhea, malaise, dizziness, leukopenia, thrombocytopenia, and generalized pain. The incidence of infection is 36.6%, with CMV disease occurring in 13.4% of patients.

Alemtuzumab is a recombinant human DNA-derived monoclonal antibody that binds to CD52. CD52 is present on the surface of almost all B- and T-lymphocytes, many macrophages, NK cells, and a subpopulation of granulocytes. The mechanism of action is hypothesized to be antibody-dependent cell lysis following its binding to CD52 cell surface markers. When used for induction therapy, alemtuzumab produces a rapid and extensive lymphocyte depletion and it may take several months to return to pre-transplant levels. Studies have demonstrated a dose of 30 mg IV at the time of transplant to be effective in preventing acute rejection [3]. Alemtuzumab has been associated with serious adverse reactions that include anemia, neutropenia, thrombocytopenia, headache, dysesthesias, dizziness, autoimmune hemolytic anemia, infusion-related reactions, and infection.

r-ATG and basiliximab were compared in a randomized prospective multicenter trial [7]. The r-ATG group demonstrated an improved combined endpoint for the incidence of acute rejection, graft loss, and patient death (19.1% vs 31.6%, $P = 0.01$). An analysis in 2011 showed that alemtuzumab improved transplant outcomes when compared to basiliximab, but produced similar outcomes in comparison with r-ATG [8]. A recent multicenter trial randomized 852 participants to alemtuzumab-based therapy (alemtuzumab followed by low-dose tacrolimus and mycophenolate without steroids) or basiliximab-based induction treatment (basiliximab followed by standard-dose tacrolimus, mycophenolate, and prednisolone [9]. The alemtuzumab group had a 58% proportional reduction in biopsy-proven acute rejection at 6 months compared with the basiliximab group (7% vs 16%; HR 0.42, 95% CI 0.28–0.64; $p < 0.0001$). Graft failure and infection rates were similar between groups.

Lymphocyte-depleting agents such as r-ATG and alemtuzumab are considered to be the most effective at preventing rejection in particular in immunologic high risk recipients, but are associated with a higher incidence of infectious disease and malignancy. Cumulative doses of lymphocyte depleting agents should be considered due to a dose-dependent association with infection and malignancy [10–12]. A recent linkage study between United States kidney transplant recipients and cancer registries detected 2763 cases of cancer in 111,857 patients [13]. Alemtuzumab was associated with increased incidences of non Hodgkins Lymphoma [adjusted incidence rate ratios (aIRR), 1.79; 95% CI, 1.02–3.14), colorectal cancer (aIRR, 2.46; 95% CI, 1.03–5.91), and thyroid cancer (aIRR, 3.37; 95% CI, 1.55–7.33). Antithymocyte globulin was associated with increased melanoma (aIRR, 1.50; 95% CI, 1.06–2.14). The authors concluded that the data highlighted relative safety with regard to cancer risk of the most common induction therapies, the need for surveillance of patients treated with alemtuzumab, and the possible role for increased melanoma screening for those patients treated with polyclonal anti-T-cell induction.

Immunosuppressive Therapies–Maintenance Therapy

The goals of maintenance immunosuppression are to prevent rejection episodes and to optimize patient and graft survival. Antirejection medications require careful selection and dosage titration to balance the risks of rejection with the risks of toxicities.

Common maintenance immunosuppressive agents can be divided into five basic medication classes:

- Calcineurin inhibitors (cyclosporine and tacrolimus);
- Antiproliferatives (azathioprine and the mycophenolic acid [MPA] derivatives);
- Target of Rapamycin (ToR) inhibitors (sirolimus and everolimus);
- Corticosteroids (prednisolone derivatives and dexamethasone); and
- Costimulatory pathway blocker (belatacept).

Maintenance immunosuppression is achieved by combining two or more medications from the different classes to maximize efficacy by targeting multiple immunologic pathways. An appropriate regimen should account for side effect profiles, patient co-morbidities, and preferences.

Calcineurin Inhibitors

Cyclosporine and tacrolimus belong to a class of immunosuppressants known as the calcineurin inhibitors. The mechanism of action involves binding with T cell cytoplasmic proteins, leading to inhibition of calcineurin phosphatase, which results in reduced IL-2 gene transcription. The final outcome is a decrease in IL-2 synthesis and a subsequent reduction in T-cell activation [14, 15]. Cyclosporine USP was first approved for use in the United States in 1983 but was associated with a variable oral absorption. The development of a newer formulation, cyclosporine microemulsion USP (i.e., modified) introduced in 1994, allowed for a more consistent drug exposure due to a more reliable pharmacokinetic profile [16]. The usual oral adult dose of cyclosporine ranges from 3 to 7 mg/kg/day in two divided doses. Tacrolimus (also known as FK506) is the second calcineurin inhibitor and was approved in 1997. Oral starting doses of tacrolimus range from 0.1 to 0.2 mg/kg/day in two divided doses. A major drawback of the calcineurin inhibitors is acute and chronic nephrotoxicity. Acute nephrotoxicity via renal vasoconstriction has been correlated with high doses and is usually reversible. Chronic calcineurin inhibitor toxicity is poorly understood as a cause of long-term allograft injury. Therapeutic drug monitoring for efficacy and safety is used for both drugs at most transplant centers. Adverse reactions specific to cyclosporine include infection, hypertension, hyperkalemia, neurotoxicity, hyperglycemia, hyperuricemia, hemolytic anemia, diarrhea, dyslipidemia, gingival hyperplasia, and hirsutism. Tacrolimus shares the

nephrotoxic profile of cyclosporine, but may be less vasoconstrictive and fibrogenic. Hirsutism and gingival hyperplasia are not as common with tacrolimus. Many of these intolerable toxicities of calcineurin inhibitors are thought to contribute to poor adherence and may lead to alloimmune injury [17].

Comparative efficacy studies between the calcineurin inhibitors have demonstrated that tacrolimus-based regimens are associated with improved short-term survival when compared with cyclosporine-based regimens [18]. Tacrolimus has become the primary calcineurin inhibitor of choice in many transplant centers, likely due to a combination side effect tolerability and favorable efficacy outcomes [19]. Prolonged release tacrolimus has been approved for use in North America and Europe, offering the potential advantage of administration ease with daily dosing.

Antiproliferatives

The antiproliferative agents are generally considered to be adjuvant to the calcineurin inhibitors or ToR inhibitors. The medications included in this class are azathioprine and the MPA derivatives. Azathioprine has been used for renal transplant recipients since the 1960s. Azathioprine is a prodrug for 6-mercaptopurine (6-MP), a purine analog. 6-MP acts as an antimetabolite and inhibits DNA replication with a resultant reduction in T-cell proliferation. The typical oral dose of azathioprine for organ transplantation is 2 mg/kg once a day. Myelosuppression (mainly leukopenia and thrombocytopenia) is a frequent, dose-dependent and dose-limiting complication (greater than 50% of patients) that often prompts dose reductions. Other common adverse events include hepatotoxicity (2–10%) and gastrointestinal disease (10–15%; mostly nausea and vomiting). Importantly, pancreatitis and veno-occlusive disease of the liver occur in less than 1% of patients following chronic azathioprine therapy.

Mycophenolate mofetil was approved for use in the United States in 1995 followed by enteric-coated mycophenolic acid (MPA) in 2004. Both agents are considered to be adjunctive immunosuppressants. Both mycophenolate mofetil and enteric-coated MPA are prodrugs for MPA. MPA acts by inhibiting inosine monophosphate dehydrogenase, a vital enzyme in the de novo pathway of purine synthesis. Inhibition of this enzyme prevents the proliferation of most cells that are dependent upon the de novo pathway for purine synthesis including T-cells.

Doses of mycophenolate mofetil range from 1000 to 3000 mg/day in two to four divided doses. Enteric-coated MPA is available in 180-mg and 360-mg tablets. The most common adverse events associated with these agents are gastrointestinal toxicity (18–54%; diarrhea, nausea, vomiting, and gastritis) and myelosuppression (20–40%). A few trials have attempted to address the comparative gastrointestinal profiles of the two formulations of mycophenolate with conflicting results [20, 21].

Comparative Efficacy–Antiproliferatives

Over the past decade, the use of azathioprine has declined markedly due in large part to the success of the MPA derivatives in achieving specific inhibition of T-cell proliferation (T lymphocytes are dependent upon the de novo pathway of DNA synthesis). Mycophenolate mofetil and enteric-coated MPA have similar safety and efficacy data in renal transplant recipients. The decision to choose one agent over another is generally based on patient profile and clinician experience. Azathioprine is the agent of choice for women desiring pregnancy, as mycophenolate has been associated with teratogenicity. When compared in a clinical trial with azathioprine, mycophenolate mofetil is associated with reduced incidence and severity of early rejection, though long-term follow up failed to demonstrate a sustained graft function or survival benefit in those patients with early rejection.

Target of Rapamycin (ToR) Inhibitors

Sirolimus is a macrolide antibiotic that inhibits T-cell activation and proliferation by binding to and inhibiting the activation of the mammalian ToR, which suppresses the cellular response to IL-2 and other cytokines [22]. Sirolimus may be used safely and effectively with either cyclosporine or tacrolimus as a replacement for either azathioprine or mycophenolate mofetil [23]. Sirolimus can also be used as an alternative agent for patients who do not tolerate calcineurin inhibitors due to nephrotoxicity or other adverse events [24]. Most centers perform therapeutic drug monitoring to reach goal concentrations. The most common adverse events reported with sirolimus are leukopenia (20%), thrombocytopenia (13–30%), and hyperlipidemia (38–57%). Other adverse effects include delayed wound healing, anemia, diarrhea, arthralgias, rash, proteinuria, pneumonitis, and mouth ulcers. Everolimus is a derivative of sirolimus and has the same mechanism of action. With a significantly shorter half-life compared to sirolimus, the steady-state for everolimus can be reached with 90–150 h. The adverse event profile of everolimus is similar to that seen with sirolimus.

Sirolimus and everolimus may have a role in calcineurin inhibitor sparing maintenance therapy. To date, the strongest evidence for replacement of calcineurin inhibition with sirolimus or everolimus is limited to select scenarios such as non melanomatous skin cancer or calcineurin inhibitor intolerance. Long-term efficacy and safety of such a strategy is unknown.

Corticosteroids

Traditional triple-therapy immunosuppressive regimens have consisted of a calcineurin inhibitor or ToR inhibitor, an antiproliferative or ToR inhibitor, and corticosteroids. Corticosteroids are associated with a variety of acute and chronic toxicities.

Table 4.2 Corticosteroid adverse effects

Organ involved	Side effects
Bone/muscle	Osteoporosis/aseptic necrosis of bone/myopathy
Cardiovascular	Hypertension/hyperlipidemia/diabetes
Ophthalmic	Narrow angle glaucoma/cataract
Psychiatric/neurological	Sleep disturbance/ mood alternation/ psychosis/ neuropathy
Skin/soft tissue	Acne/hirsutism/edema/abdominal striae/cushingoid appearance
General	Growth retardation in children

Corticosteroids have various effects on immune and inflammatory response systems, although their exact mechanism of immunosuppression is not fully understood. It is generally believed that at high doses, the agents are directly lymphotoxic and at lower believed that corticosteroids act by inhibiting the production of various cytokines that are necessary to amplify the immune response.

The side effect profile of long-term corticosteroid therapy is well appreciated and includes hypertension, hyperlipidemia, cataracts, avascular necrosis, osteoporosis, mood and appearance changes, and, in children, growth retardation (Table 4.2). Due to these common toxicities of corticosteroids, avoidance or sparing regimens have been supported in the literature, although more studies are needed to help better characterize which patients should follow these protocols [25–28].

Costimulatory Pathway Blocker

Belatacept was approved for use in the United States in 2011 as the first intravenous biologic agent for maintenance immunosuppression in renal transplant recipients. Belatacept use results in the blockade of the CD80 and CD86 ligands, found on antigen presenting cells [29]. The CD80 and CD86 proteins are responsible for stimulating CD28 on inactive T-cells, an essential costimulatory interaction. The interaction of the T cell receptor with a foreign antigen presented by an antigen presenting cell, without complementary costimulation, induces T-cell anergy [30]. Belatacept may be used in place of calcineurin inhibitors in combination with mycophenolate mofetil and corticosteroids. Randomized controlled trials have demonstrated similar patient and allograft survival between belatacept and cyclosporine [31, 32]. Belatacept was found to improve renal function, however the incidence of acute rejection was found to be significantly increased. Additional long-term benefits of belatacept when compared calcineurin-based regimens may include improvement in blood pressure and lipid levels [30]. Belatacept requires access to an infusion-center, a home infusion service, or an infusion suite to ensure appropriate IV administration.

The most common adverse effects associated with belatacept are infectious (urinary tract infection, upper respiratory infection). Other adverse effects include peripheral edema, anemia, leukopenia, hypotension, arthralgia, and insomnia. Belatacept has a black-box warning for increased risk of developing post-transplant lymphoproliferative disorder. Due to this risk, it is recommended

that belatacept only is used in patients who present with proven pre-existing immunity to Epstein-Barr virus.

Rejection

Allograft rejection is an important cause allograft dysfunction and a strong indicator of allograft loss following kidney transplantation. Advances in the field of immunogenic laboratories, HLA technology, and newer immunosuppressants have significantly reduced the incidence of allograft rejections. Both acute cellular rejection (ACR) and antibody-mediated rejection (AMR) are the process of allograft injury from T cell-mediated pathological changes or specific antibodies mediated injuries to the transplanted kidney (Fig. 4.2). Although AMR occurs less frequently than ACR, AMR is recognized with endothelial injury mediated by antibodies. Histopathology is consistent with significant endothelial injuries and infiltration of neutrophilic in the peritubular capillaries with or without fibrin thrombi, and hemorrhages. In some patients, the presence of donor-specific antibody (DSA) is a strong

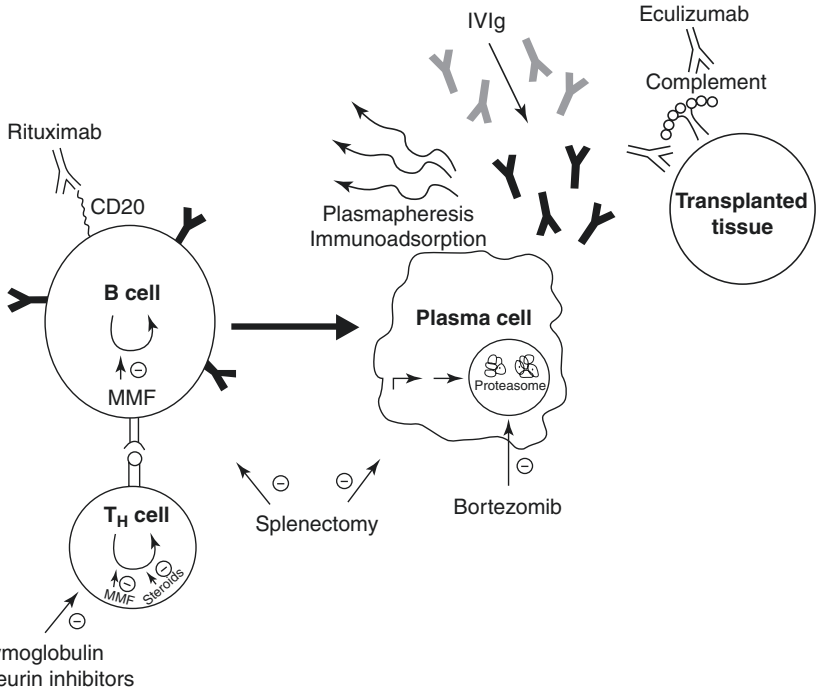

Fig. 4.2 The Immunomodulatory and anti-inflammatory action of IVIG. IVIg immunoglobulin-γ, MMF mycophenolate mofetil, TH cell T-helper cell. (Adapted, with permission, from Levine and Abt [33])

predictor of antibody-mediated rejection which might lead to allograft injury and failure following transplantation. No randomized controlled trials have been published regarding management of AMR.

Treatment of Acute Cellular Rejection Episodes

Acute cellular rejection (ACR) is generally treated with a course of high-dose methylprednisolone (250–1000 mg/day IV for 3–5 days), which is usually sufficient to ameliorate the rejection episode. If the acute rejection episode is resistant to the initial course of steroids, a second course may be administered or the patient may begin therapy with a lymphocyte depleting agent.

Antibody–Mediated Rejection

The presence of pre-formed antibodies, high PRA and donor-specific antibodies (DSA) are a major barrier to successful transplantation and are major risk factors for subsequent antibody-mediated rejection (AMR). Traditional immunosuppression does not significantly affect the humoral immune system and is ineffective at management AMR, which is a leading cause of allograft loss in kidney and heart transplant recipients. Without some form of intervention, antibody formation and rejection can be a major cause of morbidity and mortality. The major strategies employed for treatment of AMR include plasmapheresis and intravenous immune globulin (IVIG), rituximab, bortezomib, and eculizumab.

In plasmapheresis or plasma exchange, patient plasma is removed and replaced with albumin or fresh frozen plasma. Plasmapheresis produces a rapid reduction of circulating antibodies. The purpose of IVIG administration is to decrease anti-HLA alloantibody synthesis. Additional mechanisms of IVIG include inhibition of complement-mediated injury, reduced B-cell proliferation and NK cells and a decrease in phagocytosis. Most patients require 4–5 plasmapheresis sessions and concomitant use of IVIG. In patients at risk for bleeding, the use of fresh frozen plasma should be considered while the use of albumin should be limited.

Rituximab is a chimeric monoclonal anti-CD20 antibody targeting B-cells. This agent directly inhibits B-cell proliferation and induces cellular apoptosis through complement-mediated antibody-dependent cellular cytotoxicity and cell death. Overall, it appears that rituximab may provide beneficial effects in managing AMR when used in combination with other therapies.

Bortezomib is a proteasome inhibitor approved for treatment of multiple myeloma. It works by inducing cell-cycle arrest and apoptosis of plasma cells. It also has been shown to exert numerous indirect effects on circulating B- and T-cells. Treatment protocols using bortezomib have utilized doses ranging from 1 to 1.3 mg/m^2 from 1 to 4 cycles. Most commonly observed adverse effects include peripheral

neuropathy, hematologic effects (thrombocytopenia, neutropenia, anemia), asthenia, paresthesia, and rash. Limited published data documents bortezomib use in kidney transplantation protocols. When used in combination with other accepted modalities, it is difficult to discern whether there is an additional benefit when adding on bortezomib in patients at risk of AMR.

Eculizumab is a humanized monoclonal antibody directed against complement protein C5. It inhibits the cleavage to C5a and C5b; thus, preventing the generation of the membrane attack complex (MAC) and reducing antibody-dependent cell lysis. Trials are ongoing to assess the efficacy of complement inhibition in the treatment of antibody-mediated rejection.

Maintenance Immunosuppressive Therapies–Common Drug-Drug Interactions

Interactions of Metabolism Oxidative metabolism by CYP isozymes is the primary method of drug metabolism. The purpose of drug metabolism is to render drugs more water-soluble in order to optimize elimination. Cyclosporine, tacrolimus, sirolimus, and everolimus are all substrates of the CYP3A isozyme system. The majority of CYP-mediated metabolism takes place in the liver; however, CYP is also expressed in the intestine, lungs, kidneys, and brain. Two types of interactions usually occur with medications metabolized via the CYP enzyme system, inhibitory interactions and inducing interactions. Enzyme inhibition occurs when there is enzyme inactivation or mutual competition of substrates at a catalytic site. This usually results in a reduction of drug metabolism leading to increased medication concentrations. Enzyme induction interactions are opposite and occur when there is an increased synthesis or decreased degradation of CYP enzymes. This type of interaction can produce decreased concentrations of medications. Being CYP3A substrates, it would be anticipated that cyclosporine, tacrolimus, sirolimus, and everolimus would all experience similar pharmacokinetic drug-drug interactions (DDIs). Table 4.3 details the clinically relevant DDIs that occur with the calcineurin due to inhibition or induction of the CYP isozyme system.

Immunosuppressive Drug Complications

Infections

Solid organ transplant recipients are at increased risk of infectious diseases, which are a major cause of early morbidity and mortality. The prevalence of post-transplant infection depends on risk factors, environmental exposures, and the degree of

Table 4.3 CNI drug interaction

CsA or TAC concentration ⬆	CsA or TAC Concentration ⬇	CsA or TAC increases other drugs toxicity
Amiodarone, dronedarone, lidocaine and quinidine	Carbamazepine, pentobarbital, phenobarbital, phenytoin, primodone,	Statin: Myopathy
Diltiazem, verapamil	Rifabutin, rifampin	Dabigatran: anticoagulant concentration
Azole antifungal agents	Efavirenz, etravirine, nevirapine, tipranavir	Antipsychotic agents: Additive QTc prolongation with TAC
Macrolide antibiotics	Doxorubicin or vinblastine	Colchicine toxicity.
HIV protease inhibitors	St. Johns Wort	
Metochlopramide	Orlistat	

immunosuppression. Anti-infectives are universally prescribed in this population as prophylaxis or treatment. Common infectious agents which require prophylaxis include Pneumocystis jirovecii and cytomegalovirus. Routine vaccinations are recommended prior to and after transplantation, while live vaccines should be avoided post-transplant.

Cardiovascular Disease

Cardiovascular disease is the leading cause of death in organ transplant recipients. Reduction of modifiable risk cardiac risk factors, including hypertension and hyperlipidemia, is critical to optimizing post-transplant survival. Well known causes of post-transplant hypertension include the use of corticosteroids and the calcineurin inhibitors. Corticosteroids cause sodium and water retention, thus increasing blood pressure, whereas calcineurin inhibitors are associated with a number of effects that may result in hypertension, including reduced glomerular filtration rate (GFR) and renal blood flow (RBF), increased systemic and intrarenal vascular resistance, sodium retention, reduced concentrations of systemic vasodilators (i.e., prostacyclin, nitric oxide), and increased concentrations of vasoconstrictive thromboxanes.

Hyperlipidemia is seen in up to 60% of heart, lung, and renal transplant patients and greater than 30% of liver transplant patients. Elevated cholesterol levels in transplant patients are due to a culmination of factors such as age, genetic disposition, renal dysfunction, diabetes, proteinuria, body weight, and immunosuppressive therapy. Control of hypertension and hyperlipidemia requires lifestyle modification, medical therapy, and frequent evaluation and testing.

Neoplasia

Transplant recipients are at greatest risk for the types of cancers associated with viral infections, such as PTLD, cervical, and vulvovaginal cancers. Solid-organ tumors like colorectal and lung cancers are two to three times higher in transplant recipients when compared with the general population. The American Cancer Society and American Transplant Society recommend cancer screening for most transplant adults. Nonmelanomatous skin cancer remains the most common malignancy after organ transplantation. Transplant recipients should be advised of simple skin cancer prevention strategies and establish routine surveillance with a dermatologist. Frequently, a reduction in maintenance immunosuppression will follow the diagnosis of a malignancy depending on the stage and perceived impact of immunosuppression on cancer progression. No guidelines are available for such strategies.

Summary

Knowledge of immunosuppression remains critical to the care of the transplant recipient. Current evidence supports the specific administration of induction and maintenance immunosuppressive agents based on patient characteristics. The astute practitioner will tailor therapy to balance the benefits of various regimens against the short and long-term toxicities of individual agents associated with each individual patient. More studies are needed to identify specific indications for current regimens, define long-term adverse effects, develop novel pharmaceutical agents targeted to optimize efficacy and minimize toxicity, and advance the goal of achieving improved long-term patient and allograft survival.

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Chapter 5
Post Kidney Transplant Immediate Complications: Delayed Graft Function and Wound

Brenda Muth

Definition and Incidence

Delayed graft function (DGF) is essentially the absence of kidney allograft function after kidney transplantation. It is a form of acute kidney injury (AKI) and is the most common complication following kidney transplantation. DGF is the result of a complex series of events, that includes donor and recipient factors, organ procurement, and perioperative events. There are as many as 18 definitions of DGF [1]. Dialysis within the first 7 days after transplantation is the most common definition and is the United Network for Organ Sharing (UNOS) definition of DGF. This definition excludes patients who dialyze more than 1 week after transplant, as well as patients who do not have an immediate decline in creatinine or are oliguric, also known as slow graft function. Other DGF definitions are based on the rate of change in creatinine, creatinine clearance, or urine output after transplantation. DGF is most common in recipients of deceased donor kidneys, especially from donors after circulatory death (DCD). The incidence of DGF is approximately 4% in living donor (LD) kidney transplantation, 25% in donation after brain death deceased donor (DBD) kidney transplantation and upwards of 40% in DCD kidney transplantation [2, 3] Fig. 5.1. The incidence of DGF has risen due to the increased utilization of expanded criteria donors (ECD) and DCD kidneys [4]. DGF in living donor kidney transplantation (LD) is unexpected since the ischemia-reperfusion injury is attenuated as the donor is hemodynamically stable and warm and cold ischemia times are limited.

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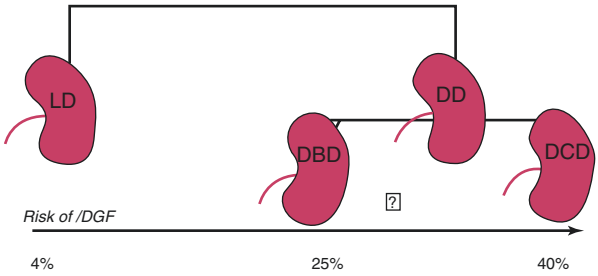

Fig. 5.1 Type of kidney transplant and risk of DGF

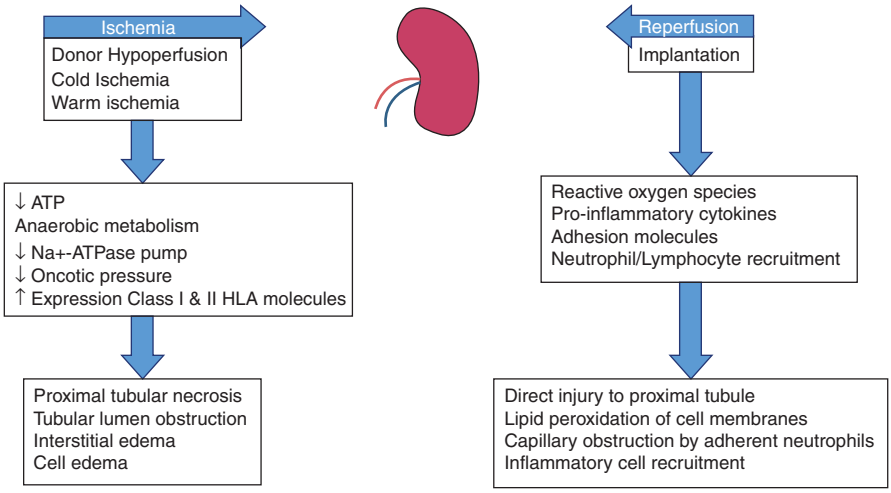

Fig. 5.2 Pathophysiology of DGF

Pathophysiology (Fig. 5.2)

DGF is the consequence of ischemia-reperfusion injury, involving pre-transplant kidney injury, and innate and adaptive immune responses after implantation causing ischemic acute tubular necrosis [5]. The ischemic injury may begin prior to donor death due to hypovolemia and hypotension and continues with brain death in DBD, hypoperfusion in DCD, and also clamping of the renal artery in LD. Ischemia results in rapid depletion of ATP leading to anaerobic metabolism causing lactic acidosis, inhibition of the sodium-potassium-ATPase pump leading to cell edema, and decreased oncotic pressure causing interstitial edema, disruption of the cytoskeleton, proximal tubular cell detachment with tubular obstruction and increases the expression of MHC class I and class II molecules [6, 7]. Implantation with resultant reperfusion causes the release of reactive oxygen species, pro-inflammatory cytokines and adhesion molecules which cause direct injury especially to the proximal tubule, lipid peroxidation of cell membranes and neutrophil recruitment causing capillary obstruction by adherent neutrophils [6, 8] (Fig. 5.2).

Lymphocyte activation along with inflammatory cell recruitment and upregulated MHC class I and II molecules enhances the immunogenicity of the allograft [8].

Risk Factors for DGF (Fig. 5.3)

A combination of donor, recipient and perioperative factors contribute to the development of DGF. Certain donor characteristics are associated with DGF and may affect the quality and outcomes of the transplanted organ. Irish developed a risk prediction model for DGF incorporating the most significant factors for DGF: cold ischemia time (CIT), warm ischemia time (WIT), DCD, donor history of hypertension, donor cause of death due to anoxia or stroke, terminal serum creatinine, age and BMI [3]. Also in the risk model are recipient risk factors for DGF: black ethnicity, male gender, previous transplant, diabetes, peak panel reactive antibody, pretransplant blood transfusion, number of human leukocyte antigen (HLA) mismatches, BMI and duration of dialysis. The factors with the most significance in the risk model are CIT, terminal serum creatinine, DCD, donor age and recipient BMI [3]. Total ischemia time (from the time the donor renal artery is clamped until the clamp is released after implantation) of more than 14 h was associated with an increased risk of DGF, especially in older donors [9]. In a paired analysis, kidneys with CIT >15 h had a significantly higher risk of DGF than kidneys with shorter CIT [10]. BMI $\geq$ 35 kg/m^2 was associated with higher risk of DGF, likely due to longer WIT during implantation in obese patients [11]. Risk factors for DGF in LD are similar to the Irish risk profile; however additional risk factors for DGF in LD include right nephrectomy and open nephrectomy likely due to longer WIT, and ABO incompatibility [12]. LD kidney transplant via paired exchange will have longer CIT if the donor's kidney is shipped to another transplant center; this is an additional factor in DGF [12].

Donor	Recipient	Living donor Recipient
Age	BMI	Right nephrectomy
BMI	Male gender	Open nephrectomy
Cold ischemia time	Black ethnicity	ABO incompatibility
Warm ischemia time	Previous transplant	Kidney paired exchange
Cardiac death donor	Blood transfusion	
Hyptertension	Number of HLA mismatches	
Anoxia cause of death	Duration of dialysis	
Stroke cause of death		
Terminal serum creatinine		

Fig. 5.3 Risk factors for DGF

Prevention

Prevention of DGF starts with the procurement of the kidney and preservation. Methods of organ preservation include preservation solutions, cold storage, and machine perfusion. Kidneys are flushed with a preservation solution prior to undergoing cold storage [13]. University of Wisconsin solution is the most commonly used preservation solution; its electrolyte composition mimics the intracellular environment, has an osmotic agent to reduce endothelial cell edema, and adenosine to stimulate ATP production [13]. Kidneys are cold stored at 0–5 °C. to reduce the metabolic rate. Limiting CIT by transplanting the kidney as early as possible will reduce the risk of DGF. Machine perfusion, also known as "pumping the kidney" is another method of reducing ischemia. Machine perfusion circulates preservation solution through the kidney and supplies energy substrates for metabolism, removes byproducts of metabolism [14], and can be used as a diagnostic tool to monitor vascular resistance [15]. Machine perfusion reduces DGF in deceased donor kidneys, especially ECD kidneys compared to cold storage [15, 16], and has become more common as more marginal kidneys are procured for transplantation, with approximately 45% of kidneys undergoing machine perfusion in 2015 [14]. Limiting warm ischemia time during kidney implantation reduces the risk of DGF [17]. Once the kidney is implanted, it is important to maintain adequate intravascular volume and avoid hypotension. The use of anti-thymocyte globulin induction to reduce DGF is mixed. Comparison of anti-thymocyte globulin to basiliximab in patients with long CIT at risk for DGF found no difference in DGF rates, however, the anti-thymocyte globulin group had a lower rate of rejection in [18]. In patients at high risk for rejection and DGF may have a lower risk of DGF with anti-thymocyte globulin possibly through blunting the inflammatory and immune responses to IR injury [19].

Duration (Fig. 5.4)

DGF recovers with incremental changes in kidney function. DGF begins to recover at post-transplant day 10 in 50% of patients, another 33% begin to recover between days 10–20, and the remainder recovers after day 20 [6]. DGF that persists beyond 90 days is considered primary nonfunction, and is uncommon, with 2–15% of patients having primary nonfunction [6]. PD patients whose DGF was treated with PD had a shorter duration of DGF compared to hemodialysis [20]. It is possible that the more rapid fluid shifts or inflammatory response related to exposure to a synthetic membrane prolong AKI in hemodialysis; conversely, PD patients may still retain some native kidney function and thus become dialysis independent sooner.

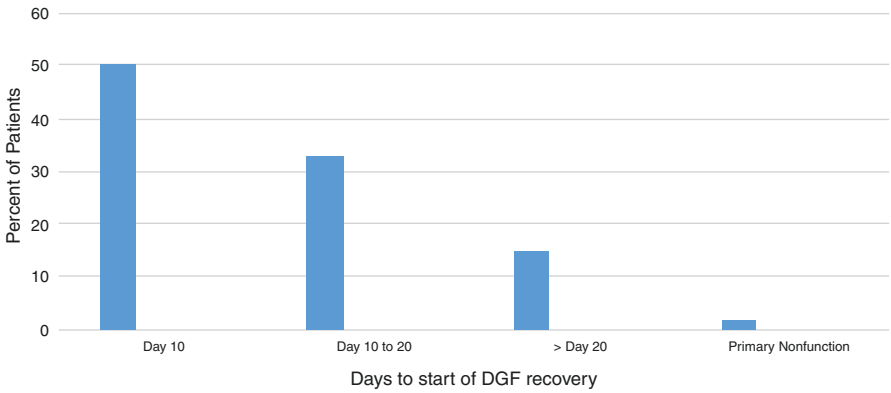

Fig. 5.4 Delayed graft function recovery

Management

Similar to acute kidney injury, management for DGF is supportive. Diuretics have not been shown to prevent AKI, shorten the duration of AKI or reduce the need for dialysis [21]. A trial dose of Lasix 1.0–1.5 mg/kg may be helpful for control of volume in a patient who is not anuric [22]. In order for loop diuretics to be effective, the tubule must have perfusion, with secretion at the proximal tubule and no tubular obstruction [21, 22]. Based on the current DGF definition, all patients receive dialysis. Indications for dialysis include hyperkalemia (K+ $\geq$ 6.0 or ECG changes), hypervolemia (anasarca, uop <100 ml/day, hypoxia), metabolic acidosis (pH < 7.2) or uremic symptoms (nausea, hiccups, dysgusia, fatigue, altered mental status) [23] (Fig. 5.5). All dialysis patients have a pre-transplant "dry weight," the weight at which they are considered euvolemic. It is important to consider the patients dry weight when determining fluid management, diuretic use or dialysis. Fluid boluses should be used to support intravascular volume, however, in an anuric or oliguric patient, may lead to volume overload. In general, patients are maintained approximately 2 kg above their dry weigh to prevent ischemic injury. A select group of patients may continue peritoneal dialysis post-transplant with low volume dwells, provided their peritoneum is intact. It is important to avoid nephrotoxins such as NSAIDs. Renin-Angiotensin-Aldosterone agents are usually held due to the risk of developing hyperkalemia and confounding changes in creatinine, however, they can be used in select circumstances if the clinical condition warrants it. Though calcineurin inhibitors (CNI) are known nephrotoxins, there is no evidence that avoiding CNIs reduces the risk of DGF [4, 5, 24]. It is important to avoid rejection, especially in a kidney recovering from IR injury. According to Kidney Disease Improving Global Outcomes guidelines, immediate CNI use has not been shown to delay kidney recovery, and achieving therapeutic levels is effective in preventing acute

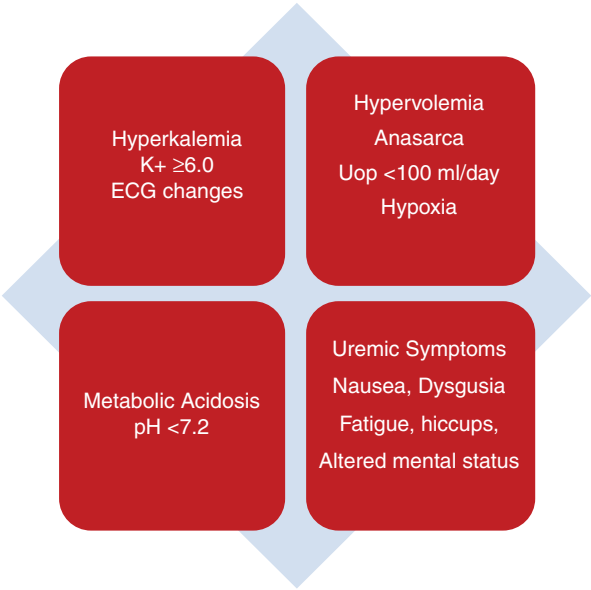

Fig. 5.5 Indications for dialysis

rejection [25]. Discharge tacrolimus level ≥8 ng/mL compared with levels <8 ng/mL did not affect DGF [24]. However, patients with poor graft function after transplant, including prolonged DGF, may benefit from conversion from CNI to belatacept, especially in ECD kidneys as these kidneys may not tolerate the vasoconstrictive effects of therapeutic CNI levels [26]. Sirolimus, with its antiproliferative effects, has been shown to prolong DGF recovery [27]. DGF patients are universally anemic and may need erythrocyte stimulating agents. Almost all are hypertensive, it is important to avoid hypotension in a kidney recovering from AKI. A systolic blood pressure of 140–160 is acceptable early post-transplant to ensure adequate renal perfusion [28]. A very important part of DGF management is patient and family education, as well as multidisciplinary support from social work, pharmacy, the dialysis team and the inpatient and clinic nursing staff.

Monitoring

Monitoring of graft function includes urine output, serial labs including basic metabolic panel, CBC and calcineurin levels, daily weights and blood pressure. The patient is assessed each day for the indication for dialysis, while inpatient, then in clinic 3 times/week after discharge until the patient establishes sufficient allograft function free from dialysis [29]. Obtaining an ultrasound prior to discharge is helpful to ensure patent vasculature and no obstruction. It is important to biopsy a kidney with DGF to evaluate for rejection [4]. A common practice is allograft biopsy in the first 7–14 days post-transplant if there is no improvement in graft function [29].

Outcomes: Readmission, Graft Function, Rejection, Graft Survival, Death (Fig. 5.6)

Importantly, DGF following kidney transplantation is associated with 30-day readmission, poorer graft function, acute rejection, graft failure and death [1, 3, 4, 30, 31]. Patients with DGF are often medically complex and have a high likelihood of readmission within the first 30 days after transplantation [29, 32]. A common cause of readmission is surgical and wound complications [29]. Understandably, DGF is associated with poorer long-term allograft function, with higher serum creatinine in DGF compared to patients without DGF [1, 33, 34].

DGF is associated with shorter kidney allograft survival compared to no DGF [1, 3, 4, 6, 12, 29]. Kidneys at risk for DGF may have donor-derived histopathologic changes, and the effect of IR injury may worsen pre-existing histopathology, thus shortening the life of the allograft. LD, which has the best long-term graft survival, is also negatively impacted by DGF with 2.3-fold risk of allograft failure compared to LD without DGF [12]. Acute rejection superimposed on IR injury will also reduce allograft survival [35, 36].

DGF is a risk factor for rejection [1, 4, 6, 18, 29, 37, 38]. The increased expression of MHC class I and class II molecules and the inflammatory response to IR injury places the already injured allograft at risk for acute rejection. High rates of rejection, as high as 50% were noted in the early transplant era [1, 37]. Others have confirmed the risk of rejection in the modern era of immunosuppression [18, 34, 38]. DGF patients have a higher risk of both T-cell mediated rejection (TCMR) and antibody-mediated acute rejection (ABMR) [38]. Interestingly, DGF patients have a higher rate of acute rejection beyond 1 year after kidney transplantation [18, 39]. Optimizing immunosuppression by using anti-thymocyte globulin [18] and targeting therapeutic calcineurin inhibitor levels early after transplant reduces the risk of rejection [35]. DGF patients managed in a specific DGF outpatient clinic had lower rejection rates, likely due to close management of immunosuppression and monitoring of graft function [29].

The association of DGF with patient survival is mixed. Many have found that DGF is an independent risk factor for death with a functioning graft [31, 32, 40]. Narayanan noted that cardiovascular disease and infection were more common

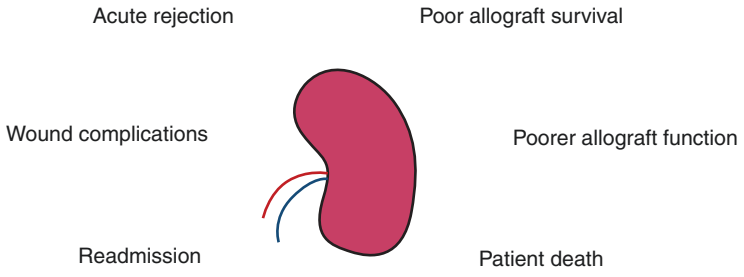

Fig. 5.6 Complications of delayed graft function

causes of death in those with DGF compared to those without DGF [40]. Others have found no association between DGF and patient death [1, 29]. It may be the complex interplay of DGF, immunosuppression and the comorbidities of the kidney transplant recipient such as pre-existing diabetes and cardiovascular disease, result in fatal cardiovascular events or infection.

Wound Complications (Fig. 5.7)

Wound complications are a common complication after kidney transplant and result in rehospitalization, significant cost, and morbidity. Wound complications include wound infection, fascial dehiscence, and incisional hernias. The incidence of wound infection after kidney transplantation is approximately 5%, and incidence of an incisional hernia is 3–5% [41, 42]. A kidney transplant is considered a clean-contaminated case, as the bladder is opened and some urine may spill into the operative field. Post-transplant immunosuppression also increases the risk for infection. Wound infections may be superficial (above the fascia) or deep (below the fascia). Superficial infections are more common and are generally caused by skin organisms or urine spill during the ureteral anastomosis. Superficial wound infections are treated by opening the wound and allow healing by secondary intention, antibiotics are used if cellulitis is present [42]. Deep wound infections are treated with either surgical or percutaneous drainage or antibiotics [42].. Wound infections occur early after transplant, usually in the first month [43], hernias develop later, an average of 12.8 months and can be difficult to repair [41, 44]. Immunosuppressive medications such as corticosteroids and sirolimus delay wound healing.

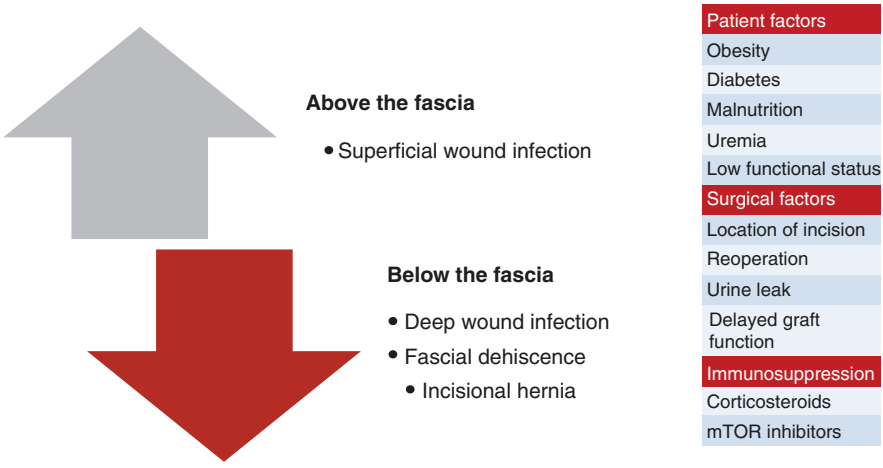

Fig. 5.7 Wound complications and risk factors

Risk factors for wound complications include obesity (BMI ≥30 kg/m2), the location of the incision, urine leak, reoperation, diabetes, DGF, malnutrition, low functional status, uremia and immunosuppression [11, 41, 42, 44–47]. Sirolimus, because of its anti-proliferative effects, is a risk factor for perinephric fluid collections, superficial wound infections, and incisional hernia, especially in obese patients [47]. To avoid early post-transplant wound complications, it is recommended to avoid using sirolimus until 3 months after transplant and to taper steroids as quickly as clinically possible. Though PD is not a common dialytic therapy post-transplant, PD was associated with a higher risk of wound leak and wound infection compared to hemodialysis [20].

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Chapter 6
Post Kidney Transplant: Cardiovascular Complications

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Introduction

Renal transplantation remains the gold standard to improve survival in end-stage renal disease (ESRD). Cardiovascular disease (CVD) is the leading cause of mortality in the general population as well as in renal transplant recipients (RTR). The risk of cardiovascular events (CVEs) is significantly reduced months after transplantation when compared to those with ESRD on the waiting list. Although the mortality is lower than those on the waiting list, certain implicated factors particular to RTRs collectively keep this risk from reaching that of the general population [1, 2]. Immunosuppressive agents and their concomitant effects on hypertension, lipid and glucose metabolism, episodes of graft rejection, and need for dialysis after a failed transplant adds to the complicated post-transplant cardiac risk milieu.

For the purposes of this chapter, CVD will be a broader term referring to specific causes of mortality from congestive heart failure (CHF), ischemic heart disease (IHD), cerebrovascular disease, arrhythmias, and peripheral arterial disease (PAD). Compared to the general population, RTR has a rate of cardiac death that is ten times higher and a rate of fatal and non-fatal cardiac events that is 50 times higher [3–5]. Almost 40% of RTRs have had a cardiac event by 3 years post-transplantation [6]. Meier-Kriesche et al. showed the cardiac arrest, myocardial infarction, and arrhythmias to be the most common causes of cardiovascular death at 45.1%, 31.1%, and 12.8% respectively [5], while CHF and myocardial infarction account for the most common causes of overall CVEs [4]. Additionally, as the presence of PAD prior to transplantation confers high morbidity and mortality in ESRD [7, 8], a history of amputations to be considered a relative contraindication to renal

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transplantation in some centers is a paradox. Albeit, Patel et al. recently revealed that severe PAD, as defined by a low ankle-brachial index, independently predicts graft failure and mortality in RTR. Finally, as shown by Abedini et al., cerebrovascular disease, specifically hemorrhagic and ischemic strokes, was prevalent in nearly 9% of RTR at 6.7 year follow-up with an incidence of 1.3% per year, with similar rates revealed by Oliveras [9, 10]. The incidence of CVD across all fronts in RTR, although higher than that of the general population, is one-fifth that of the population on dialysis [1, 2, 11, 12]. A better understanding of the transplant specific risk factors can help confer a lower risk and thus perhaps improve survival.

Epidemiology

CVD is responsible for the highest number of known deaths in RTRs, according to the 2008 U.S. Renal Data System (USRDS) annual report [2]. Although the overall probability of death has decreased from the late 1990s to 2009 in deceased and living donor transplant recipients following the first year, mortality secondary to CVD is almost two times that of deaths from infection and malignancy [13, 14]. In fact, the risk of death from all causes remains elevated directly after transplantation surgery until approximately 90–110 days (Table 6.1). The recipient's cardiovascular risk status and the kidney donor profile index help to establish the number of days to the equal risk of death and days to equal survival post-transplantation compared to the waitlisted ESRD patients [15, 16].

Risk Factors

Traditional risk factors of age, gender, smoking, diabetes, and tobacco use remain strongly associated with CVEs in a RTR. The presence of PAD, CAD, or cerebrovascular disease further increases the total lifetime risk of CVEs. Although the list of risk factors remain generally similar in a RTR versus the general population, transplant-specific risk factors, such as rejection episodes, deceased versus living donation, time on dialysis prior to transplant, CMV infection, and immunosuppressive therapy, add a deeper layer of complexity to a recipient's cardiovascular risk profile [2].

Table 6.1 Adjusted relative risk of death amongst 23,275 deceased RTRs in comparison to 46,164 waitlisted ESRD patients [16]

Days since transplantation	Relative risk of death	
<14 days	2.84	
106	1.00	Risk equal
244	0.32	Survival equal

Hypertension

Poorly controlled blood pressure has been associated with the development of chronic allograft nephropathy from deceased as well as living donors. The detection of a relationship is problematic as chronic renal insufficiency causes hypertension. Nevertheless, hypertension independently has profoundly deleterious effects on the development and progression of PAD, left ventricular hypertrophy (LVH), and cerebrovascular disease. By use of ambulatory blood pressure monitoring and office readings, Mallamaci et al. reviewed the relationship of blood pressure readings with estimated GFR (eGFR) in 260 renal transplant patients, most of which were cadaveric, with a median duration of follow up of 3.7 years; they found that 24-h systolic (greater than or equal to 130), daytime (greater than or equal to 135/85), and nighttime blood pressure readings (greater than 120/70) are associated with worsening renal dysfunction [17]. The largest study by researchers from the University of Heidelberg examined the relationship of graft function with uncontrolled systolic and diastolic blood pressure readings in 29,751 renal transplant recipients in the Collaborative Transplant Study. During the seven-year study period, each incremental rise in systolic of 10 mm Hg above 140 and that in diastolic blood pressures above 90 predicted a relative increase in the risk of graft failure [18] (Table 6.2)

The ALERT (Assessment of Lescol in Renal Transplantation) trial sought to further identify risk factors for cardiovascular disease in RTRs. A significant association of sudden cardiac death was found with systolic blood pressure (HR, 1.07 per 5 mm Hg, 95% confidence interval [1.00–1.14]) and pulse pressure (HR, 1.11 per 5 mm Hg, 95% CI [1.03–1.19]). Interestingly, no association was found between systolic blood pressure or pulse pressure with the incidence of non-fatal myocardial infarction [19].

Diabetes Mellitus

Diabetes after renal transplantation accelerates the loss of renal function via increasing insulin resistance more so than by reduction of insulin secretion [2, 20, 21]. Implicated risk factors are both traditional in nature, such as increasing age, family

Table 6.2 Association of increased blood pressures at year 1 post renal transplantation with higher graft failure risk over 6 years [18]

Systolic blood pressure, mm Hg	Relative risk	Diastolic blood pressure, mm Hg	Relative risk
<140	1.00	<90	1.00
140–149	1.16	90–99	1.07
150–159	1.37	100–109	1.13
160–169	1.57	>=110	1.42
179–179	1.63		
>=180	2.06		

history of type 2 diabetes, the racial predilection of African-Americans and Asians, and genetic polymorphisms, as well as transplant-specific, such as the use of calcineurin inhibitors (CNIs) and glucocorticoids. Steroids are thought to diminish uptake of glucose peripherally and synthesis of glycogen, meanwhile increasing gluconeogenesis [20]. The range of reported incidence is quite wide, quoted anywhere from 3% to 53% [2, 20, 22] as the definition and terminology of diabetes post-transplantation has changed over time. In 2003, a consensus document by a panel of experts defined new-onset diabetes post-transplantation as fasting blood glucose of greater than or equal to 126 mg/dl or 2-h post meal blood glucose of 200 mg/dl [20]. Mostly, studies have found the development to occur within 3–6 months post-transplantation [2, 20, 23].

An 8-year, observational, prospective Norwegian study published by Hjelmesaeth et al. assessed the incidence of cardiac death, nonfatal myocardial infarction, and patient survival in transplant recipients with newly diagnosed diabetes mellitus. In accordance with previous studies, new-onset diabetes after transplantation developing within 3 months of the post-transplant period (NODAT) showed three times increased the risk of adverse cardiac events [24] (Table 6.3). Nagaraja et al. showed estimates for patient survival with and without NODAT with the latter group being followed for a median of 11 years. Both the development of diabetes within three (HR 2.52, 95% CI [1.27–5.01]) and 12 months (HR 2.24, 95% CI [1.16–4.32]) conferred an association to lowered survival [21]. Significant risk factors for the development of NODAT were age and impaired fasting plasma glucose of 101 mg/dl or higher at 3 months post-transplantation [21].

To help predict the development of NODAT, Chakkera et al. designed and validated predictive risk models in a cohort of 474 nondiabetic patients undergoing kidney transplantation. Age of 50 years or older, maintenance corticosteroids, use of gout medications, BMI greater than or equal to 30, fasting glucose of 100 mg/dl or greater, fasting triglycerides of 200 mg/dl or greater, and a family history of type 2 diabetes projected the likelihood of development of NODAT. A limitation of this study was the predominance of Caucasian transplant recipients in the study cohort [25, 26].

Strategies to help minimize the incidence of NODAT include reducing steroid doses for the restoration of insulin sensitivity [27]. Although both cyclosporine and tacrolimus are diabetogenic, tacrolimus has a higher cumulative incidence of development of diabetes [2, 28], with hypothesized mechanisms, such as decrease of pancreatic beta-cell proliferation [29] and/or increase in sodium glucose co-transporter

Table 6.3 Kaplan-Meier estimates: comparisons of patient survival amongst RTRs without diabetes, new-onset PTDM (NODAT), and diabetes before transplantation [24]

Months since baseline	No diabetes	NODAT	Diabetes before transplantation
20	95%	90%	95%
60	85–95%	75%	60%
100	70–80%	60%	<30%

(SGLT) 1 expression in the small intestine [30]. Avoidance of both tacrolimus and cyclosporine, as well as a quicker tapering of steroids, may be a strategy in a certain population of patients where the risk of rejection is less of a concern [2]. The use of belatacept, as an immunosuppressive option in selective EBV+ recipients rather than a CNI, is an alternative approach; at the 1 year mark, belatacept has been shown to correlate with a lower incidence of development of NODAT, as well as with a generally improved cardiovascular risk profile of patients (improved blood pressure and cholesterol control) in the BENEFIT and BENEFIT-EXT trials [31].

Smoking

Kasiske et al. examined several cardiovascular risk factors comparing their prevalence in 1500 RTRs. Similar to diabetes, cigarette smoking had a greater association on the development of IHD in RTRs than what would be expected [32]. Smoking has been associated in multiple studies with mortality and long-term graft failure [33, 34]. In a large retrospective cohort analysis of over 41,000 RTR in USRDS, Hurst et al. found that smoking was associated with a higher risk of graft loss (HR 1.46, 95% CI [1.19–1.79]) and death (HR 2.32, 95% CI [1.98–2.72]) when compared to non-smokers [34]. In light of these validated findings, several transplant programs across the country endorse smoking cessation as a part of their pre-waitlisting requirements.

Chronic Kidney Disease, Proteinuria, and the Burden of Fibrosis

Chronic kidney disease (CKD) has been implicated as a risk factor for CVEs in the general population independent of its association with diabetes, hypertension, and hyperlipidemia. The ALERT trial was one of the first of many to confirm that a higher serum creatinine is associated with risk of cardiac death [19]. In a post-hoc analysis of the FAVORIT (Folic Acid for Vascular Outcome Reduction in Transplantation) trial analyzing over 3600 participants with an average GFR of 49 ml/min, there were over 500 CVE with a median follow up for 3.8 years. At a GFR of less than 45 ml/min, a strong correlation between all-cause mortality and CVEs was found. RTRs with a GFR of less than 30 ml/min carried a higher hazard ratio than those in the 30–44 ml/min group [35]. The progression of cardiovascular disease in RTR with CKD seems to be associated with uremia, elevated phosphorus, anemia, and hyperparathyroidism [2, 11, 36–40]. Connolly et al., in a prospective study with 379 RTR with a median follow up of more than 6 years, found hyperphosphatemia to be an independent prognosticator for mortality, after adjustment of traditional risk factors [36].

Logically, the strategy to help improve graft function would be to reduce long-term use of nephrotoxic medications, such as CNIs. The use of mammalian target of rapamycin (mTOR) inhibitors as an adjunct to a low dose CNI or as a replacement agent, as well as the use of belatacept in place of CNI, are methods that have been employed across transplant centers. In the ELEVATE trial, of greater than 700 individuals enrolled, 359 patients were converted to everolimus at approximately 14 weeks after transplantation. eGFR was higher in the everolimus group when compared to the cyclosporine group but not when compared to the tacrolimus group. Rejection rates were higher in the everolimus group as well as a small risk of an increase in donor-specific antibodies (DSAs) was evident. However, risk factors of diabetes and CMV infection were lower in the everolimus group, concluding that this may be an alternative choice to the use of cyclosporine in RTR predisposed to such co-morbidities and thus at a higher risk of CVE [41]. Belatacept's use has generally been reserved in the low-immunologically risk, EBV + RTR population. Adams et al. retrospectively analyzed 745 RTR with either belatacept or a standard tacrolimus-based treatment regimen. Their findings included improved eGFR in the belatacept arm versus tacrolimus (63.8 ml/min/1.73 m^2 vs 46.2 ml/min/1.73 m^2 at the end of 4 years). Although the rate and severity of rejection (acute cellular) were higher in recipients in the early transplant period on a completely CNI-free, belatacept regimen, the graft survival rates were similar in the two groups at 4 years. Using CNI-based therapy (tacrolimus) early in the transplant period in combination with belatacept helped to reduce rates of rejection until tacrolimus therapy was tapered over 2 months (after a 3 month induction period), at which time a higher rate and degree of rejection were once again seen. In an attempt to reduce the higher rates of rejection, tacrolimus induction was extended to 11 months post-transplantation while belatacept therapy was continued. The number of rejections were much improved and comparable to that of the tacrolimus arm [42]. Minimizing the number of acute rejections over a lifetime of a RTR attenuates the degree of fibrosis, thus progression of CKD in a graft, improving its long-term survival and thus lowering the recipient's cardiovascular disease burden.

Proteinuria can occur in the presence or absence of CKD in a transplant recipient. Potential causes include acute and/or chronic rejection, transplant glomerulopathy, tubulopathy, glomerulonephritis (recurrent or de novo), reflux nephropathy, and renal vein thrombosis. Graft survival is significantly lower in those with persistent proteinuria (greater than or equal to 2 g per day) [43]. Independently, proteinuria is associated with a higher risk of cardiovascular death; Roodnat et al. found the presence of proteinuria in over 700 RTR after one-year post-transplantation to be associated with an increased rate of graft failure and increased the relative risk of death correlating with the degree of proteinuria [44] (Table 6.4).

Evaluation of graft function in its post-transplant course typically requires serial monitoring of GFR, urine protein-creatinine ratio, as well as frequent use of protocol biopsies at some transplant centers. Transplant biopsies carry with them the risk of bleeding and are invasive but are considered the "gold standard" in terms of guiding therapy in the presence of varying degree of fibrosis. Urinary markers of kidney fibrosis studied in RTRs have yielded interesting results. Park et al. recently

Table 6.4 Comparison of the approximate relative risk of death in increasing levels of proteinuria [44]

Proteinuria (g/day)	All	Cardiovascular	Non-cardiovascular
0	1	1	1
2	1.25–1.4	1.25	1.3–1.5
3.5	1.75	1.5	1.75–2
4.5	2	1.5–1.75	2.25

Table 6.5 Variables associated with CVEs after renal transplantation [46]

Variable	Hazard ratio (p-value < 0.05)	Variable	Hazard ratio (p-value)
Prior cardiovascular event	4.59	Single rejection	1.43 (0.19)
Diabetes mellitus	3.94	Overweight at transplant	1.54 (0.06)
Tobacco history	2.89	Delayed graft function	1.23 (0.38)
Obesity at transplant	2.67	Deceased donor	1.23 (0.49)
Multiple rejections	2.05	Male gender	1.14 (0.54)
Dialysis >1 year	1.79	Age > 45 years	1.11 (0.64)

evaluated alpha 1 microglobulin (α1m), monocyte chemoattractant protein-1 (MCP-1) and procollagen amino-terminal propeptides of type I and type II collagen (PINP and PIIINP) concentrations in the urine secondary to their association with fibrosis. They found that elevated urine concentrations of α1m, MCP-1, and PINP are associated with higher CVD events and risk of death, providing a possibility of closer, noninvasive monitoring in RTRs [45].

Transplant-Specific Risk Factors

Many risk factors for the development of cardiovascular disease in the general population are analogous to that in the transplant population; however, the application of these risk factors to RTRs miscalculate the actual greater incidence of CVEs [32, 46]. This proposes the presence of additional risk factors particular to the transplant population [47], such as CMV infection [48, 49], graft failure leading to renal replacement therapy, duration of dialysis prior to receiving a transplant or after, episodes of acute rejection, and deceased versus living donor transplantation [46, 50] (See Table 6.5). Dialysis duration of greater than 1 year prior to transplantation signifies a higher risk of all-cause mortality and nonfatal CVE [46, 51–53]. Israni et al. retrospectively analyzed over 23,000 RTRs from 14 different transplant centers (The PORT [Patient Outcomes in Renal Transplantation] Study). The investigators validated traditional risk factors of increasing age (greater than or equal to 65, HR 4.99, 90% CI [3.60–6.91]), gender (males, HR 1.22, 90% CI [1.07–1.40]), history of diabetes (HR 2.00, 90% CI [1.75–2.28]), BMI (greater than or equal to 35, HR 1.55, 90% CI [1.24–1.94]), history of cardiovascular disease (greater than or

equal to 2, HR 5.89, 90% CI [4.91–7.08]), and history of malignancy (HR 1.38, 90% CI [1.10–1.73]) as risk factors for coronary heart disease in the first year after transplantation. By the same token, they verified transplant-specific risk factors of donor type (deceased, HR 1.24, 90% CI [1.08–1.43]), time on dialysis prior to transplantation (greater than 2 years, HR 1.41, 90% CI [1.11–1.73]), presence of delayed graft function (DGF) (HR 1.22, 90% CI [0.99–1.50]), and acute rejection (HR 2.21, 90% CI [1.71–2.86]), as additional contributors of risk for development of IHD [54].

Lipid Metabolism

Secondary to CKD and use of immunosuppressive therapy, the pattern of hyperlipidemia in a RTR comprises of raised or neutral levels of total and LDL cholesterol (depending on the absence or presence of CKD, respectively), high triglycerides, and low HDL. Mechanistically, lipoprotein lipase and hepatic lipase are both reduced leading to decreased clearance of intermediate density lipoprotein (IDL) and elevated triglycerides [2, 55]. CNIs increase total and LDL cholesterol (cyclosporine more so than tacrolimus), while corticosteroids increase total, LDL, and HDL cholesterol as well as triglycerides. mTOR inhibitors, such as everolimus or sirolimus, mainly increase triglycerides, but also affect total, LDL, and HDL cholesterol as well; after dose reduction or discontinuation of the drug, however, this effect improves or is reduced over 1–2 months [2, 56, 57].

HMG-CoA reductase inhibitors, i.e. statin therapy, in the realm of renal transplantation have yielded ambiguous results. Brennan et al. presented a review of 13 trials where the effects of statins were studied in RTRs. Study design differences led to varying conclusions on their benefits. Although statins play a substantial role in decreasing risk of acute rejection in heart transplantation, this finding did not pan out as well in RTRs. Generally, however, statins did confirm benefits in terms of total and LDL cholesterol reductions, decrease in atherosclerosis progression, and improved endothelial function. The lower number of cardiovascular deaths and nonfatal coronary events in RTRs on statin therapy was seen, although this was not found to be statistically significant [58, 59].

FAVORIT followed more than 4000 RTRs and found no difference in intervention for elevated LDL in cardiovascular mortality. The ALERT randomized more than 2000 RTR to receive either placebo or statin therapy. The group treated with fluvastatin was associated with a decrease in the incidence of a myocardial infarction when followed over the span of 8 years; high LDL, triglycerides, and total cholesterol increased this risk, meanwhile, high HDL decreased the risk, similar to findings in the general population. In terms of cardiovascular death as an end-point, though, no significant association was found [2, 19].

Obesity

Obesity in the general population has been strongly implicated in the development of risk factors for CVD such as diabetes, hypertension, and CKD. In the dialysis population, a higher BMI has been found to be associated with better survival; this phenomenon- the "obesity paradox" or "reverse epidemiology"- has been noted in other patient populations, such as those with malignancy, elderly patients in the hospital, or those with long-standing heart failure [60–62]. Conversely, in the transplant realm, obesity is associated with a higher risk of DGF. An association with five-year graft loss, death secondary to cardiovascular disease, and all-cause mortality was contingent on the time period of transplantation [62]. Putative rationale for an increased rate of DGF includes an environment of raised levels of cytokines with a propensity for inflammation and surgical challenges in transplanting (prolonged surgery time), leading to a greater amount of ischemia-reperfusion time [62–64].

Congestive Heart Failure

CHF accounts for up to 25% of all CVD-related hospitalizations, followed by IHD (5%) and cerebrovascular disease (9.4%) 2 years after renal transplantation [65]. Rigatto et al., in their analysis of 638 RTR for a median of 7 years, found the incidence of CHF to be much higher than in the general population. Concurrent presence of IHD, hypertension, and anemia was implicated factors in their cohort, contributing to the development of CHF [66] as well as the presence of uremic cardiomyopathy pre-transplantation [2, 67]. Long-standing hypertension determines the development of LVH in ESRD and RTRs [19, 66]. Left ventricular mass index and left ventricular volume index measured via echocardiogram have been shown to decrease 2 years after transplantation; a long history of hypertension, requirement of more than one antihypertensive drug, and presence of high pulse pressure in RTR with non-dilated ventricles and low pulse pressure in those dilated ventricles are factors associated with no regression [68]. Alternatively, when the left ventricular mass index was measured via cardiac MRI in RTR and those on dialysis, there was no significant regression noted; left ventricular mass assessments obtained via echocardiogram can be quite variable secondary to their dependency on volume status [69]. Thus, cardiac vulnerabilities related to long-term uremic cardiomyopathy persist post renal transplantation [69–71]. Strategies to halt the progression of LVH have included improved blood pressure control, use of mTOR inhibitors, or withdrawal of CNIs [72, 73].

Ischemic Heart Disease

Traditional risk factors of age, gender, hypertension, and diabetes remain statistically significant in the development of IHD post-transplantation. In addition, acute rejection has been shown to be an adverse risk factor [66]. Other risk factors include total cholesterol level and history of coronary artery disease pre-transplantation [19]. The PORT study found that the overall incidence of CVE post-transplantation (defined as myocardial infarction, cardiac death, and coronary intervention) was 3.1%, 5.2%, and 7.6% at 1, 3, and 5 years respectively. Nonfatal myocardial infarctions constituted the majority of the events in the first year (49%); this event rate dropped to 39% after the first year with the risk of cardiac death increasing from 13% to 23%, and coronary interventions remaining the same [2, 11, 54]. Development of myocardial infarction after transplantation portends a higher risk of graft loss as well as increased risk of death, especially after the cardiac event [74]. Reduction of risk factors as well as recognition of baseline aspects which predict mortality after such events are the key to potentially diminishing the morbidity and mortality associated with IHD.

Arrhythmias

LVH is associated with myocardial fibrosis both in the sub-endocardial region as well as diffusely [75]. Fibrosis, also propagated by ischemic episodes, leads to unpredictable conduction abnormalities, increasing the likelihood of sudden cardiac death presumably from arrhythmias [2, 11, 76]. According to USRDS registry data, new-onset atrial fibrillation occurs in 3.6% of the renal transplant population at 1 year and 7.3% at 3 years [77]. CKD, in the general population, forms a predisposition for the development of atrial fibrillation, thus increasing mortality reportedly as high as 35.6% at 1 year in those with CKD stages 3–5 with atrial fibrillation [78]. Atrial fibrillation is associated with a four to five time higher risk of cerebrovascular disease and twice the risk of cardiovascular death [78–80].

Cerebrovascular Disease

Abedini et al. sought to uncover the incidence and risk factors of cerebrovascular disease (ischemic and hemorrhagic strokes) in the ALERT trial. Diabetes, previous cerebrovascular events, age, and renal function proved to be risk factors for ischemic strokes, while diabetes, polycystic kidney disease, LVH and systolic blood pressure were associated risks for hemorrhagic strokes. The prevalence of cerebrovascular disease, over an average follow up period of 6.7 years in this study, was 8.6%, with an approximate incidence of 1.3% yearly [9]. These rates were similar when compared to other cohorts [9, 10, 46, 81].

Table 6.6 Approximate survival comparisons of waitlisted patients to RTRs in PAD patients with pre-emptive transplant and in PAD patients who are waitlisted on dialysis [7]

Survival time (days)	PAD + Dialysis−	PAD + Dialysis+
Waitlist		
0	1	1
500	0.8–0.9	0.85
1000	0.7	0.65–0.7
1500	0.5	0.5
1825	0.3–0.4	0.4
Transplant		
0	1	1
500	0.9–0.95	0.9
1000	0.9–0.95	0.85
1500	0.85–0.9	0.7
1825	0.7–0.8	0.6–0.7

Peripheral Arterial Disease

PAD confers up to a four to six-fold increase in mortality due to CVEs [82] and occurs frequently in elderly, diabetics, and in individuals with CKD, ESRD, coronary artery disease, and hypertension [8]. As PAD is prevalent in the population awaiting renal transplantation and carries with it a high mortality burden, Cassuto et al., with a cohort of over 26,000 patients in the United Network for Organ Sharing (UNOS) database, retrospectively investigated any probable mortality benefit of undergoing preemptive transplantation. They found a substantial five-year survival benefit (68.1% in those who received a kidney transplant vs 34.5% in those on the waitlist) in those with PAD who underwent living or deceased donation pre-emptively (HR 0.27, 95% CI [0.21–0.33]) or after dialysis was initiated (HR 0.47, 95% CI [0.44–0.50]) [7] (Table 6.6). Certainly, this study raises important implications for aggressive screening of PAD and promotes the need for transplant evaluations in advanced CKD or ESRD populations.

Management

Screening

In a Cochrane analysis, thirteen studies were included in a meta-analysis to investigate an appropriate non-invasive screening tool to detect CAD in potential RTRs. Dobutamine stress echocardiography had pooled sensitivity and specificity of 0.79 and 0.89 respectively, while myocardial perfusion scintigraphy had slightly lower values of 0.74 and 0.70 [83]. Prospective RTRs at high risk of need for revascularization should be the only individuals considered for coronary angiography as overall revascularization rate observed is quite low [83–85].

Choice of Anti-Hypertensives

Both ACE inhibition (ACEI) and angiotensin II type 1 receptor blocking (ARB) have shown to increase patient and graft survival [86]; their use is also favored for their well-recognized benefit of proteinuria reduction [87]. At a retrospective study done at the Medical University of Vienna in over 2000 patients, the use of ACEI or ARB resulted in fewer graft losses (10-year graft survival of 76% in users versus 71% in non-users). Propensity score analyses favored the use of either of these anti-hypertensives in terms of functional (death-censored) graft failure (HR 0.58, 95% CI [0.47–0.72]), actual graft failure (HR 0.58, 95% [CI 0.47–0.72]), and patient death (HR 0.63, 95% CI [CI 0.49–0.81]) [86]. Dihydropyridine calcium antagonists are beneficial in terms of their effect on LVH as well as hypertension [73]. Amlodipine or nifedipine are often the anti-hypertensive of choice immediately after renal transplantation or when nephrotoxicity secondary to CNI is in question [87].

Steroid Tapering or Withdrawal

Decreasing dose of steroids to 5 mg within the first few months has a favorable effect on insulin sensitivity [27]. In a 6 month multicenter study of 538 patients randomized to either a regimen of tacrolimus, MMF, and daclizumab induction therapy versus a tacrolimus, MMF, and steroid regimen, Rostaing et al. showed that the former regimen resulted in a significantly lower incidence of NODAT (5.4% vs 0.4%) when compared to the cohort on a steroid regimen [88]. In a pilot study, Boots et al. compared tapering steroids over 3–6 months to discontinuation of steroids within 1 week of transplantation in 62 patients who were followed for a median of 2.7 years. Graft survival and acute rejections were similar in incidence [89]. Experiences with alemtuzumab induction in low immunological risk living RTRs who have received belatacept-based regimens have shown rejection free allograft survival without the use of CNIs and steroids [90]. Recently, however, 6070 RTR were studied in the Austrian Dialysis and Transplant Registry by Haller et al. in a retrospective cohort study. Their findings suggested that steroid withdrawal after IL-2 induction has an increased risk of graft loss up to 18 months after transplantation [91]. Certainly, the strategy to withdraw steroids is grossly dependent on the baseline immunological and diabetogenic risks of the recipient as well as induction agents.

Lifestyle Modifications

Increasing physical activity and losing weight are included in the conventional recommendations for RTRs [87]. Similar to the general population, decreased physical activity pre-transplantation has been shown to be associated with increased

mortality rates [92] thus many centers use the level of physical activity with measures such as a six-minute walking test as an important transplant evaluation criteria. As there is no suggestion of harm with exercise and much data to propose physical activity and prevention of obesity in the general population, the same recommendations are in place by the International Society of Nephrology- Kidney Disease: Improving Global Outcomes (KDIGO)- for RTRs [87].

Conclusion

The incidence of technical challenges, postoperative complications, the rate of rejection, and even graft survival have improved over time in the realm of kidney transplantation. Although CVD continues to carry a high burden of morbidity and mortality in RTRs, since the 1980s, CVD death rates have overall declined likely secondary to improved detection, recognition, and potential minimization of modifiable risk factors [2]. As the vast majority of risk factors occur prior to even the development of CKD, access to health care and prevention by a primary care provider or nephrologist are paramount to halting and potential regression of arteriosclerosis and its pathologic sequelae. In terms of transplant-specific risk factors, the approach to minimization includes tailoring post-transplant induction and maintenance immunosuppression, balancing robust immunosuppression in an effort to avoid acute or chronic rejection with the toxicities associated with their use, and continued vigilance, avoidance, and treatment of shared cardiovascular risk factors with the general population.

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Chapter 7
Post Kidney Transplant: Infectious Complication

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Introduction

Due to the iatrogenic immunosuppression given to prevent graft rejection recipients of solid organ transplant (SOT) are at higher risk of infection than the non-immunosuppressed population. Individual risk of infection is a composite of epidemiologic exposure and net state of immunosuppression. Epidemiologic exposures can be both community-based or nosocomial. Community exposures can be remote contact, such as exposure to the endemic mycoses; *Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum,* or *Mycobacterium tuberculosis* and *Strongyloides stercoralis*. Exposure and acquisition can also be short term such as exposure to respiratory viruses or food borne pathogens such as salmonella, *Listeria monocytogenes, Campylobacter jejuni* immediately prior to transplant. Recipients who are ill prior to transplant, as in the case of liver transplant, or those renal transplant recipients dialyzed at a community center can be exposed to nosocomial organisms, such as multi-drug resistant (MDR) gram negative organisms, resistant gram positive organisms, Clostridium difficile and Aspergillus spp. Beyond simple exposure, the immunosuppressive regimen itself contributes to infectious risk, but high dose alone does not impart risk. The composite of dose, duration and sequence of immunosuppressive therapy results in net risk contribution. Additionally, comorbid conditions that can be considered functionally immunosuppressive such as diabetes, malnutrition, neutropenia, alcoholic cirrhosis, and autoimmune diseases will

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play into the net immunosuppressive state. Immunomodulating viral infections such as cytomegalovirus (CMV), Epstien Barr virus (EBV), other herpes viruses such as human herpes virus 6 and 7, and hepatitis B and C virus can result in further immunosuppression, and thereby increase risk of opportunistic infection. Finally, the presence of foreign material, such as intravenous and urinary catheters, which are common at time of transplant and beyond, impair the host natural barrier defense systems, creating an environment conducive to infection. The transplant provider will need to consider all these factors when weighing the infective risk of an individual patient [1].

One of the most predictive aspects of the immunosuppressive regimen on infection risk is temporal distribution from date of transplant (Fig. 7.1) [1, 2]. In the first month after transplantation patients are exposed to the highest intensity immunosuppression, however have not accruded significant immunosuppressive duration to be at risk for opportunistic infections. In the first month, 90% of infectious complications will be surgical related. Infectious organisms include skin flora, such as staphylococcus and streptococcus as well as members of Enterobacteriacae including *Escherichia coli* and Klebsiella species. Of note these patients can be at risk for nosocomial organisms, such as methicillin-resistant S. aureus (MRSA), vancomycin-resistant enterococcus (VRE) or resistant gram negative organisms, including Pseudomonas aruginosa. Patient's risk factors should be considered, particularly if they have recent healthcare exposure, either from hospital admission, dialysis center or residence at long-term care centers. Overall risk of infection depends on surgical complexity, duration of recovery, and complexity of the post-operative course. Additionally, in the first month, the patient is also at risk for donor derived infection. These infections are uncommon due to pre-donation screening practices. Infection can be from community acquired organisms or nosocomial organisms. While case reports exist of uncommon pathogens being transmitted via organ donation, the more common clinical concern is unknown or known bacteremia or fungemia in the donor and/or recipient. Finally, reactivation of HSV is possible in the first month, but less common in the setting of universal CMV prophylaxis.

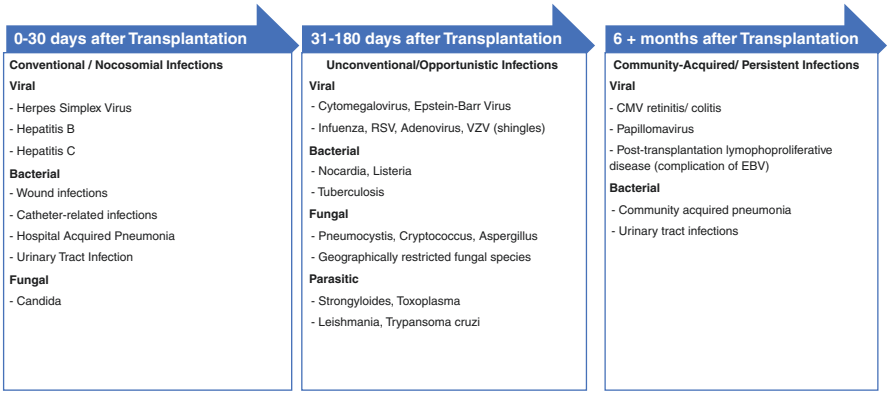

Fig. 7.1 Time line for common infections after transplant

In the following 6 months after transplantation patients can continue to be at risk of residual pathogens related to complexity of post-operative course. However, it is this time period (day 35–180) that patients are at highest risk for opportunistic infections (OI) such as Nocardia, pneumocystis, listeria, cryptococcal disease, and endemic fungal infections. Immunomodulating viruses such as CMV, EBV, VZV, adenovirus, RSV, HCV, HBV and parasitic infections such as *Strongyloides*, toxoplasmosis, leishmania, and *Trypanosoma cruzi* are also a concern. Risk is highest in the first 1–3 months after surgery when immunosuppression is most intense, and sufficient exposure time has elapsed. Patients with chronic or multiple rejection episodes resulting in prolonged exposure to immunosuppressive drugs will have prolonged duration of risk for opportunistic pathogens. Unlike traditional medicine, where a key pathogen is likely to be the major cause of the infected clinical picture, opportunistic infections are known to occur concomitantly, likely due to their immunomodulating effects and resultant intensified immunosuppressed state in the patient. For example, it has been shown that CMV infection increases the risk of pneumocystis pneumonia [3]. Therefore, if an infectious etiology of disease is identified, the transplant provider should continue to search for other opportunistic pathogens until they are ruled out, to prevent graft loss and patient mortality due to inadequate or inaccurate treatment.

After 6 months has elapsed from transplant most centers consider patients to be at a lower risk of rejection and down titrate immunosuppressive regimen intensity. In these patients, standard community-acquired organisms will account for >80% of infection. Therefore, if a patient presents with pneumonia symptoms 10 months post operatively, without history of complication after transplant surgery, it would be appropriate to empirically treat for community acquired pneumonia as the care team would for any general medicine patient. However, a minority of patients will have chronic or progressive viral infections such as CMV, EBV. As previously mentioned, these patients will continue to be at risk for OI due to the immunosuppressive effects of the virus.

In order to prevent OI in transplant recipients, transplant providers will provide antimicrobials prior to disease processes. There are a couple methods to provide infection prophylaxis to transplant recipients. The first approach is Universal Prophylaxis. This method of infection prevention results in the entire population at risk receiving drug to prevent infection. Alternatively, a provider could consider utilizing Preemptive Monitoring/Treatment. In this method of prophylaxis, the population at risk are monitored for early signs of infection and do not receive drug until signs are present. This decreases drug exposure in a population, thereby reducing treatment related toxicity and microbial resistance; however this must be balanced with risk of disease. The recommended prophylactic method after transplant will differ based on organism, as well as individual patient characteristics. Of course, prevention differs from Therapeutic Treatment, in which a patient in an at risk population contracts active infection and receives therapeutic dosages of drug to treat or mitigate a disease process. These differences should be kept in mind throughout this chapter. The following sections are not all inclusive, but will outline specific aspects of transplant infectious disease, and highlight both prevention and

treatment of the most common and/or concerning opportunistic pathogens. Throughout this chapter multiple drug therapies will be reviewed, however in the setting of opportunistic infection, the key to mitigation of infection is to allow host immune reconstitution. The presence of opportunistic infection suggests an imbalance between rejection prevention with iatrogenic immunosuppression and infection. Simply stated, the infected transplant patient is likely over-immunosuppressed and therefore is not at risk for rejection. While this is not always the case clinically, and the balance is more delicate and intricate than that of current scientific understanding, lightening of immunosuppression is prudent, particularly in the setting of severe or life threatening infection.

Donor Derived Infection

Per recent consensus guidelines, infection in the donor is not an absolute contraindication to organ donation, however donors must go through thorough evaluation for overall infective risk and appropriately screened according to UNOS guidelines [4]. Required donor screening tests include; hepatitis B surface antigen and core antibody, hepatitis C serologies including nucleic acid amplification (NAT) on all donors, human immunodeficiency virus (HIV) antibody, HIV NAT, syphilis, cytomegalovirus (CMV) serology, Epstein-Barr virus (EBV) serology, blood and urine cultures [5]. Additional site specific serologies may be collected based on the presence of donor risk factors such as Trypansoma cruzi and human T-cell lymphotropic virus (HTLV-1), or based on geographic location of origin such as coccidiomycosis, strongyloides or West Nile virus NAT. These screening tests are done to guide treatment of the recipient; the donor would not receive drug therapy in the setting of positive serologies. However, the donor could receive antibiotics in the setting of active bacterial infection identified prior to become a donation candidate.

Additionally, determination of donor infective risk should include both laboratory studies as well as pertinent information from the patient's history. Elements to consider in regard to HIV, HBV and HCV risk include recent sexual exposures or sexually transmitted diseases, history of drug use, recent receipt of hemodialysis (HCV risk factor only) or current or recent incarceration [6]. The donor medical team should take efforts to obtain a general medical history as well as recent medication exposure. Additionally, country of origin and previous travel history should be investigated along with any animal exposures to further determine less common, but possible transmissible pathogens. Overall, risk-benefit analysis should be conducted as to whether donation outweighs the risks of possible infection transmission to the eventual recipients; keeping in mind the overall risk of transmission is low.

Some factors to consider when determining if the donor organs are suitable for donation in the setting of infection include the overall susceptibility of the organism. Bacteremia, pneumonia or urinary tract infection can be managed in both

donor and recipient, in the setting of susceptible organisms. Even in the setting of meningitis organs can be donated if the offending pathogen has been isolated, and targeted therapy exists, as in the setting of pneumococcal disease [7]. However, if a potential donor has a history of multidrug resistant organisms that require toxic drug therapy, especially nephro or hepato toxic regimens, serious consideration should occur. Possible central nervous system (CNS) infection is frequently a concern in the donor. Some donor characteristics that could be prompt investigation of a possible underlying infectious etiology contributing to their initial presentation would be cerebrovascular accident in an individual without risk factors (i.e. in the young donor), fever at presentation without etiology and altered mental status or seizures at presentation. It is important to remember than many clinical findings on presentation can have confounding diagnoses. For example, in the 2005 case of donor derived rabies infection, the donor presented with fever, difficulty swallowing and confusion, which would allude to a CNS infection, however the donor also had a positive toxicology screen for cocaine, and imagining consistent with intracerebral hemorrhage. After isolation of rabies a friend reported an incidental bat exposure [8]. In a 2005 report of West Nile virus donor transmission, the donor presented with a traumatic brain injury and epidural hematoma. After the fact his wife reported he had incidental mosquito exposure, and fevers before presentation [9]. In summary, while donor derived infection is uncommon, inadequate screening can have devastating consequences. A multidisciplinary team approach to donor screening is essential to appropriate and safe organ allocation.

Pneumocystis

Pneumocystis jiroveci is an opportunistic pathogen that causes pneumonia (PJP) in immunosuppressed hosts. It's cell wall contains components of both fungi & protozoa. It is found in three identifiable forms; trophozoite, cyst, and sporozoite (intracystic). Due to its slow replication rate (7–10 days) it is difficult to grow in tradition culture media. The gold standard diagnostic method is using Gomori methamine silver nitrate stain of tissue samples/respiratory secretions. However, this method stains cysts which only account for 5–10% of the infectious burden. Clinically molecular diagnostic methods, such as PCR, are preferred and provide rapid and reliable results. Pathogenesis of pneumocystis is via aerosolization of small inoculation. Only 10–100 cysts required to cause disease in the immunocompromised host. It is also thought to be caused by reemergence of latent infection. There is serologic evidence of infection in most people after 4 years of age. Pneumocystis is spread via human or environmental sources and its virulence is tied to T lymphocyte dysfunction, similar to most OI [10]. Universal prophylaxis is typically employed to prevent disease due to its devastating consequences and high associated mortality (as high as 50% with treatment) [11]. Risk of disease without prophylaxis is relatively low;

only 5–15%. While patients are at risk for PJP in between 1–6 months post operatively, the first 6–8 weeks after transplant or during rejection treatment are the highest risk time periods. Contributors to infection include; prolonged corticosteroids, autoimmune flares, prolonged neutropenia, graft rejection and invasive CMV infection. Universal prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX) is the treatment of choice after solid organ transplantation Breakthrough infection while on TMP/SMX is rare. TMP/SMX will also provide protection from infection by *Toxoplasmosis gondii*, Nocardia spp., *Listeria monocytogenes* and standard urinary pathogens. Typical dosing strategies vary between a single strength (80/400 mg) to double strength (160/800 mg DS) tablet daily. Additionally, a DS tablet 3 times weekly dosing strategy can be utilized and is sufficient to prevent PJP. Alternative regimens for those patients with sulfa-allergies or toxicity (most commonly hyperkalemia and cytotoxicity) include; atovaquone, dapsone and inhaled pentamidine. These alternatives are less efficacious, more costly and less palatable than TMP/SMX. Additionally, there is a risk of extrapulmonary pneumocystis in the setting of prophylaxis with inhaled pentamidine [12].

PJP disease has a subacute to acute onset, occurring over days to weeks. Symptoms include low grade fever, sweats, and flu-like symptoms. Findings on auscultation are minimal. Patient reported dyspnea and hypoxia typically outweigh radiographic findings. On radiography, interstitial infiltrates with perihilar predominance then leads to progressive consolidation. This finding is described as “ground glass opacities”. TMP/SMX is the treatment of choice. It is 100% bioavailable, although initial treatment is often given intravenously due to the need for ventilator support. Response to therapy is typically seen in 3–4 days. Treatment courses range from 14–21 days. In some settings, longer therapy may be warranted. It is recommended to concomitantly lighten of immunosuppression. When respiratory support is needed, adjunctive corticosteroids are recommended. Common side effects associated with TMP/SMX include nephrotoxicity and bone marrow toxicity including thrombocytopenia and neutropenia. Some treatment alternatives that can be used in the setting of intolerance include; clindamycin and primaquine, intravenous pentamidine, dapsone and trimethoprim. All are associated with high rates of adverse effects. Treatment is typically followed by >6 months of prophylaxis, although there is no clinical consensus [10].

Immunomodulation Viruses

Cytomegalovirus (CMV)

CMV is a ubiquitous herpesvirus present in 40% to >70% of general population. It is one of the most common infections in transplant patients and is an independent risk factor for graft loss and mortality. Reactivation of latent infection occurs in >50% of seropositive patients. Onset is typically early after transplantation, ranging from the first 1–4 months with the highest risk in the first 5–13 weeks. Pathogenesis

relies on dysfunctional T cells which then results in uncontrolled CMV replication. Disease manifests in the non-immunocompromised individual asymptomatically, or in a mononucleosis-like clinical picture. Immunosuppressed patients will have unexplained fever, leukopenia, and end organ manifestations [13, 14].

Prevention is based on exposure related risk stratification. Serostatus is determined via donor and recipient IgG. Patients without exposure transplanted with allografts from CMV IGG positive donors are of highest risk (D+/R−). Seropositive recipients (R+) are considered moderate risk. Unexposed donor recipient pairs (D−/R−) are low risk. Prior to effective prophylaxis the incidence of CMV after SOT was approximately 20–60%. Currently, prophylactic measures depend on the transplant center, although universal prophylaxis is preferred in high risk individuals per consensus guidelines [13, 14]. High risk individuals typically receive prophylaxis with valganciclovir (VGC), the oral prodrug of ganciclovir (GCV). Low risk patients are not considered at risk for CMV associated disease and therefore guidelines do not endorse prophylaxis with CMV specific antiviral therapy, although they do endorse the use of acyclovir to prevent HSV reactivation [14]. Universal prophylaxis is preferred at many transplant centers due to the many indirect effects of CMV infection including allograft rejection/injury, bacterial superinfections, and immunomodulatory effects resulting in infection with other opportunistic pathogens, or PTLD. Additionally, there is a possible association with chronic allograft dysfunction including vanishing bile duct syndrome after liver transplant, bronchiolitis obliterans in lung transplants, and chronic glomerulopathy after renal transplant. The direct effects of disease treatment, such as therapy toxicities, are also prevented with prophylaxis [1].

To best outline treatment, it is necessary to differentiate CMV infection from CMV disease. CMV infection describes the presence of virus as detected by culture (throat swab, urine), molecular techniques (PCR, antigenemia), and/or serological status changes. In the setting of infection, the patient may be asymptomatic and treatment is not always indicated. In contrast, symptoms must be present to be classified as CMV disease. Signs & symptoms of CMV include fever, leukopenia and possible end organ involvement including colitis, hepatitis, pneumonitis, meningioencephalitis, and pancreatitis. In the setting of CMV disease, treatment is indicated. Infection is usually detected in the laboratory by measuring circulating virus in blood via either antigenemia or PCR. Antigenemia (leukocyte pp65 Ag) is more sensitive and specific assay then PCR, however is more laboratory intense, and requires adequate leukocytes to conduct. A positive antigenemia is considered to be >5 cells/slide. CMV DNA PCR has largely replaced antigenemia. It is considered detectable at levels >250 IU/mL, although this varies between laboratories. Treatment of infection is indicated in the setting of high viral load, or significant symptoms. Ganciclovir is the treatment of choice given at a dose of 5 mg/kg Q12h (adjust for renal function). The oral prodrug, valganciclovir is used as step down therapy and in the outpatient setting at a treatment dose of 900 mg by mouth twice daily (adjust for renal function).

Presentation of CMV disease typically occurs 1–4 months after SOT in the absence of prophylaxis. With prophylaxis, disease occurs 1–4 months after

discontinuation of the prophylactic agent. A recent study in high risk patients demonstrated reduction in late onset CMV when prophylaxis was extended from 100 to 200 days [15]. This is now the standard prophylactic interval for high risk patients. Symptoms of CMV disease include a mono-like, fever, malaise, arthralgias, myalgias, leukopenia, and organ specific complaints, most commonly colitis. Diagnosis is typically determined via tissue histology in combination with clinical suspicion and molecular diagnostic methods from tissue samples (PCR) End organ disease warrants treatment with IV ganciclovir (5 mg/kg Q12 hrs, renal adjustment) for at least 2 weeks. As CMV is an immunomodulating virus it is important to rule out concomitant opportunistic infections in the setting of disease. Additionally, reduction of the immunosuppressive burden in warranted. The current CMV consensus guidelines recommend lightening immunosuppression in cases of severe disease and/or high viral load (VL), nonresponse to antiviral therapy (including suspected antiviral resistance), and neutropenia [13, 14]. In practice, the antimetabolite component of a multidrug immunosuppressive regimen is typically targeted for dose reduction over the CNI or corticosteroid, as reduction of the antimetabolite will lighten immunosuppression and reduce iatrogenic myelosuppression while preserving the important antirejection role of the CNI and preventing adrenal insufficiency in patients receiving chronic prednisone.

Drug-resistant CMV is an emerging clinical condition that is associated with extensive patient morbidity and mortality, and places a significant burden on the health care system. The incidence of GR-CMV while receiving prophylactic valganciclovir is low (0–3%); however, recent literature suggests that the incidence is increasing [16]. Previously described risk factors for development of GR-CMV include prolonged GCV exposure (median of 5 months) and unchecked viral replication in the setting of antiviral exposure including lack of prior viral exposure (D+/R−), high immunosuppressive burden, high disease burden, and inadequate drug delivery. When resistance occurs, outcomes are poor. Recently published literature describes rates of virologic failure and recurrence from 20% to 30% and mortality as high as 30% [17, 18]. Available treatment options are limited, are associated with efficacy concerns, and possess significant toxicities. Although novel antivirals are currently under investigation for this indication, their course to market has been plagued with efficacy and safety issues. Prevention of the development of resistance appears to be the most efficacious treatment at this time. Preventive measures should focus on reduction of unchecked viral replication in the setting of antiviral exposure, particularly inadequate drug delivery.

Epstein Barr Virus

Epstein Barr virus (EBV) is a gamma herpes virus that targets oropharyngeal epithelial cells and B-lymphocytes causing B-cell activation and proliferation. It is ubiquitious with 90% of adults infected by the age of 40. EBV has proliferative

potential with viral survival advantage resulting from expansion of the pool of host B lymphocytes. Primary infection typically occurs in childhood and is asymptomatic. In teenage years and adulthood, it manifests as mononucleosis. Its reactive and transforming potential is inhibited by the competent immune system, however in the immunosuppressed host can result in uncontrolled proliferation of infected B lymphocytes leading to a lymphoma-type picture known as post-transplant lymphoproliferative disorder (PTLD). PTLD occurs in approximately 1% to 16% of solid organ transplants and ranges in severity from benign polyclonal lymphocytosis to highly malignant lymphomas. While direct causation is unclear, the EBV genome can be found in >90% PTLD occurring within first year after transplant suggesting direct correlation. However, the etiology of late onset PTLD is less clear, with up to 45% of cases being EBV negative [19, 20]. The risk of developing PTLD depends on allograft type, exposure to lymphocyte-depleting therapies, and the serologic status of the donor and recipient. The highest risk is in EBV-seronegative recipients of EBV-seropositive donor organs (D+/R-). The frequency of PTLD is increasing, though to be due to increased potency of mainstay maintenance immunosuppressive drug therapy. The optimal strategy for the prevention of PTLD has not been established, although limiting patient exposure to aggressive immunosuppressive regimens, rapid withdrawal and tapering of immunosuppressive agents, and anti-viral prophylaxis appear to lower the risk.

Unlike CMV, universal prophylaxis for EBV is not recommended due to the lack of clinical literature demonstrating any efficacy of anti-virals in the prevention of PTLD in EBV-seropositive recipients. This lack of preventive effect is likely due to anti-viral drugs mechanisms. Currently available antiviral agents (acyclovir, ganciclovir, etc) are only active in the setting of lytic EBV replication required for horizontal spread of virus from host to host, and do not inhibit replication in latency that is found in EBV-seropositive recipients [21]. For this reason, only patients at high risk for, or experiencing de novo EBV infection, such as unexposed pediatric patients, should be considered candidates for antiviral therapy [22, 23].

BK Polyoma Virus

BK is a ubiquitous polyoma virus with an affinity for the transplanted kidney. In 1978 the first case report of BK virus induced nephropathy of a kidney transplant was described. Since that time, BK virus has become one of the leading infectious causes of graft loss, occurring in 10–80% of infected kidney recipients. Approximately 30–40% of kidney recipients display BK virus reactivation following transplant, which may progress to severe allograft dysfunction known as BK virus nephropathy [24]. Symptoms mirror rejection. Typical presentation is approximately 10–13 months post-transplant. Diagnosis of BK viral nephropathy requires a combination of molecular diagnostics and with clinical correlation. No

pathognomonic sign or symptom indicates disease. Urinalysis will demonstrate pyuria, hematuria and cellular casts consistent with interstitial nephritis. Urine cytology can demonstrate “Decoy cells”, or cells with enlarged nucleus & single large intranuclear inclusion. PCR of patient serum is 100% sensitive and 88% specific. Quantitative PCR of blood and urine can be used to monitor. While PCR positivity in urine is not diagnostic it may predate clinical symptomology. Histology will demonstrate Intranucleic inclusion bodies and tubulointerstitial inflammation. It has been suggested that utilization of more potent immunosuppression may have played a role in the rise of BK virus allograft nephropathy (BKVAN) [24]. Existing treatment of BK virus infection and nephropathy is not well defined and options are limited. Currently, a reduction of immunosuppressive therapy combined with close monitoring of BK viruria and viremia remains the mainstay of management. Other potential therapies include cidofovir, leflunomide, IVIG, and potentially quinolones. Studies utilizing antiviral agents were not randomized, and immunosuppression was concomitantly lightened. Quinolones are theorized to exert their effect by inhibiting DNA topoisomerase activity and SV40 large T antigen helicase [25]. Screening for BK viremia provides the opportunity to reduce immunosuppression and subsequently clear BK viremia prior to developing nephropathy [26].

Tuberculosis

Tuberculosis (TB) refers to disease caused by any organism in the Mycobacterium tuberculosis complex; tubercle bacillus (*M. tuberculosis*), *M. bovis*, *M. africanum*, *M. microti,* or *M. canetti*. Incidence after transplant is 20–74 times the incidence in the non-immunocompromised population. It is less common in developed countries with incidence of 1.2–6.4%; in endemic areas incidence after transplant can be as high as 15% [27]. Risk factors include lymphocyte-depleting induction such as OKT3 and anti-thymocyte globulin administration, diabetes, chronic liver disease (in kidney transplant recipients), immunomodulating viral infections and previous TB exposure [28]. Transplant recipients tend to have atypical presentation associated with high morbidity & mortality; which can be further increased by concomitant diabetes of chronic liver disease. Additionally, the drugs used to treat TB are associated with significant toxicities and many pertinent drug interactions.

Pathogenesis is due to latent reactivation in the majority of patients, although acquisition from the graft has been described in case reports [29]. Presentation is typically early; in the first 9 months after transplant in approximately 60% of cases. Signs and symptoms are most commonly pulmonary, but can be disseminated and extrapulmonary at a higher frequency than in the non-immunosuppressed population. TB in the transplant recipient is frequently associated with other infections in up to 23% of cases, including CMV, nocardia, community acquired pneumonia,

urinary tract infections and aspergillosis. Fever is considered to be the unifying symptom [27].

Gold standard therapy for the non-transplant patient with TB is isoniazid, rifampin, pyrazinamide plus the addition of ethambutol and/or streptomycin. Unfortunately, there are major issues related to this regimen in transplant recipients. Rifampin has significant induction effects on CYP 3A4 mediated liver enzymes. This contributes to a potential for graft loss up to 25%. Increased calcineurin inhibitor dosage 3–5 times the previously stable dosing is recommended. The use of rifabutin, which has less induction effects, can be considered. Additionally, backbone therapies are associated with significant hepatotoxicity (isoniazid and pyrazinamide) as well as nephrotoxicity (streptomycin). Ethambutol levels can be increased by competitive metabolic pathways with calcineurin inhibitors resulting in ototoxicity. The quinolones can be considered as alternative agents, or in combination in the setting of concern for drug resistant TB. Reduction of immunosuppression may be beneficial if severe manifestations are present or there is late diagnosis; steroid suppression of macrophages has been suggested as most important disease modulator. Duration of treatment with the 3 drug regimen is at least 1 year [30].

Screening and prophylactic treatment prior to transplant is essential. Screening tools include the purified protein derivative (PPD), Interferon gamma release assays and chest radiography. Tests for intradermal delayed type hypersensitivity to purified protein derivatives of TB are considered the standard screening test with approximately 80% sensitivity in the non-immunosuppressed population. However, PPD has up to 70% anergy in transplant recipients; although repeating the test can increase results by 10% via a booster effect. Additionally, there is an 8 week lag to positivity after exposure. Interferon gamma release assays (QuantiFERON Gold-IT, T-SPOT.TB) tests for INF-gamma production against TB antigens. The QTF-G.IT is an ELISA for ESAT-6, CFP-10, and TB7.7 with approximately 80% sensitive. T-SPOT.TB is an ELISPOT for ESAT-6, CFP-10 with approximately 90% sensitive. Advantages include lack of false positivity in the setting of previous BCG vaccination, no boosting effect, no reader bias, and 95% specificity [30]. Finally, chest radiography can be used to identify nodules. However, this method is less sensitive in areas where chronic granulomatous disease is more common, such as areas with endemic mycoses. In the setting of a positive screen the gold standard treatment is isoniazid × 9 months. Treatment can be initiated prior to transplant and completed post-transplant.

Nocardia

Nocardia is a ubiquitous, environmental saprophyte. It is an aerobic, gram positive rod which has a characteristic branching, beading, or filamentous pattern on gram stain. It is naturally found in soil, organic material and water. Nocardia belongs to

the genus actinomycetes and includes 12 clinically relevant species with *N. asteroides* complex being the most common, accounting for 90% of infection. Prevalence in the transplant population is 0.7–3%. It is most common in heart, liver, kidney recipients. Disease is typically manifested as pulmonary infection, however nocarida has a predilection to dissemination to the brain. Treatment of disease caused by *N. asteroides* complex is TMP/SMX 15 mg/kg/day divided 2–4 times daily. Alternative therapies include imipenem plus amikacin, third generation cephalosporins, minocycline and linezolid. *N. farcinica*, *N. nova*, *N. otitidiscaviarum* have high rates of sulfa resistance, therefore combination therapy should be employed empirically. TMP/SMX used for PJP prophylaxis can prevent nocardiosis and is more effective if given daily [31].

Cryptococcus

Cryptococcus is a ubiquitous environmental saphrophyte found in soil, and associated with bird droppings. It is a budding, encapsulated yeast. *C. neoformans* accounts for the majority of infection and is widely distributed. *C. gattii* is also pathogenic, but less commonly isolated. Evidence suggests the pathophysiology to be related to both reactivation and primary infection. Incidence after solid organ transplant is approximately 3% with mortality as high as 50% in patients with central nervous system (CNS) disease. Presentation is disseminated disease in more than half of cases; usually with CNS involvement. Isolated pulmonary disease is more common in patients receiving CNI based regimens, which is thought to be due to the theoretical anti-cryptococal activity of CNIs via targeting of fungal calcineurin homologs. Diagnosis is determined via culture, histology and/or cryptococcal antigen (CrAg) of serum. In the setting of cryptococcal meningitis approximately 90% of patients will have positive serum CrAg; with approximately 80% positive in the setting of pulmonary disease. CSF CrAg can also be obtained for diagnosis of cryptococcal meningitis. Magnetic resonance imaging (MRI) is more sensitive for CNS diagnosis than CT and will show non enhancing lesions. Cryptococcosis can manifest as meningioencephalitis, disseminated disease, or severe pulmonary disease [32].

Treatment requires induction therapy with amphoteracin and flucytosine (100 mg/kg/day) × 14 days. This is followed by consolidation with high dose fluconazole (400–800 mg/day) × 8 weeks. Finally, maintenance/suppression follows with lower doses of fluconazole (200–400 mg/day) × 6–12 months. In the setting of isolated pulmonary disease fluconazole 400 mg/day × 6–12 months can be sufficient and will spare the use of nephro & cyto-toxic induction agents. Although lightening of immunosuppression is recommended it's important to be aware that immune reconstitution syndrome (IRIS) can be confused with worsening cryptomeningits. Routine prophylaxix is not recommended [33].

Toxoplasmosis

Toxoplasmosis is an infection by the protozoan parasite *Toxoplasma gondii*. In most of the general population, this infection is generally asymptomatic or only mildly symptomatic. However, in the solid organ transplant population, toxoplasmosis can cause significant morbidity and mortality. The reason for increased risk of disease in the transplant population is twofold; firstly iatrogenic immunosuppression increases the risk of reactivation of latent disease, and secondly, there is a possibility of transmission via serologic mismatch. Heart transplant recipients have the greatest risk for toxoplasmosis, but disease can occur in kidney, liver, and pancreas transplants.

When *T. gondii* is latent, it can be found in cysts that form in muscle tissues, as well as the brain and phagocytic cells. When it is spread to seronegative recipients through a donor mismatch, the infection becomes disseminated due to the lack of protective immunity. Disease is usually early post-transplant; typically within the first 3 months. The clinical presentation in immunocompromised patients varies in severity depending on degree of immunosuppression and timing of appropriate anti-toxoplasmosis treatment. Symptoms are initially nonspecific and can include fever, respiratory, or neurological symptoms. Severe disease involves myocarditis, encephalitis, pneumonitis, or multi-organ involvement.

Prophylactic therapy is recommended. The first line agent is trimethoprim-sulfamethoxazole (TMP/SMX) 80–160 mg qday or 160–320 mg 3–7 times weekly. For patients with allergy to sulfa drugs the alternative prophylactic therapy is pyrimethamine 25 mg/day. There is a lack of clinical consensus regarding the duration of prophylactic treatment; ranging from 6 weeks to 6 months in D+/R− patients. Some centers will employ lifetime prophylaxis in high risk recipients.

First line treatment for toxoplasmosis is as follows: pyrimethamine 200 mg PO once, followed by 50–75 mg PO QD; sulfadiazine 4–6 g/day in four divided doses; and folinic acid 10 mg PO QD to prevent pyrimethamine induced bone marrow toxicity. In sulfa-allergic patients, the sulfadiazine would be replaced with either IV clindamycin 1.2–4.8 g/day or PO atovaquone 750 mg QD. The duration of treatment is at least 6 weeks, or until the symptoms resolve [34].

Listeria Monocytogenes

Listeria monocytogenes is an aerobic, gram positive coccobacillus. Approximately 2–10% of the general population is colonized with this organism. It is an uncommon pathogen with only 0.7 case/100,000 population. At risk populations include infants (10 cases/100,000 population), the elderly (1.4 cases/100,000 population) and immunosuppressed populations such as patients with HIV, patients receiving cancer chemotherapy, diabetics, cirrhotics, and patients receiving dialysis and transplant

recipients. Listeria is a food borne pathogen that can be associated with undercooked chicken, hot dogs, deli meat and unpasturized dairy products such as cheese and milk. Common clinical manifestations of listeriosis include bacteremia, meningitis, and gastroenteritis. End organ infections such as pneumonia, abscesses, endocarditis, and peritonitis are possible. Treatment is a combination of ampicillin and synergistic gentamicin. Listeria is universally resistant to cephalosporins. If listeria is a suspected pathogen, addition of ampicillin to the choice empiric cephalosporin is prudent; i.e. in the setting of meningitis. In the setting of penicillin allergic patients the recommend alternative is vancomycin and gentamicin or TMP/SMX and rifampin. Treatment duration is typically at least 3 weeks and post treatment suppression can be used, particularly in the setting of significant immunosuppression. TMP/SMX used post-transplant for PJP prophylaxis will also prevent listeriosis. Patients are counseled to microwave hot dogs, deli meat and avoid unpasteurized dairy [35].

Endemic Fungi

Histoplasmosis

Histoplasma capsulatum is a soil borne organism found in soil rich in bird and/or bat feces endemic to the Americas, Africa, Asia. The United States endemic areas include the Ohio & Mississippi River valleys. Manifestations of histoplasmosis include isolated pulmonary disease, disseminated, and CNS infection. The urinary antigen is used to detect disease, with >90% rates of detection. A serum antigen test also can be employed; 80% of patients with disseminated disease will be positive. This test can have cross reactivity with other fungi, most notably, blastomycoses. Antigen testing can also be used to monitor response to treatment.

Amphotericin for 1–2 weeks is recommended for treatment of moderate to severe pulmonary disease and disseminated histoplasmosis. Amphotericin is followed by itraconazole maintenance for at least 12 weeks and can be lifelong in immunosuppressed patients. No treatment is necessary for mild-moderate isolated pulmonary. Of note, itraconazole is more effective than other azoles, however agents that penetrate the CNS, such as fluconazole or voriconazole may have a role in CNS disease. Therapeutic drug monitoring is recommended; with goal itraconazole levels >1 but <10 mcg/mL [36].

Blastomycosis

Blastomyces dermatitidis is a dimorphic fungi found in richly organic soil endemic to the midwest, south-eastern, south-central united states, and the Canadian provinces bordering the Great Lakes. Diagnosis is via culture or histology. A urinary

antigen test is available, however this test cross reacts with other fungi, notably histoplasma. Manifestations range from subclinical to acute/chronic pneumonia. Disease can progress to fulminant multilobular pneumonia and acute respiratory distress syndrome. It also can manifest as cutaneous, osteoarticular, genitourinary, or CNS disease in 25–40% of cases. Isolation of fungus is either via culture or direct histologic observation. Treatment is necessary in the case of severe disease or for immunosuppressed patients. The treatment of choice is amphotericin for 1–2 weeks followed by itraconazole x 12 months. Fluconazole has limited activity and is not recommended [37].

Coccidiomycosis

Coccidiomycosis, or "Valley Fever", is a disease caused by *Coccidioides immitis* and *Coccidioides posadasii*. It is endemic to southern Arizona, California, southern New Mexico and west Texas. There is a 4–9% risk of infection in transplant recipients in endemic areas. Fifty-sixty five percent of patients with have subclinical infection. Diagnosis is via culture or histology. The most common presentation is similar to community acquired pneumonia. Five to ten percent of patients will have residual pulmonary sequelae (nodules). Extrapulmonary coccidomycosis is uncommon in the non-immunocompromised population (0.5%) but can be as high as 30–50% in transplant recipients.

No treatment is necessary for mild pulmonary infection in the non-immunosuppressed population. However, in the setting of severe disease or immunocompromised patients amphotericin is the drug of choice. Less severe disease treatment or stepdown therapy can be with fluconazole or itraconazole. Prophylaxis is employed after solid organ transplant if the patient is residing in an endemic area & with positive serologies [38].

Parasitic Infection

Strongyloides Stercoralis

Strongyloides is a tropical soil dwelling nematode with a complex life cycle in humans that involves the gut, heart, lungs. Infection can manifest as chronic and limited or acute and disseminated and frequently involves the central nervous system. Dissemination is usually accompanied by gram negative bacillus blood stream infection. The treatment of choice is ivermectin. The preferred alternative is albendazole.

Trypanosoma Cruzi

Trypanosoma cruzi is the pathogen which causes Chaga's disease. It is a protozoan carried by the reduvid bug. Disease is transmitted via a "blood meal" (bite). It is endemic to Central and South America, where 40–50% population infected. The pathogen has a predilection for infection of muscular tissue & neuroglial cells. T. cruzi has a chronic, latent phase, which in the setting of iatrogenic immunosuppression can result in reactivation. Reactivation then results in inflammation and resultant tissue destruction. This is most significant in the setting of heart transplant where myocarditis can result in heart failure. Disease can also be manifested as meningioencephalitis, or megacolon. Beyond reactivation, disease can also be transmitted via transfusions [39].

Conclusion

In summary, due to their iatrogenic immunosuppression and resultant T cell dysfunction, transplant recipients are at high risk for both common infections, such as urinary tract infection and pneumonia, as well as opportunistic infections. Common infections, treatment, prophylaxis are summarized in Table 7.1. Risk varies with dose, duration and sequence of immunosuppression. By utilizing these predictive risk factors, the transplant clinician can select the best empiric therapies to cover suspected infections in each unique patient scenario. Care should also be taken to prevent disease when applicable, as the preventative agents are better tolerated, and in many cases, infection itself puts both patient and the allograft at risk of negative outcomes.

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Table 7.1 Common infections post-transplant

Infection	Causative agent	High risk period of infection	Primary prophylaxis	First-line treatment	Alternative agents	Rate/regions of infection
Bacterial						
Tuberculosis	*Mycobacterium tuberculosis complex*	0–9 months post-transplantation	N/A	Combination of: (1) isoniazid (2) rifampin (3) pyrazinamide (4) Ethambutol +/− streptomycin	Rifabutin Fluoroquinolones	Non-endemic regions: 1.2–6.4% Endemic regions: 15%
Nocardia	*Norcardia spp.*	2–6 months post-transplantation	*N/A *will be covered by TMP/SMX if being used for PJP prophylaxis	TMP/SMX 15–20 mg/kg divided Q6–8 hours +/− alternative agents if non-asteroides complex suspected	Imipenem + Amikacin third Gen Cephalosporins Minocycline Linezolid	0.7–3%
Listeria	*Listeria Monocytogenes*	2–6 months post-transplantation	*N/A *will be covered by TMP/SMX if being used for PJP prophylaxis	Ampicillin + Gentamicin	Vancomycin + Gentamicin TMP/SMX + rifampin	0.7 cases/100,000 people
Viral						
CMV	*Cytomegalovirus*	5–13 weeks post-transplantation	High Risk: Valgancyclovir Low Risk: Acyclovir	Ganciclovir 5 mg/kg q 12 hours	Resistant Infection: IVIG Foscarnet	20–60% without prophylaxis

(continued)

Table 7.1 (continued)

Infection	Causative agent	High risk period of infection	Primary prophylaxis	First-line treatment	Alternative agents	Rate/regions of infection
EBV	*Epstein-Barr Virus*	2 months-1 year post-transplantation	Not recommended	Primary (de novo) Infection *: Acyclovir	Ganciclovir *Treatment has not been shown to be beneficial in preventing reactivation	90% of adults infected by age 40 Development of PTLD: 1–16%
BK	*BK Polyoma Virus*	10–13 months post-transplantation	N/A	Reduction of immunosuppressive therapy + monitoring	Cidofivir Leflunomide IVIG Fluoroquinolones	10–80% of kidney transplant recipients
Fungal						
Cryptococcous	Most Common *Cryptococcus neoformans* Less Common *Cryptococcus gattii*	2–6 months post-transplantation	Not recommended	Induction amphotericin + flucytosine (100 mg/kg/day) × 14 days. Consolidation Fluconazole: 400–800 mg/day × 8 weeks Maintenance Fluconazole 200–400 mg/day × 6–12 months	Posaconazole Voriconazole (less available data)	3%
Histoplasmosis	*Histoplasma capsulatum*	2–6 months post-transplantation	N/A	Amphotericin 1–2 weeks followed by itraconazole for at least 12 weeks to indefinite therapy	*CNS Disease* Fluconazole Voriconazole	Endemic regions include: North America, South America, Asia, Africa

Blastomyces	*Blastomyces dermatitidis*	2–6 months post-transplantation	N/A	Amphotericin 1–2 weeks followed by itraconazole for at least 12 months	Fluconazole is not recommended	Endemic regions include: Midwestern, south-eastern, south-central regions of the United States. Great Lakes region of Canada.
Coccidiomycosis	*Coccidiodies immitis* *Coccidiodies posadasii*	2–6 months post-transplantation	Yes: transplant recipients with positive serologies and living in endemic region	Severe Disease: Amphotericin Less Severe Disease: Fluconazole Voriconazole		4–9% risk of infection in endemic regions of Arizona, California, New Mexico, West Texas
Parasitic						
Strongyloides	*Strongyloides stercoralis.*	2–6 months post-transplantation	N/A	Ivermectin	Albendazole	N/A
Protozoan						
Toxoplasmosis	*Toxoplasma gondii*	First 3 months	Yes; TMP/Sulfa Alternative: pyrimethamine	Pyrimethamine 200 mg × one dose, then 50–75 mg daily Sulfadadiazine 4–6 g/ day in 4 divided doses Folinic Acid 10 mg daily	Sulfa Allergy Clindamycin IV or Atovaquone PO instead of sulfadiazine	Generally asymptomatic in general population
Other						
Pneumocystis Pneumonia	*Pneumocystis jerovicii*	6–8 weeks post-transplantation	Yes; TMP/SMX Alternatives: Atovaquone, Dapsone, Pentamidine	TMP/SMX Adjunct corticosteroid therapy	Clindamycin Primaquine Pentamidine Dapsone Trimethoprim	Without prophylaxis 5–15%

*Nocardia etc is not targeted ppx, however will receive PPX for this if TMP/SMX is used for PJP ppx

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Chapter 8
Post Kidney Transplant: Malignancies

Maha Mohamed

Introduction

In the modern era of immunosuppression, solid organ transplant (SOT) survival and the annual rate of rejection have improved. However, this increase in immunosuppressive efficacy has come with an increased rate of post-transplant infection and malignancies [1]. It is now recognized that the potency of immunosuppression medications and oncogenic viruses increase the risk of post-kidney transplant malignancies [2], and malignancy post kidney transplant is a major cause of morbidity and mortality among recipients with otherwise successful transplantation. In this chapter, we will review general issues of cancer following kidney transplantation.

Epidemiology

Post kidney transplant malignancy incidence rates and types are associated with factors related to both donor and recipient factors as well as the organ transplanted [2]. These factors include pre-existing donor related malignancy, pre-transplant recipient related malignancy, and *de novo* posttransplantation malignancy. Post SOT cancer risk is elevated, with an estimated standardized incidence ratio (SIR) of (2.1, 95% CI 2.06–2.14) [2]. Moreover, the cancer risk is significantly elevated among infection-related malignancies (Table 8.1) [2–5]. Studies have shown an overall 2–4 times increased risk of cancer compared to the general population [2, 6, 7]. This risk is particularly high among viral-driven malignancies like post-transplant

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Table 8.1 Cancer risk in kidney transplant recipients

Author (reference #)	Year	Source	Organ transplanted	Cohort (n)	Cancer type	The reported rate of occurrence
Angles et al. [2]	1987–2008	SRTR	Kidney (58.4%)	175,732	Non-Hodgkin lymphoma	194.0 per 100,000 persons-years
					Lung	173.4 per 100,000 person-years
					Liver	120.0 per 100,000 person-years
					Kidney	97.0 per 100,000 person-years
Kotton et al. [3]	2005–2014	SRTR	Kidney	No report	PTLD	0.6%
			Pediatrics kidney		PTLD	2.4%
Kim et al. [5]	1989–2009	Single center Korea	Kidney	2461	Overall malignancy	5.64%
					Malignant lymphoma	13%
Yanik et al. [4]	1998–2010	SRTR	Kidney 58%	187,384	Non-Hodgkin lymphoma	12.7%
Yanik et al. [4]	1998–2010	US Cancer Registry	Kidney 58%	187,384	Non-Hodgkin lymphoma	63.4%

lymphoproliferative disorder (PTLD) due to Epstein - Barr virus (EBV), Kaposi Sarcoma (Human Herpes Virus 8), and anogenital cancer (Human Papillomavirus) [7]. Previous studies estimated the cancer incidence for kidney transplant recipients is as high as 40% among recipients 20 years post-transplantation, compared to 6% among age-matched non-transplant population [8]. Post solid organ transplant malignancy is reported to occur in more than 30 organs, with the highest occurrences in the kidney (58%), liver (22%), heart (10%), and lung (4%) [2].

Post kidney transplant malignancy may be either a recurrence of pre-transplant cancer that is not related to transplant or cancer that contributed to the transplant. Studies have shown there is significant variability among recurrence rates of different cancers [9]. Although malignancy can be transmitted from the donor through transplantation, the quantified risk evidence is lacking [1]. In an analysis performed by the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS), data showed that 1–2% of deceased donor transplantations were performed using organs from a donor with a history of cancer [10, 11]. Exact recurrence rates in this transplant population are unavailable, as literature describing donor-related cancer transmission is limited to anecdotal reports, registries, and

retrospective studies [12]. Evidence supporting post-cancer solid organ transplant is extracted from large registries, the Israel Penn International Transplant Tumor Registry, OPTN, and UNOS [13].

Skin Cancer

Non-melanoma skin cancer is the most commonly reported malignancy post-kidney transplant [8, 14, 15]. All skin cancers after kidney transplant represent 40–50% of all post kidney transplant malignancy [16]. The most reported skin cancers after kidney transplant are squamous cell skin cancer (SCC), basal cell skin cancer (BCC), Kaposi sarcoma, Merkel cell carcinoma, and malignant melanoma (MM) (Table 8.2) [16–19]. The reported incidence of squamous cell skin cancer is 65–250 times higher in kidney transplant recipients compared to the general population, with a histology that is more aggressive and poorly differentiated [8, 14, 18, 20, 21].

A pre-transplantation history of skin cancer is a risk factor for post- kidney transplant skin cancer [22]. Previous studies recommend a 2-year waiting period before transplantation for candidates with a history of high-risk SCC [22]. Additionally, azathioprine is implicated in predisposing patients with melanoma and non-melanoma skin cancer through its synergistic effect with ultraviolet light via chronic oxidative stress damage and DNA mutation [1, 23].

Post-transplant Lymphoproliferative Disorder

Post-Transplant Lymphoproliferative Disorder (PTLD) remains a serious, fatal complication after transplant. Multiple studies have shown that donor and recipient EBV serostatus, recipient age, type of solid organ transplanted, induction therapy, and immunosuppressive maintenance regimen and duration are risk factors for

Table 8.2 Skin cancer incidence in transplant recipients

Author (reference #)	Year	Source	Organ transplanted	Cohort (n)	Cancer type	The reported rate of occurrence
Moloney et al. [16]	1994–2001	NRT & NCR	Kidney	Not reported	Non-melanoma	69.3%
					Carcinoma in situ	19.2%
Zwald [17] and Hartevelt et al. [19]	1966–1988	Dutch single center	Kidney	764	SCC	250 times higher compared to general population
					BSC	10 times higher

NCR National Cancer Registry, *NRT* National Renal Transplant

PTLD [24–27]. However, the role of host genetic variability [28, 29], the predictive value of peripheral blood EBV DNA, and the association between the recipient's primary kidney disease and PTLD remain controversial [30–32].

The World Health Organization (WHO) classifies PTLD as a spectrum of lymphoid tissue disorders, ranging from infectious mononucleosis (EBV infection) to lymphoma [30]. PTLD has a bimodal distribution. The early disease occurs mostly among pediatric recipients and within the first two-years after transplantation; late peak occurs in later years post-transplantation [2, 8, 33].

The variability in the risks factors for early versus late PTLD varies support it's heterogenic etiology. Non-Hodgkin's lymphoma is high among young transplant recipients at high risk of primary EBV infection [2, 34, 35].

Pathogenesis

Post kidney transplant malignancy is multifactorial. Risks associated with post-transplant malignancy include male gender, older age, intensity and duration of immunosuppressive regimen, history of viral infection, and sun exposure [36–40]. Furthermore, all reports indicated that type of solid organ transplanted, genetic predisposition, history of pre-transplantation malignancy, and vintage dialysis are associated risk factors for post solid organ transplant malignancy [1, 39, 41, 42]. The direct oncogenic effect of immunosuppressive medications, like calcineurin inhibitors, antimetabolites, and B and T cell depleting agents' impact on the immune-surveillance function, curtail post-transplantation carcinogenesis.

Clinical Presentation

The presentation of post solid organ transplant malignancies usually contain symptoms of the organ involved eg. Lymphadenopathy; gastrointestinal tract, lung, central nervous system, or mass related effect; and malignancy related symptoms such as fever, unexplained weight loss, night sweats,.

Treatment

Reduction of immunosuppression medications is the mainstay therapeutic approach for malignancy in post solid organ transplant patients [30, 43]. However, a reduction in immunosuppression alone might not be sufficient to control the disease [44]. Furthermore, there is a scarcity of data regarding the role of antiviral therapy in cancer treatment. In the face of higher incidence of post-kidney transplant malignancies and their associated poor outcomes, prevention by surveillance remains the

most important tool. Mammalian Target of Rapamycin inhibitors (mTORi) use in kidney transplant have been shown to reduce the risk of new SCC and be effective in treating Kaposi Sarcoma [45].

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Chapter 9
Post Kidney Transplant: Hypertension

Vikram Patney and Fahad Aziz

Introduction

Hypertension is highly prevalent in patients with advanced chronic kidney disease and End Stage Renal Disease (ESRD) patients and frequently persists even in patients who receive kidney transplants. Uncontrolled hypertension in kidney transplant recipients is well-known to be associated with shortened allograft and patient survival. Cardiovascular (CV) disease is the most common cause of death with a functioning allograft and hypertension accounts for a substantial portion of this increased CV risk.

Hypertension was the second most common primary cause of cardiovascular hospitalization in the first 2 years post-transplant [1]. Left ventricular hypertrophy (LVH) is a risk factor for congestive heart failure (CHF) and death in renal transplant recipients and systolic blood pressure was found to be the only predictor of de novo left ventricular hypertrophy (LVH) at 5 years after renal transplant [2]. Hypertension is associated with allograft dysfunction, death-censored graft failure, and death [3]. Better controlled systolic blood pressure, even after several years of a kidney transplant, is associated with improved graft and patient survival in renal allograft recipients [4]. Optimal control of blood pressure (BP) in kidney transplant recipients may help reduce the risk of death due to CV disease and also help to prolong allograft survival.

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Epidemiology

Hypertension is highly prevalent in individuals with chronic kidney disease (CKD) increasing from ~ 36% in CKD stage 1 to ~84% in CKD stages 4 and 5 [1]. After kidney transplantation, the blood pressure rises in the early post-operative phase due to saline loading and induction of high dose immunosuppression. Blood pressure control typically improves with improvement in glomerular filtration rate (GFR) after this immediate post-operative phase. Even then after the first year post-transplantation, up to 85% patients were hypertensive based on the presence of systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or treatment with anti-hypertensive drugs [5]. A study using ambulatory blood pressure monitoring (ABPM) found that only 5% of renal transplant recipients were normotensive as defined by a BP < 130/80 mm Hg and also identified 29% of patients with nocturnal hypertension. BP assessed by ABPM proved to be a stronger predictor of renal graft damage than traditional immunologic factors [6]. The high prevalence of uncontrolled hypertension in renal transplant patients and the associated shortened allograft and patient survival make BP control an important therapeutic target.

Risk Factors and Pathogenesis

The interplay between multiple recipients, donor, transplant and immunosuppression-related factors are usually responsible for the development of post-transplant hypertension. Blood pressure and the need for antihypertensive therapy correlate inversely with the GFR. The need for antihypertensive medications in post-transplant patients rose from an average of 0.7 in patients with CKD stage 1, to 2.3 in those with a GFR in the CKD stage 5 range [7]. A decline in GFR over time has been seen to correlate with a rising BP [8].

Donor-Related Factors

In recipients without any family history of hypertension, the transplantation of a kidney from a donor from a “hypertensive” family results in less withdrawal and more introduction of antihypertensive therapy than a donor kidney from a “normotensive” family. In recipients with a family history of hypertension, this hypertensive effect of the transplanted kidney is blunted. In recipients, without familial hypertension, the transplantation of a “hypertensive” kidney causes a tenfold larger increase in the need for antihypertensive therapy as opposed to transplantation of a “normotensive” kidney, with similar blood pressure control [9]. Other donor-related factors that may increase the risk of post-transplantation hypertension are

pre-existing donor hypertension, subarachnoid hemorrhage, advanced donor age, prolonged ischemia time, and use of right kidney [10]. Recipients of lesser quality kidneys (expanded criteria donors) show a higher incidence of hypertension and cardiovascular mortality post-transplant [11].

Recipient Related Factors

In addition to essential hypertension, the original kidney disease, diabetes, obesity and excessive weight gain may contribute to the occurrence of post-transplant hypertension [10]. Loss of vascular compliance due to long-standing hypertension may contribute to the elevation of blood pressure [11]. Secondary hypertension may develop before or after the transplant.

Transplant renal artery stenosis (TRAS) is an important cause of secondary hypertension in these patients. TRAS is reported to occur in 1–23% of kidney transplant recipients. It usually occurs 3–24 months after the procedure, but earlier and later presentations are not uncommon [12]. The presentation of these patients is similar to native renal artery stenosis and should be suspected in patients with resistant hypertension associated with hypokalemia, accelerated target organ damage, declining allograft function, and worsening of allograft function after initiating angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). Noninvasive imaging with renal artery duplex is often used to screen for TRAS. This may need further workup with CT angiography with a small amount of contrast or CO2 angiography. Non-contrast MR Angiography may also be beneficial before the definitive angiographic diagnosis of hemodynamically significant stenosis. It is important to maintain a high index of suspicion for TRAS because it is a potentially correctable cause of severe hypertension.

Primary hyperaldosteronism The presence of hypokalemia in association with resistant hypertension may indicate the presence of primary hyperaldosteronism. In the general population, primary hyperaldosteronism is estimated to affect at least 20% of patients with resistant hypertension; a similar prevalence is likely in renal transplant recipients [11]. The diagnosis of hyperaldosteronism relies on finding an elevated aldosterone to renin ratio followed by confirmatory testing to demonstrate the non-suppression of aldosterone production after sodium or volume loading. Adrenal imaging with CT scan can be utilized to differentiate adenoma from hyperplasia. Adrenal venous sampling should be done to confirm laterality of excessive aldosterone production before consideration of a surgical treatment option for an adenoma [13]. Mineralocorticoid receptor antagonists like Spironolactone may play an important role I the medical management of patients who are not surgical candidates.

Obstructive sleep apnea (OSA) may develop after transplant due to excessive weight gain. The prevalence of OSA was found to be similar in patients after transplant as compared to waitlisted patients and may contribute to the presence of

resistant hypertension in patients after transplant [14]. Polysomnography should be considered in the workup of patients with resistant or uncontrolled hypertension after renal transplant.

Transplant-Related Factors

Immunosuppressive medications, as well as transplant dysfunction due to any cause, may contribute to the occurrence or worsen of hypertension.

Immunosuppressive Medications

Corticosteroids The incidence of steroid-related hypertension after renal transplantation has been estimated to be about 15% [15]. Steroids exert their hypertensive effect via multiple mechanisms including sodium retention due to mineralocorticoid effect, decreased vasodilator production and increased responsiveness to vasoconstrictors [16]. No differences in BP were observed between the steroid avoidance, early steroid withdrawal, and standard steroid therapy groups in a small randomized, open-label multicenter study. A significantly higher incidence of acute rejection was seen in the steroid avoidance and early steroid withdrawal groups as compared to standard steroid therapy [17]. There were no differences in allograft survival among the three groups in the study. It is likely that the "hypertensive" effect of steroid therapy at standard doses is offset by lower cumulative immunotherapy thus leading to the negligible overall effect of steroids on BP [16].

Calcineurin Inhibitors (CNI) CNI cause afferent arteriolar vasoconstriction by increasing the activity of the sympathetic nervous system, intrarenal RAAS, endothelin-1, vasoconstrictor cytokines and by decreasing the production of nitric oxide and vasodilator prostaglandins [18–21]. Hypertension due to CNI may be associated with hyperkalemia, hypercalciuria, and acidosis. This is thought to be due to a stimulatory effect of CNI on the sodium chloride cotransporters NCC) similar to what is seen in Familial hyperkalemic hypertension. The resulting sodium retention and volume excess often respond to thiazide diuretics which antagonize the NCC [22]. In comparison to Cyclosporine, patients treated with Tacrolimus show lesser nephrotoxicity and easier BP control but a higher incidence of Post-transplantation diabetes mellitus [23].

Transplant Dysfunction

Formerly normotensive post-transplant patients who present with new-onset hypertension should be investigated for acute rejection with a low threshold for a kidney biopsy. A subset of antibody-mediated rejection who present with malignant

hypertension has been described. These patients may have antibodies the Angiotensin II receptor (AT_1 receptor) and are seen during the first week after transplant [24]. Other causes of allograft injury that reduce GFR like chronic allograft nephropathy and recurrent disease may also present with new or worsening BP control. Other causes of acute deterioration of allograft function in the early post-transplant setting like a vessel kinking, hydronephrosis, Page kidney, lymphocele or urinoma are rare but may present with hypertension [25].

Blood Pressure Measurement in Diagnosis

Office BP readings are most commonly used in the management of post-transplant patients but may be associated with "white coat" hypertension where office BP readings are high in the setting of well-controlled BP outside the office setting. Office BP measurement will also miss patients with "masked" hypertension who have normal BP readings in the office but elevated out of office readings. Home blood pressure measurement (HBPM) and ambulatory blood pressure measurement (ABPM) can be utilized in patients who have progressive allograft dysfunction in the setting of normal BP readings. HBPM may be in an important tool in the assessment of BP control in these patients and has been shown to have better concordance with ABPM [26]. Several studies in the general population have shown that SBPM is associated with improved control as well as prognostic value compared to office measurements [26]. ABPM is thought to be a more sensitive method for diagnosing hypertension than is sole reliance on office BP in renal transplant recipients. In addition, ABPM allows evaluation of the diurnal variation of blood pressure which may be an important data point in predicting the risk of future decline in allograft function [27]. In patients with nocturnal non-dipping or reverse dipping patterns significantly greater loss of kidney function has been seen as compared with those with normal dipping pattern [28]. Hence consideration of SBPM and ABPM in the management of hypertension in post-transplant patients is imperative as opposed to over-reliance on BP measurements to assess control and manage therapy.

Antihypertensive Agents in Renal Transplant Recipients

There are no randomized control trials looking at the optimal antihypertensive regimen in the kidney transplant recipients. The selection of antihypertensive therapy in this patient population should be guided based on the other comorbid conditions.

A. **Calcium channel blockers (CCB):**
   CCBs are usually well tolerated antihypertensive agents. By decreasing the renal vasculature resistance, they can counter the vasoconstrictive effect of CNIs. Reimsdijk et al. found that the patients on CCB post-transplant had better serum creatinine and blood pressure control at month 3 and 12th after the

transplant as compared to the patients on other antihypertensive regimens [29]. However, other studies have shown that CCB, an ACE I and an alpha-blocker are equally effective as antihypertensive regimen [30].

Due to inhibition of CYP3A4, dihydropyridine calcium channel blockers (diltiazem, verapamil, and nicardipine) are not recommended in the transplant patients as they increase the tacrolimus and CsA levels [31, 32].

B. **Renin-Angiotensin-Aldosterone system (RAAS) Inhibition:**
It is well established that RAAS inhibition can slow the progression of CKD in diabetic and non-diabetic proteinuric patients [33–35]. However, the role of RAAS inhibition remains a subject of debate in the kidney transplant recipients. Multiple trials have been conducted to show the efficacy of RAAS inhibition in the kidney transplant recipients but none of them showed a clear benefit of RAAS inhibition both in terms of graft or patient survival [36–39]. The discussion shows that there is no definitive evidence showing the ACE inhibitor or ARB in patients with the healthy renal transplant.

C. **Thiazide Diuretics:**
Thiazide diuretics can be used as an effective treatment for hypertension in the renal transplant recipients. Many studies have shown that thiazide diuretics can be an effective antihypertensive medication in the kidney transplant recipients [40–42].

D. **Beta-blockers:**
In a small study, the role of Beta-blocker was evaluated in the kidney transplant recipients with hypertension. A significant blood pressure reduction was seen in hypertensive patients with their native kidneys in situ [43]. In another randomized clinical trial, Suwelack et al. compared quinapril with atenolol. They did not find a difference in terms of kidney function or blood pressure control at 5 years after the transplant, however quinapril lowered proteinuria significantly [44].

Blood Pressure Goals and Treatment Summary

Based on the discussion above, lower blood pressure goals ($\geq$ 130/80 mmHg) may be beneficial given the observational data linking prolonged graft survival with lower levels of BP in kidney transplant recipients. Good blood pressure control is more important than using any particular agent in Hypertensive Renal Transplant Recipients.

A. **Hypertension in first few weeks to months after kidney transplantation:**
Hypertension in first few weeks to months after kidney transplantation is usually secondary to (1) Volume overload, (2) Delayed graft function, (3) A higher dose of corticosteroids, and (4) A higher dose of CNIs.

The treatment of hypertension during early after transplant should focus more on (1) Volume optimization with a loop or thiazide diuretics, (2) Use of beta blockers and Calcium channel blockers, (3) By improving kidney function and improved potassium, ACE I or ARBs can be used earlier after transplant.

B. **Immunosuppression strategies and better blood pressure control:**
From the discussion above, we can conclude that:

1. Low dose prednisone is usually safe to use for long-term immunosuppression with no significant impact on the blood pressure.
2. None of the CNI is better in terms of blood pressure control.
3. With improved metabolic risk profile, consider switching CNIs to Belatacept when it's feasible
4. mTOR inhibitors are not associated with better blood pressure control

C. **Special Situations post-transplant and use of antihypertensive agents:**

1. Associated cardiac issues (Coronary artery disease or Arrhythmias): Consider using beta-blockers as a first-line antihypertensive regimen.
2. Associated heart failure or volume overload: Consider use of diuretics for volume optimization with use of beta blockers, ACE inhibitors or ARBs and spironolactone for long-term use.
3. Associated proteinuria (With the recurrence of glomerulonephritis in the allograft or transplant glomerulopathy): Consider using ACE I or ARB and spironolactone for decreasing proteinuria.
4. Post-transplant thrombotic microangiopathy: Consider initiating ARBs

Conclusion

Post-transplant hypertension is common in kidney transplant recipients. Though associated with increased cardiovascular morbidity and mortality with poor graft outcomes, there are no randomized control trials to look at the optimal blood pressure in kidney transplant recipients. The choice of antihypertensive should be individualized based on other co-morbid conditions.

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Chapter 10
Diabetes in Kidney Transplant Recipients

Subarna M. Dhital

Introduction

Hyperglycemia after kidney transplantation is a common problem. It can be a continuation of preexisting diabetes, a transient issue attributable to transplantation variables, or a new onset of diabetes that will be sustained long-term. While post-transplantation diabetes confers worse patient and graft survival, limited available evidence suggests that improved glycemic control reduces those effects. Multiple insulin and non-insulin agents are available for managing glycemic abnormality in kidney transplant recipients.

Definitions

Patients who undergo kidney transplantion can have preexisting specific type of diabetes. The American Diabetes Association (ADA) classification of diabetes illustrated in Table 10.1 [1] offers information about particular pathophysiologic types of diabetes that can have subsequent worsening in glycemic control after kidney transplantation. Various terminologies have been used for describing hyperglycemia noted after transplantation including steroid diabetes, new onset diabetes mellitus, transplant-associated hyperglycemia. "New onset diabetes after transplant" (NODAT) was the recommended terminology for this entity by the first

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Table 10.1 Types of diabetes

Categories of diabetes	Specifics
Type 1 diabetes	Absolute insulin deficiency from autoimmune beta-cell destruction
Type 2 diabetes	Insulin resistance with a progressive loss of beta-cell insulin production
Gestational diabetes mellitus	Diabetes diagnosed in the second or third trimester of pregnancy without a clear history of overt diabetes before gestation
Specific types of diabetes due to other causes	Examples: Monogenic diabetes syndromes Diseases of exocrine pancreas Drug- or chemical-induced diabetes

American Diabetes Association Classification of Diabetes [1]

international consensus guideline published in 2003 [2] and had been the standard terminology for a while. However, this terminology implies that there was no pre-existing diabetes, which is hard to ascertain in all patients. To mitigate this concern, the 2013 international consensus meeting recommended the term posttransplantation diabetes mellitus (PTDM) to describe newly diagnosed diabetes in posttransplantation period [3].

For this chapter, we will use the following terminologies for clarity:

- Preexisting diabetes
- Posttransplantation diabetes mellitus
- Posttransplantation prediabetes

Diagnosis

There is a lack of data on the long-term micro- or macro-vascular outcomes based on glycemic status in PTDM to give precise diagnostic cutoffs for kidney transplant patient population. Hyperglycemia in immediate postoperative period is present in nearly 90% of kidney transplant recipients but it is not sustained long-term [3]. Furthermore, transient events such as infections, acute critical illness, graft rejection therapies can introduce brief hyperglycemic periods which do not necessarily ensure future sustained hyperglycemia. As a result, diagnostic criteria used in defining glycemic status are subject to skewed results based on the time point of evaluation after transplantation. Accordingly, varying diagnostic criteria have been used in clinical studies to diagnose PTDM [4]. The most recent international consensus guideline provides certain specifics for making a diagnosis of PTDM [3]:

- Formal diagnosis of PTDM should be made only after the transplant recipients are on a stable immunosuppression regimen, have stable kidney allograft function, and do not have acute infections.
- ADA criteria (Table 10.2) for diagnosis can be used with the caveat that glycated hemoglobin (HbA1c) test performed within a year of transplantation will likely underestimate PTDM.

Table 10.2 ADA criteria for the diagnosis of diabetes and prediabetes

Diabetes:
Fasting plasma glucose ≥126 mg/dL (fasting = no caloric intake for at least 8 h)
OR
2-h plasma glucose ≥200 mg/dL during oral glucose tolerance test (using 75-g of anhydrous glucose dissolved in water)
OR
HbA1c ≥ 6.5% (with the laboratory using a method that is NGSP certified and standardized to the DCCT assay)
OR
Random plasma glucose ≥200 mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis
Prediabetes:
Fasting plasma glucose 100–125 mg/dL
OR
2-h plasma glucose during 75-g oral glucose tolerance test 140–199 mg/dL
OR
HbA1c 5.7–6.4%

ADA American Diabetes Association, *HbA1c* glycated hemoglobin, *NGSP* National Glycohemoglobin Standardization Program, *DCCT* Diabetes Control and Complications Trial

Epidemiology

Diabetes is a leading cause of kidney transplants. Organ Procurement Transplant Network/Statistics on Donation and Transplantation in the United States (OPTN/SRTR) reported that nearly 46% of patients on 2015 transplant waiting list had diabetes [5]. Hyperglycemia is observed in nearly 90% of kidney transplant recipients during the first few weeks after transplantation [3]. The reported incidence of PTDM is wide and ranges from 10% to 74% [4]; these reports are limited by varying criteria used to define PTDM. The prevalence of PTDM reported in randomized control trials evaluating immunosuppressant regimen may be more illuminating. In a prospective randomized clinical trial named ADVANCE, at 24 weeks post-transplantation, PTDM prevalence was approximately 17% using ADA criteria for the diagnosis [6]. Using the same criteria for PTDM diagnosis, another clinical trial reported nearly 36% prevalence of PTDM at 5 years after transplantation [6]. Overall, the epidemiological evidence suggests a high prevalence of preexisting diabetes, high rates of hyperglycemia in the immediate posttransplantation period that improves or resolves in the majority, and is followed by progressive gradual increase in the rates of diabetes.

Risk Factors and Pathophysiology

The patients with preexisting diabetes are at risk of worsening glycemic control after transplantation. Several risk factors have been identified in patients without preexisting diabetes that confer high risk for developing PTDM. Many of these

factors are similar to the general risk factors for the development of type 2 diabetes ("non-transplant-specific"). There are additional risk factors specific to the processes of transplantation and immunosuppression. Furthermore, presence of additional risk factors that can raise the rates of macro- or micro-vascular complications from diabetes (for example, hypertension, dyslipidemia) are also highly relevant in this patient population.

General Risk Factors

Age >40 years, African American and Hispanic ethnicity, family history of type 2 diabetes, certain histocompatibility antigen (HLA) phenotypes, higher body weight, presence of prediabetes, positive hepatitis C virus serology are associated with a higher risk for PTDM [2, 7]. Increase of relative risk for PTDM with some of these risk factors are: ~90% when age is 45–59 years, 160% for age ≥60 years, 32–68% in black patients, 35% in Hispanic patients, 70–80% with BMI >30 kg/m^2 [8]. Elevated liver enzymes (suggestive of hepatic fat deposits) appear to be associated with higher risk of developing PTDM [9]. Higher pretransplantation HbA1c (above 5.4%) appears to correlate with PTDM risk in a continuous fashion [10].

Association with Certain Candidate Genes

Genome-wide association studies (GWAS) are experimental designs used for detecting associations between genetic variants (Single Nucleotide Polymorphisms, SNPs) and certain diseases or traits in population samples [11]. However, these are "associations" and causal link or mechanisms need to be established separately. Still, they can offer insights into the genetic underpinnings of diseases. Over 100 common variant signals have been identified for type 2 diabetes [11]. However, only ~10% of heritability is explained by the common variants [12]. Large-scale studies looking at lower frequency variants have not been able to expand the observed heritability much [13]. Genetic variants involving CDKAL1, KCNQ1 and TCF7L2 were found to be significantly associated with PTDM risk in a meta-analysis of available genetic data in kidney transplant populations [14]. However, the causal relationship and mechanism has not been fully elucidated and our current understanding of their relevance is in the preliminary stages.

While the findings from GWAS have brought forth several candidate genes for further studies, their utility as clinical tools to assess risk for individual patients is not yet defined.

Transplantation Related Risk Factors

Immunosuppressive agents used after transplantation, surgical stress and inflammation, infectious complications, intravenous glucose use, nutritional interventions including enteral and parenteral nutrition can contribute to hyperglycemia.

(a) Immunosuppressive agents: They are considered major modifiable risk factors in PTDM. A variety of agents are used in the induction and maintenance immunosuppression regimen. There is a significant variation in the choice of regimen depending on specific transplant center [15]. Major classes of immunosuppressants used in kidney transplant recipients and their relevance for glycemic outcomes are as follows:

- Glucocorticoids (methylprednisolone, prednisone): Nearly 70% of adult kidney transplant recipients are on a glucocorticoid medication 1 year after transplantation [5]. They are thought to affect glucose balance by reducing insulin production through beta cell dysfunction and also an increase in insulin resistance through the effects on insulin signaling cascade, alteration in circulating fatty acid concentration that interferes with glucose utilization in peripheral tissues [16]. Hyperglycemic effect is dose dependent and the higher dose used immediately post-transplantation is likely to cause significant hyperglycemia that might improve or resolve after dose reduction of glucocorticoids. Clinical trials have evaluated glycemic outcomes comparing early glucocorticoid withdrawal vs. chronic low dose glucocorticoid use along with other maintenance immunosuppressants. In a double-blind randomized trial, 5 years after transplantation, PTDM prevalence was similar between these two groups, however, insulin use was lower among the early glucocorticoid withdrawal group [17]. While the benefits are not clear, the risk of acute rejection is increased by steroid avoidance or early withdrawal [18]. Thus the consensus is to avoid glucocorticoid regimen decisions just based on glycemic concerns [3].
- Calcineurin inhibitors (tacrolimus, cyclosporine): Increased PTDM risk with calcineurin inhibitors, particularly with tacrolimus, has been noted since the beginning of the use of these agents in kidney transplant immunosuppression [19, 20]. The DIRECT study, a clinical trial that evaluated tacrolimus vs cyclosporine with new onset diabetes as the primary outcome, showed higher prevalence of PTDM or prediabetes in the tacrolimus group 6 months following the transplantation [21] Metaanalysis of calcineurin inhibitor sparing regimen has shown a lower incidence of PTDM supporting the relationship between calcineurin inhibitors and hyperglycemia [22]. However, not all studies have shown consistent hyperglycemic effects of calcineurin inhibitors. Precise mechanism underlying the increased hyperglycemia risk is not fully understood. Cell and animal studies suggest reduced beta cell insulin content with calcineurin inhibitor use [23, 24].

Tacrolimus (but not cyclosporine) also appears to potentiate the damages of insulin resistance to beta cells reflected by distinct beta cell transcriptional changes, lower insulin content and secretion [24]. This is consistent with the observation of higher diabetogenic potential of tacrolimus compared to cyclosporine only in patients with pre-transplant hypertriglyceridemia, a marker of insulin resistance [25]. Hypomagnesemia is common with calcineurin inhibitor use and it is considered an independent risk factor for PTDM in kidney transplant recipients through its effects on glucose cellular transport, reduced insulin secretion and alteration in insulin signaling pathways [26].

- Antimetabolite agents (mycophenolate mofetil, azathioprine): These agents have not been found to be associated with diabetogenic effects [27].
- Mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus): Sirolimus is associated with high risk of PTDM in kidney transplant recipients [28]. Data with everolimus is limited. In a retrospective database study, compared to a reference transplant group, everolimus-treated patients had lower PTDM prevalence 3 years following transplantation [29]. However, a metanalysis of studies involving conversion from calcineurin inhibitor to mTOR inhibitor post kidney transplant showed no differences in PTDM between sirolimus vs everolimus; mTOR inhibitors were associated with non-significant trend towards increased PTDM compared to calcineurin inhibitor based regimen [30]. Physiology of mTOR induced hyperglycemia is not fully clear. Animal and in-vitro studies suggest both impaired insulin secretion and increased insulin resistance as possible mechanisms [31].
- Biologic agents used for induction therapy: Interleukin 2 receptor antagonists, IL2-RA, (e.g., basiliximab, daclizumab) or lymphocyte depleting agents (e.g., antithymocyte globulin, antilymphocyte globulin, alemtuzumab) are used in induction regimen which is recommended for most of the patients receiving kidney transplant [32]. A prospective clinical trail comparing single dose rabbit anti-thymocyte globulin (rATG) vs divided dose rATG showed a lower incidence of PTDM in patients induced with single dose rATG [33]. Reduced systemic inflammation with consequent lowering of insulin resistance, better renal tubular epithelial function, lower incidence of hypomagnesemia was hypothesized as putative explanation for the difference in glycemic outcomes. Renal transplant recipients receiving basiliximab, an IL2-RA, were noted to have higher rates of hyperglycemia in a retrospective study [34]. Study authors speculated an interference with immunological balance stabilizing beta cell function as the causative mechanism. Metanalyses show no significant difference in prevalence of PTDM in transplant receipients who received alemtuzumab compared to IL2-RA or ATG [35, 36].

(b) Surgical stress, inflammation and infections: Hyperglycemia is common with surgical stress and is thought to be related to transiently reduced insulin responsiveness that can last a few days to weeks following a variety of surgical procedures

[37]. Surgical stress could be contributory to hyperglycemia in the early postoperative period in kidney transplant recipients as well. Inflammation, in general, has strong relationship with metabolic abnormalities including diabetes and hyperglycemia [38]. Organ transplantation being an active immunological phenomenon with significant inflammatory activity, we can expect a role for inflammation to exacerbate hyperglycemia. Hepatitis virus C infection has been linked to PTDM putatively through impaired insulin sensitivity [39]. Association with cytomegalovirus infection has been rather inconsistent [40]. Despite these associations, it is difficult to be certain about precise contribution of any of these factors in the observed glycemic abnormality since multiple factors are likely interacting in a complex pattern at the same time.

(c) Other therapeutic and nutritional interventions: Intravenous dextrose, vasopressor agents, enteral and parenteral nutritional interventions are likely to worsen hyperglycemia.

Consequences of Hyperglycemia in Kidney Transplant Recipients

Preexisting diabetes, PTDM are associated with reduced patient survival in kidney transplant recipients [41, 42]. Posttransplant prediabetes was found to be associated with a 4.5 fold increased risk of new onset diabetes but not with reduced graft function or survival in a study [43]. Even glycemic abnormality noted early during transplantation (10 weeks posttransplantation) was found to be a significant predictor of death on the longer term [44]. The increase in mortality is primarily attributed to increased cardiovascular diseases [45]. Data on the impact on graft survival is variable with some studies showing increased rejection rates but not the others [4, 46]. Infectious complications are observed with higher rates in patients with preexisting diabetes or PTDM. Micro- and macro-vascular complications similar to that in general diabetic population is observed in transplant recipients as well but the rate of development appears accelerated [47].

Management of Diabetes/Hyperglycemia in Kidney Transplant Recipients

Even if there is a strong association between hyperglycemia and certain adverse outcomes, the question of whether a specific intervention normalizing hyperglycemia reduces the risk of those outcomes should be considered. This complexity is apparent in general diabetic population where glucose control is not the sole determinant of micro- and macro-vascular complications; there is a complex interplay of comorbidities (for example, hypertension, dyslipidemia, smoking, obesity), specific

agent used for reducing glucose, in determining the complication risk reduction [48]. It needs to be noted that there is a paucity of good quality data in kidney transplant recipients to inform decision making about glucose targets, appropriate choice of pharmacologic agents to achieve glycemic control [49]. In that context, extrapolation of recommendations for management of general diabetic patients with modifications based on understanding of drug interactions, altered physiology in transplant recipients is reasonable.

Goals of Glycemic Management in Kidney Transplant Recipients

In the immediate post-operative period there is a high prevalence of transient hyperglycemia. Reduction of acute complications from hyperglycemia is the goal at that time. Subsequent long-term management is geared towards reducing the risk of micro- and macro-vascular complications related to diabetes with added concerns about effects on graft function. Although immunosuppressive agents used are major modifiable risk factors for PTDM and worsening of glucose control in preexisting diabetes, the risk of graft rejection is a significant concern. The current consensus is to choose and use immunosuppression regimen with the best outcome for patient and graft survival and to manage the consequent diabetes independently [3].

A meta-analysis of studies looking at specific perioperative glycemic targets versus postoperative outcomes revealed that in patients with diabetes, a moderate glycemic target (150–200 mg/dL) was associated with reduced postoperative mortality and stroke compared to glycemic target of >200 mg/dL and no significant additional benefit with tighter glycemic control aiming for glucoses <150 mg/dL [50]. ADA recommends initiating insulin therapy for persistent hyperglycemia of ≥180 mg/dL and aiming for target glucose range of 140–180 mg/dL once treatment with insulin is started in critically ill and noncritically ill hospitalized patients [51]. Adequate data does not exist in kidney transplant patients to guide specific glucose targets for this particular patient population [3], however, it appears reasonable to use the target of 140–180 mg/dL for hospitalized patients recommended by ADA.

Glycemic Management Considerations Immediately Post-transplantation

All hospitalized patients should have blood glucose tested upon admission [52]. Those with pre-existing diabetes or blood glucose >140 mg/dL should have hemoglobin A1c tested if not performed within the prior 3 months [51]. Bedside point of care (POC) capillary glucose testing should be performed for at least 24–48 h for those with established diagnosis of diabetes or blood glucose >140 mg/dL [52]. Multiple variables are at play in determining hyperglycemia in the acute

posttransplantation setting- surgical stress, high dose glucocorticoid use, vasopressor agents, dextrose containing intravenous fluids, enteral or parenteral nutrition-which are likely to cause significant variability in glucoses. This demands for an intervention that can be titrated and adjusted closely; intravenous (IV) insulin infusion with rates adjusted based on frequent POC glucose test results is the ideal option for this purpose. Previous diabetes treatment including oral agents, non-insulin injectable agents, subcutaneous insulin regimen should be stopped in patients with preexisting diabetes and managed with continuous IV insulin infusion. Once there is reasonable stability and particularly after a stable nutrition is established, the patient can be transitioned off the IV insulin infusion to subcutaneous insulin regimen.

(a) Continuous IV insulin infusion: It is a safe and effective modality for achieving glycemic control rapidly in critical care as well as noncritical care settings [53]. Hypoglycemic events are comparable to subcutaneous regimen use in noncritical care settings except when patients are eating while on continuous insulin infusion when the rates of both hyperglycemia as well as hypoglycemia increase. Validated written or computerized protocols that adjust infusion rates based on glucose changes and insulin dose requirement should be used to manage continuous IV insulin infusion [51].

(b) Transition from IV insulin infusion: Multiple variables can affect the decision to transition from IV insulin infusion to alternative treatment regimen. Use of transition protocols has been associated with lower morbidity and costs of care [51]. Administering 60–80% of daily insulin infusion dose as basal insulin is suggested to transition off the IV insulin infusion [52, 54]. However, extrapolation of this recommendation is problematic in transplant patient population because of significant and relatively rapid reduction in glucocorticoid doses in early postsurgical period which can increase hypoglycemia risk if the insulin dose is based on prior time period with higher glucocorticoid dose. The decision to transition should take into account variables such as stability of glycemic control, vasopressors use, dose of glucocorticoids, cardiac instability, renal function, mode of nutrition (parenteral, enteral feeding). Ideally, these variables should be stable before transitioning. However, if there is protracted IV insulin use, subcutaneous insulin administration can be considered while continuing IV insulin infusion; the dose of basal insulin and prandial insulin can be determined based on IV insulin requirements and IV insulin infusion discontinued after titrating subcutaneous insulin doses [55]. Patients with preexisting diabetes should always be transitioned to a subcutaneous basal-bolus insulin regimen. However, in those without pre-existing diabetes, if the IV insulin requirement is <1 unit/h, scheduled insulin may not be required during transition (only correction scale insulin in the beginning may suffice) [52]. There should be an overlap of 1–2 h between subcutaneous basal insulin administration and discontinuation of IV insulin infusion [52].

(c) Patients receiving enteral or parenteral nutrition: Enteral and parenteral nutrition can be independent drivers of hyperglycemia regardless of preexisting diabetes or insulin resistance [56]. Consequently, any interruption in their supply

means that if there is insulin in the system that was controlling hyperglycemia driven by these nutritional agents, the patients are likely to become hypoglycemic. In devising subcutaneous insulin regimen, rapid-acting or short-acting insulin use that matches the pattern of enteral or parenteral nutrition appears safer. An example of suggested approach is in Table 10.3.

(d) Glycemic management considerations at the time of patient discharge: While insulin is the preferred therapy during the hospital stay, on discharge, certain subset of patients can be considered for non-insulin agents. Patients with pre-existing type 1 or type 2 diabetes can resume their previous insulin, oral and/or

Table 10.3 Considerations in enteral and parenteral nutrition

Continuous enteral nutrition:
Use basal insulin only if there is demonstrated basal insulin needs (previous diagnosis of diabetes, requiring insulin during fasting state to control glucose)
Avoid disproportionally increasing basal insulin to control hyperglycemia. Instead, titrate rapid-acting insulin analogues or regular insulin to achieve glycemic control
If using rapid-acting insulin analogues, test POC glucose every 4 h, and administer a scheduled dose + correction scale based supplementation
If using regular insulin, test POC glucose every 6 h and administer a scheduled dose + correction scale based supplementation
Specify holding off rapid-acting insulin analogue or regular insulin if enteral feeding is interrupted in the insulin orders. Basal insulin can be continued
Cyclical enteral nutrition:
Decide on basal insulin dose informed by previous basal insulin requirements
If using NPH insulin as the basal insulin, giving it at the time of initiation of enteral nutrition is preferable to avoid hypoglycemia related to its peaking effect
Depending on the length of enteral nutrition cycle, could choose rapid-acting insulin analogues every 4 h or regular insulin every 6 h
Aim to have the last dose of rapid-acting insulin analogue 4 h prior and regular insulin 6 h prior to stop time of feeding
Perform POC glucose and use supplemental correction of the same insulin type during the feeding cycle
Bolus enteral nutrition:
Administer rapid acting insulin analog or regular insulin with each bolus feeding.
Watch for insulin stacking if the frequency of bolus feeding is <4 h while using rapid-acting insulin analogues or <6 h when using regular insulin
Eating while on cyclical or bolus enteral nutrition:
These episodes should be managed by similar strategy of using basal-bolus insulin in patients without enteral feeds (e.g. bolus of rapid-acting insulin dose determined based on a carbohydrate counting ratio or a fixed dose with consistent carbohydrate intake)
Parenteral nutrition:
Regular insulin can be added to parenteral nutrition
Using separate intravenous insulin initially can help determine the dose
It is pragmatic to avoid aiming for tight glycemic control just through insulin added to parenteral nutrition as the hypoglycemia means parenteral nutrition will need to be changed/stopped; use subcutaneous insulin injections to supplement additional insulin needs

non-insulin injectables. Transition to oral agents 1 or 2 days before discharge is preferable [57]. Some issues to consider are:

- Even if the previously used regimen had maintained good glucose control, the use of immsuppressive agents are likely to worsen the glucose control necessitating glycemic regimen adjustment
- Altered renal function might change the half lives of insulin or oral agents
- Change of immunosuppressive agents/dose subsequently could alter the requirements of glucose control agents

In many cases, discharging the patient on the hospital basal-bolus insulin regimen with a close follow-up arranged to assess glycemic status and insulin needs might be more pragmatic as many patients are likely to have resolution of marked hyperglycemia of perioperative period [58].

Pharmacologic Options for Glycemic Management in Kidney Transplant Recipients

A variety of antihyperglycemic agents are available including insulin, oral agents, non-insulin injectable agents. Given the lack of adequate data on their efficacy and safety in kidney transplant recipients [49], the decision to use a particular agent is based on the data from general population and understanding of their pharmacologic properties.

(a) Insulin: Various preparations of insulin are available with distinct pharmacologic properties (Table 10.4). IV infusion of regular insulin is an ideal choice when rapid correction of hyperglycemia is required, there are multiple variables at play, dose requirements of insulin are uncertain or glucose control is not achieved despite multiple dose titration of subcutaneous insulin. When subcutaneous insulin regimen is used, use of "sliding scale" alone is discouraged. Basal-bolus insulin regimen has proven superior to sliding scale alone in surgical patients [59]. Components of basal-bolus insulin therapy are outlined in

Table 10.4 Pharmacokinetic properties of common insulin preparations

Insulin	Onset	Peak	Duration
Rapid-acting insulin analogues (aspart, glulisine, lispro)	5–15 min	1–2 h	4–6 h
Regular insulin	30–60 min	2–3 h	6–10 h
NPH insulin	2–4 h	4–10 h	12–18 h
Premixed 70/30 NPH/regular	30–60 min	2–6 h	12–18 h
Premixed insulin analogues	5–15 min	2–4 h	14–24 h
Glargine	2 h	None	20–24 h
Detemir	2 h	None	12–24 h
Insulin degludec	2 h	None	>40 h

NPH Neutral Protamine Hagedorn

Table 10.5 Basal-bolus insulin therapy

Patients have POC glucose tested before meals (every 6 h if NPO) and at bedtime		
	Dosing considerations	Types of insulin used
Basal insulin	Approximately 50% of total daily insulin dose (TDD) requirement Can use weight based dosing if no other clinical evidences to guide insulin requirements (0.2–0.3 units/kg/day) Can use evidence from previous insulin use if available (e.g. home dose requirements in well-controlled patients with good compliance, extrapolation of hourly intravenous insulin requirements in fasting state)	Glargine once a day Detemir once or twice a day NPH twice a day (2/3rd of total dose in AM, 1/3rd in PM) Degludec once a day
Bolus insulin (combination of prandial coverage and correctional insulin)		
Prandial dosing (insulin not given if the patient skips meal)	Approximately 50% of total daily insulin dose requirement Can use weight based dose or dose based on clinical experience as above Split the total dose equally into 3 mealtime doses; use of consistent carbohydrate intake is essential with fixed dosing Carbohydrate counting based dosing allows flexibility (500/TDD gives an insulin: carbohydrate ratio to use)	Rapid-acting or regular insulin before meals and at bedtime If NPO, use regular insulin every 6 h or rapid-acting insulin every 4–6 h for correction
Correction scale (insulin given even if patient skips meal)	Calculate insulin sensitivity factor (ISF) to design a scale (1700/TDD gives an ISF) Using the above ISF, for glucoses >target threshold, a scale can be devised for patient use	

Table 10.5. NPH insulin is considered good choice for use in hyperglycemia driven by predisone or prednisolone as their peak action at 4–8 h and duration of activity of 12–16 h match NPH's profile [60]. However, the benefit does not appear to be significantly better when compared to glargine in clinical use [61].

(b) Oral agents and non-insulin injectables: For preexisting type 2 diabetes, PTDM, if the overall insulin requirement during the hospital management is not significantly high, considering oral and non-insulin injectable agents is reasonable. However, given a high variability in glucoses in the early post-operative period, it is more prudent to decide about non-insulin agents only after 1 week post-transplantation [3]. Table 10.6 outlines the currently available major classes of these antihyperglycemic agents. Studies of these agents in kidney transplant population are quite limited. Limited available evidences are as follows:

- Metformin: Major concern with metformin use in kidney transplant patients has been with reduced renal function and the risk of lactic acidosis. There are no randomized controlled trials evaluating this issue. However, a pharmacy claims study evaluating metformin use in kidney transplant revealed

Table 10.6 Oral and non-insulin injectable antihyperglycemic agents

Antihyperglycemic agent	Comments (in the context of type 2 diabetes use)
Biguanides (metformin)	Weight neutral/loss, potential CV benefits, GI side effects common, contraindicated with eGFR<30
SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)	CV benefits, reduced progression of diabetic kidney disease with canagliflozin and empagliflozin. eGFR based contraindications. Genitourinary infections, increased risk of bone fractures and amputations with canagliflozin
GLP-1 receptor agonists (exenatide, exenatide extended release, liraglutide, lixisenatide, albiglutide, dulaglutide)	Injectable agent, weight loss, CV benefit with liraglutide, contraindication for exenatide and caution with lixisenatide with eGFR<30, increased risk of side effects in patients with renal impairment, GI side effects common, FDA Black Box warning of thyroid C-cell tumors
DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin)	Modest HbA1c reduction, weight neutral, potential heart failure risk with saxagliptin and alogliptin, can be used in renal impairment with dose adjustment
Thiazolidinediones (pioglitazone, rosiglitazone)	Weight gain, increased heart failure risk, risk of osteoporosis, generally not recommended in renal impairment because of fluid retention
α-Glucosidase inhibitors (acarbose, miglitol, voglibose)	Significant GI side effects, avoid if eGFR <25
Sulfonylureas (glyburide, glipizide, gliclazide, glimepiride)	Weight gain, FDA warning on increased CV mortality based on studies in older agent tolbutamide, high risk of hypoglycemia with glyburide in CKD
Meglitinides (repaglinide, nateglinide)	Useful for targeting prandial glucose excursions, hypoglycemia, weight gain
Bile acid sequestrants (colesevelam)	Modest HbA1c reduction, GI side effects, may decrease absorption of other medications
Dopamine-2 agonists (bromocriptine)	Modest HbA1c reduction, dizziness, nausea, fatigue, rhinitis common
Amylin mimetics (pramlintide)	Injectable agent, weight loss, prandial insulin sparing property, no renal dose adjustment necessary

Adapted from references [62, 63]
CV cardiovascular, GI gastrointestinal, eGFR estimated glomerular filtration rate, SGLT-2 Sodium Glucose Cotransporter-2, FDA Federal Drug Admistration, GLP-1 Glucagon-like Peptide-1, DPP-4 Dipeptidyl peptidase-4, HbA1c glycated hemoglobin, CKD chronic kidney disease

significant number of patients receiving metformin and it was not associated with worse patient or allograft survival [64].

- GLP-1 receptor agonists: GLP-1 infusion appears to improve insulin and normalize glucagon secretion in renal transplant recipients with PTDM [65]. In a case series of kidney transplant recipients, involving co-administration of liraglutide with tacrolimus, there was no clinically significant alteration in tacrolimus level; 1 h and 2 h glucoses were lower with liraglutide administration although fasting glucoses were not significantly different [66].
- Thiazolidinediones: In a randomized controlled trial, pioglitazone was found to improve glycemic control, reduce daily insulin dose requirements and inflammatory markers after 4 months of followup [67]. Another short-term trial evaluating 3 months outcomes in posttransplantion prediabetes reported

improved 2 h plasma glucose [68]. Rosiglitazone has also been reported in short-term study to be safe and effective in PTDM in renal transplant recipients [69].

- DPP-4 inhibitors: A phase II clinical trial reported vildagliptin as a safe and effective treatment for PTDM after kidney transplantation using 3 months outcomes data [70]. Studies with sitagliptin have shown increases in insulin secretion and reduction of fasting and postprandial glucose in renal transplant recipients with PTDM and suggested it to be a safe and effective treatment [71–73].
- Sulfonylureas: A case report of two renal transplant recipients had suggested a possible interaction between glipizide and cyclosporine [74]. However, a subsequent study evaluating cyclosporine pharmacokinetics showed no significant interaction [75]. Gliquidone, a sulfonylurea, was reported as a safe and effective treatment option in PTDM after renal transplantation [76].
- Meglitinides: In an observational study, rate of successful treatment and the degree of HbA1c reduction was comparable to rosiglitazone-treated control at 6 months after intervention [77].

Comprehensive Evaluation and Management of Risk Factors, Comorbidities for Macro- and Micro-vascular Complications

Glycemic control is only one component of effort directed at complications risk reduction in patients with diabetes. While the relationship between glucose control and microvascular risk reduction is more direct, for macrovascular risk reduction, addressing other factors (e.g. hypertension, dyslipidemia, anti-platelet agent use) is more important. Patients should be evaluated for clinical and/or laboratory evidence of macrovascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease), microvascular disease (retinopathy, nephropathy, peripheral or autonomic neuropathy, foot ulcer) and comorbid conditions (hypertension, dyslipidemia, obesity, depression) as is practiced in non-transplant diabetic population [78]. Cardiovascular disease risk management is addressed separately in this book. A basic outline of microvascular complications surveillance and management based on ADA standards of diabetes care follows; given the lack of specific data with kidney transplant recipients, following these recommendations is reasonable:

- Dilated eye exams: Comprehensive eye examination should be performed at the initial evaluation (5 years upon diagnosis in type 1 diabetes). If there is any abnormality, at least an annual dilated eye exam should be performed subsequently. If it is normal and glycemic control is reasonable, subsequent frequency could be every 1–2 years.
- Evaluation for neuropathy: Annually (after 5 years of diagnosis if type 1 diabetes) with history taking, 10-g monofilament testing and 128-Hz tuning fork testing for vibration sensation. Patients with microvascular complications should

be assessed for symptoms and signs of autonomic neuropathy. Those with gastrointestinal symptoms should be evaluated for gastrointestinal neuropathies. Evaluation should also include genitourinary symptoms because diabetic autonomic neuropathy can cause sexual and/or bladder dysfunction.

- Foot care: Comprehensive foot evaluation should be performed annually and visual feet inspection at every visit.
- Renal function monitoring: It is per the monitoring guidelines for kidney graft function discussed elsewhere in this book.

Lifestyle Management and Prevention of Diabetes

Nutrition therapy aiming to achieve and maintain body weight goals, physical activity (in adults ≥150 min of moderate-to-vigorous intensity aerobic activity, 2–3 sessions/week of resistance exercise on nonconsecutive days; in children ≥60 min/day of moderate-to-vigorous intensity aerobic activity and at least 3 days/week of vigorous muscle- and bone-strengthening activities), smoking cessation, psychosocial support are mainstays in diabetes management strategies even when pharmacotherapy is used [79]. Intensive lifestyle management was demonstrated to improve glycemic control in 58% of patients in a study of kidney transplant recipients [80]. The same study had included patients with prediabetes (impaired oral glucose tolerance); 44% of the patients had normalization of glucose tolerance suggesting efficacy of intensive lifestyle measures in preventing diabetes. This aligns with the observations in type 2 diabetes prevention studies involving lifestyle intervention that have demonstrated consistent and sustained risk reduction across different populations [81–83]. Metformin therapy is a consideration in those with prediabetes and body mass index ≥35 kg/m^2, age <60 years, and women with prior gestational diabetes in general population [84], particularly when lifestyle interventions fail. Although there is no data on its efficacy in kidney transplant population, for those without contraindications, metformin use appears reasonable. While vildagliptin and pioglitazone have been reported to improve glucose tolerance [68], the data is insufficient to recommend their use for diabetes prevention in kidney transplant recipients. Bariatric surgery appears to be a feasible option in kidney transplant recipients with marked obesity [85, 86] although the long-term outcomes are uncertain.

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Chapter 11
Post Kidney Transplant: Obesity

Gurwant Kaur and Preethi Yerram

Introduction: Obesity Definition, Prevalence

In this chapter, we will define obesity and overweight as per World Health Organization (WHO) classification and will discuss its impact on kidney transplant (KT) candidacy with a special focus on the epidemiology, risk factors, implications and management of post-transplant obesity. It's important to recognize that obesity is preventable. Multiple factors related to post-transplant care can predispose patients to obesity or overweight; strategies to address these risk factors and prevent post-transplant obesity will be discussed in further detail. At the end of this chapter, readers should be able to identify high-risk patients for obesity during pre – Kidney transplant and post – Kidney transplant period, and understand its impact and management.

Obesity and overweight are defined as the abnormal or excessive accumulation of fat that may have deleterious effects on health. WHO classifies obesity based on body mass index (BMI) as shown in Table 11.1.

$$\begin{aligned}\text{BMI} &= \text{Weight}\left(\text{kilograms}\right)/\text{Height}^2\left(\text{meters}^2\right)\\ &= \left(\text{kg}/\text{m}^2\right)\end{aligned}$$

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Table 11.1 The International Classification of adult overweight and obesity per BMI [2]

BMI (Kg/m^2)	Classification
<18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Overweight
30.0–34.9	Obese Class I
35.0–39.99	Obese Class II
≥40	Obese Class III

Source: Adapted with permission from WHO, 1995, WHO, 2000 and WHO 2004
WHO World Health Organization

For an adult person of 70 Kg and height of 6 feet (1.8 m), the BMI would be 21.6 Kg/m^2 and the person would fall into normal weight category (as per Table 11.1). In defining overweight and obesity in children, age plays an important role. Different criteria for different age groups of children can be found at the website: http://www.who.int/mediacentre/factsheets/fs311/en/

It is to be kept in mind that BMI is a crude measure of body mass and is not a direct measure of the distribution of adipose or muscle mass or the relative contributions of fluid shifts to overall body composition.

Epidemiologic studies have identified high BMI as a risk factor for a wide range of chronic diseases, including cardiovascular disease, diabetes mellitus (DM), chronic kidney disease (CKD), cancer, and several musculoskeletal disorders [1].

Prevalence of Obesity in the General Population

Worldwide obesity has nearly tripled between 1975 and 2016 as per WHO data. The latest WHO fact sheet updated in October 2017 shows that more than 1.9 billion adults were overweight in 2016, out of which, over 650 million were obese. More recent data and updates can be accessed on WHO website: http://www.who.int/mediacentre/factsheets/fs311/en/ [2].

Prevalence of Obesity in ESRD patients

Obesity and overweight have been identified as one of the major risk factors for CKD. Obesity increases the risk for CKD and its progression to end-stage renal disease (ESRD) as shown in Fig. 11.1.

As per the United States Renal Data System (USRDS) in 2015, as far as ESRD is concerned, numbers of newly reported and prevalent cases of ESRD were 124,114 and 703,243 respectively. Prevalence of ESRD continued to rise by about 20,000 cases per year [3].

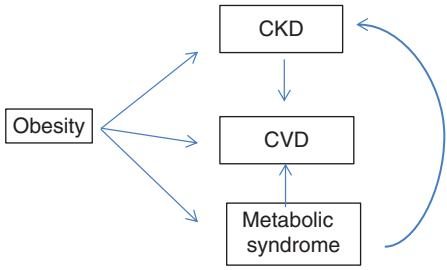

Fig. 11.1 The relation between Obesity, Cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic syndrome

Kramer et al. [4] found the increasing prevalence of obesity during the period 1995 to 2002 in incident ESRD population. As compared to the general US population, BMI was twofold higher in incident ESRD population. Increasing obesity trends in ESRD population is mirroring the trends in general adult population of US [4].

The high prevalence of obesity in ESRD patients presents a major challenge for transplantation as most transplant centers have BMI cut off for renal transplant candidacy precluding obese patients from getting transplanted.

Prevalence of Obesity in Kidney Transplant Recipients at the Time of Transplant

A rising prevalence of obesity is seen in the kidney transplant recipient (KiTR) population as well. Prevalence of obesity in end-stage renal disease (ESRD) adversely affects the rate of successful transplantation due to obesity-related medical comorbidities and concerns regarding post-transplant outcomes. Other factors involving financial and regulatory matters can also shape the final decision of transplant in obese patients [5]**.**

Friedman et al. [6] reported that the majority (60%) of subjects at the time of transplantation were overweight or obese. Between 1987 and 2001, the proportion of obese KiTR rose by 116%. The percentage of transplant recipients with BMI ≥30 kg/m^2 increased from 11.6% in 1987–1989 to 25.1% in 2000–2001 [6]. The rate of increase was grossly like that in the general population. Up to 40% died while waiting on transplant list [7].

Prevalence of Post-kidney Transplant Obesity

The reported prevalence of post-transplant obesity has been variable; up to 50% of KiTR have been noted to experience weight gain post- transplant [8]. De Oliveira [9] showed that patients gained on an average of 6.6 kg (14.5 lb) post-transplant, and the weight gain was 9.1% compared to pre-transplantation weight. Also, the prevalence

of overweight and obesity increased significantly during the follow-up period of 36 months [9]. The prevalence of overweight and obesity [9] were 26.8% and 10.7% before transplantation, and 32.5% and 16.9% after the first post-transplant year.

Impact of Pre – Kidney Transplant Obesity on Transplantation Outcomes

As mentioned at the beginning of this chapter, BMI itself is a crude way of assessing fat distribution in the body. Each transplant center has its cut off value for BMI; in general BMI > 35 Kg/m^2 is considered an exclusion criterion. Optimizing patients while on the wait list for transplant focuses on achieving target BMI and minimizing cardiovascular risk. It's debatable what the best cut off for BMI is, and also if it is really helpful for CKD/ESRD patients to lose weight for transplant surgery [10].

Diabetes is the leading cause of ESRD. DM and other co-morbidities including HTN, hyperlipidemia (HLD), and metabolic syndrome along with obesity can lead to increase in cardiovascular events and mortality in patients while waiting on the deceased donor Kidney transplant list. Factors contributing to obesity and CKD progression are shown in Fig. 11.2.

Obesity in kidney transplant recipients can increase surgical complications. More central distribution of obesity can lead to technical difficulties in performing transplant surgery and vascular anastomosis. New advances in robotic surgeries have a potential advantage [11] in such cases and are helpful to perform operations in difficult to access body cavities in obese patients. Graft and patient survival didn't show a significant difference between open and laparoscopic kidney transplantation surgeries [11]. But the availability of robotic surgery and the trained surgeon can be a limiting factor.

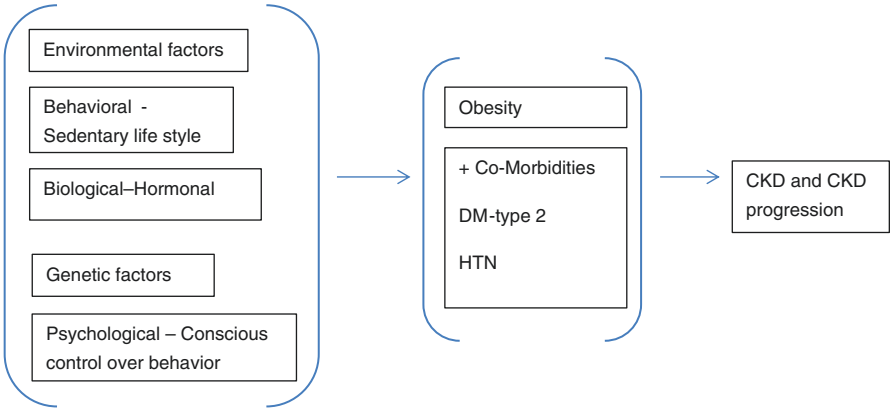

Fig. 11.2 Factors contributing to Obesity and CKD progression

Many different studies as summarized by Chan et al. [12] have shown poor short – term and long- term effects of pre-transplant obesity on post kidney transplant outcomes as listed below:

1. The higher rate of surgical site infections post-transplant. Surgical site infections are associated with a significant increase in the risk of allograft loss [13].
2. Higher rates of superficial wound breakdown [13]
3. Complete wound dehiscence
4. Increased wound infections, no difference in other surgical complications
5. Prolonged hospitalization and increased readmission rate within the first 6 months after transplant [14]
6. Effect on graft survival was variable (no effect to worse) in different studies
7. Increased risk of delayed graft function (DGF) with BMI ($\geq$35 Kg/m^2) [15]
8. Increased risk of DGF, acute rejection in the postoperative period, decreased overall graft survival with morbid obesity (BMI $\geq$ 35 Kg/m^2) and, BMI $\geq$ 35 Kg/m^{2}was independent risk factor for graft loss within the first-year post-transplant [16]
9. Very low and very high BMI (<18 or >35 Kg/m^2) before renal transplantation are associated with worse patient and graft survival [17]
10. Higher incidence of post-transplant DM [18]
11. No difference in 1-, 2-, and 5 - year patient survival [19]

A comprehensive nutritional assessment should be done as part of the pre-transplant evaluation to identify high-risk behaviors and to recognize patients who would benefit from individualized dietician services.

Modifications in diet, exercise, pharmacologic treatment, and weight reduction surgery are the different modalities available to obese patients to lose weight both before and after receiving Kidney transplant [20]. This will be discussed in further detail.

Factors Contributing to Obesity During Post-transplant Period

The major precedent to post-transplant obesity is pretransplant obesity [21]. In one study, obesity (BMI > 35 Kg/m [2]) increased the risk of graft loss post-transplant while not affecting overall mortality [22]. Another study showed that weight gain early after the transplant may put patients at risk of death and graft loss; deaths were related to cardiovascular and cancer causes [23]. Also, it is important to realize that change in weight while patients are waiting on deceased kidney transplant list had no association with post-transplant outcomes [24].

ESRD patients with chronic uremia have alterations in their metabolic processes and can have malnutrition from chronic uremia. After a successful transplant, patients feel better with improved appetite leading to improved nutritional status and weight gain.

In non- diabetic patients, glucose intolerance occurs in up to 50% after transplant surgery [25]. Immunosuppressive medications including calcineurin inhibitors (CNI) e.g. tacrolimus can impair insulin secretion from the pancreas, and its initial and maintenance doses are strongly correlated with the patient's risk of new- onset of diabetes [26].

Predisposing factors for weight gain after transplant [21, 27] **as below**:

1. Pre-transplant obesity
2. Physical inactivity
3. Immunosuppressive medications
4. Use of steroids (Polyphagia and hyperphagia) [12]
5. Improved appetite and nutritional status after transplant
6. The sense of liberation from dietary restrictions after transplant [21]

Effect of Immunosuppressive Medications

Side Effects of Immunosuppression Medications Contributing to Post-transplant Obesity and Other Components of Metabolic Syndrome

As noted below, IST can contribute to gain in weight as well as the other components of the metabolic syndrome.

Pancreatic β-cell dysfunction in the presence of insulin resistance has been described in the pathophysiology of post-transplant diabetes (PTD) in literature [28]; debate continues about their relative importance and whether PTD is a distinct entity different from type 1 and 2 DM. Among CNIs, tacrolimus is more diabetogenic and leads to insulin resistance. As compared to cyclosporine, tacrolimus is superior in terms of improving graft survival and preventing acute rejection post - transplantation [29, 30].

Impact of Steroids

A study from Brazil by C.M.C. De Oliveira et al. [9] found that there was an average of 9.1% (6.6 Kg) weight gain after 36 months of follow up as compared to pre-transplantation weight. Also, there was a significant increase in the prevalence of both overweight and obesity during the follow-up periods. Steroid avoidance alone didn't reduce weight gain in this population. Recipient factors like younger age and female sex were associated with more weight gain in post-transplant period.

Many different studies as summarized by Chan *et al* [12] have shown the effect of steroids on weight gain and body composition as below:

1. Corticosteroid dose can contribute to elevated glucose levels.
2. Weight gain in **the first- year post-transplant** is independent of cumulative steroid dose, donor source, rejection episodes, or post-transplant renal function; Cumulative steroid dose is the primary determinant of weight gain **after the first year** of transplant [31].

3. No significant difference in fat mass, lean body mass, and body fat distribution was observed on 0-, 5-, and 10 mg of maintenance steroid dose [33].
4. Another study showed that weight gain was significantly higher in KiTR on chronic low-dose steroid therapy [33].
5. Corticosteroids lead to insulin resistance and therefore PTD in a dose-dependent manner [29].

Consequences of Post-kidney Transplant Obesity

Effect on Graft and Patient Survival

Obesity is prevalent among KiTR, and it predicts increased risks of mortality, delayed graft function (DGF), higher cost, and loss of allograft [34].

Obesity was shown to be related to DGF after Kidney transplant [35] and an important factor affecting graft survival; however, patient survival was not influenced by this condition [36]. Another study [37] showed that obese KiTR had lower survival than non- obese KiTR at 1 year (76.9% vs. 35.3%) and 3 years (46.2% vs. 11.8%); myocardial infarction and cardiovascular complications were the main cause of death. The improved metabolic profile can not only reduce CVD risk but also improves graft function.

Cardiovascular Disease

Cardiac disease is the primary cause of death in the post-transplant period and graft loss due to death with a functioning graft [38]. Assessment and prevention of cardiovascular disease are vital to the care of transplant recipients.

CVD risk is high in this patient population due to the complex interaction of traditional and non- traditional risk factors including HTN, DM, obesity, hyperlipidemia, and use of immunosuppressive therapy (IST) after kidney transplantation [39], and treatment of these conditions could reduce the risk of morbidity and mortality [11].

In general population, obesity is an independent risk factor for CVD, HTN, HLD, and DM [39]. It has also been shown to be a risk factor for CVD-related mortality and congestive heart failure in KiTR [29].

Metabolic Syndrome

Metabolic syndrome (MTS) is defined by the presence of 3 or more of the following risk factors according to National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) [40]:

1. Abdominal obesity defined as a waist circumference more than 102 cm (40 inches) in men and 88 cm (35 inches) in women
2. High triglyceride level ≥150 mg/dl
3. Hypertension (blood pressure) ≥130/85 mmHg
4. Impaired fasting glucose or diabetes (fasting glucose ≥100 mg/dl)
5. High-density lipoprotein cholesterol levels <40 mg/dl in men and <50 mg/dl in women

The complex relationship between CVD, CKD, MTS, and obesity is shown in Fig. 11.1. IST can lead to dyslipidemia as one of their side effects (Table 11.2); along with above-mentioned risk factors and consequences can lead to MTS.

Obesity is an important feature of MTS and constitutes a well-known independent risk factor for MTS. Both MTS and obesity are independent risk factors for CVD and CKD in general population as shown in Fig. 11.1. CKD and MTS act synergistically and are both predictors of CVD [41]. CVD risk has been calculated as high as 50-fold greater in kidney transplant recipients (KiTR) than in general population. Prevalence of CVD was higher in kidney transplant recipients from deceased donors compared with living donors [42].

In a study by De Giorgi et al. [43] found that only BMI, but not MTS could predict major clinical events in KiTR. In general population, MTS represents an important CVD risk factor and risk of CVD events appears to be higher in females than in men [32]. Prevalence of MTS in KiTR in the post-transplant period was 22.6% after 1 year and 64% after 6 years [44].

Table 11.2 Immunosuppressive medications, their mechanism for obesity/metabolic syndrome, and their side effect

Medication	Mechanism of obesity/ MTS	Consequence
Tacrolimus	Diabetogenic Insulin resistance ↑ Insulin secretion ↓ Tissue glucose uptake ↓	New onset diabetes after transplant Increase in blood pressure
Cyclosporine	Diabetogenic Insulin resistance ↑ Insulin secretion ↓ Tissue glucose uptake ↓	New onset diabetes after transplant Elevation of blood pressure High LDL cholesterol Increased S. Uric acid levels
Sirolimus (mTOR-inhibitors)	β- cell dysfunction↓ GLUT1 synthesis ↓	Hyperlipidemia
Steroids	Hepatic glucose production ↑ Insulin secretion ↓ Adipose tissue lipolysis ↑ Insulin resistance ↑ Decreased incretin effect	Glucose level elevation Weight gain Sodium retention and high blood pressure Increase in low-density lipoprotein and total cholesterol

mTOR mammalian target of rapamycin, *GLUT1* Glucose transporter

Table 11.3 The 2014 International Consensus Guidelines on the Screening, Diagnosis, and Management of Early Post-transplant Hyperglycemia and PTD [49] (with permission)

Post-transplant (days)	Evaluation	Diagnosis	Management	
0–45	Early post-transplant hyperglycemia	**Do not diagnose with PTD**	**Day 0–7**	Insulin
			Day 8–45	Insulin Oral – hypoglycemic agents
46–365	**Screening Test** 1. OGTT 2. Fasting/random glucose 3. Hba1c[a]	Diagnosis of PTD	Lifestyle modifications Insulin Oral – hypoglycemic agents	
>365	**Screening Test** 1. OGTT 2. Fasting/random glucose 3. Hba1c			

PTD Post-transplant diabetes, *OGTT* Oral glucose tolerance test, *Hba1c* glycosylated a1c
[a]HbA1C alone <365 days may underestimate PTDM and requires corroborating

Post-transplant Diabetes

Post-transplant diabetes (PTD) is defined as development or unmasking of unrecognized diabetes in KiTR who had no previous history of diabetes [45]. Table 11.3 outlines 2014 International consensus guidelines on the screening, diagnosis, and management of early post-transplant hyperglycemia and PTD. It is associated with risks of graft loss, cardiovascular morbidity, and mortality [45]. Obesity is associated with 73% increased the risk of PTD [46].

Incidence and prevalence of PTD has varied in accordance with different IST regimens, diagnostic criteria, and demographics. It was reported in up to 50% [47] of KiTR in the era of steroids and azathioprine; 2–53% [48] with the introduction of steroid-sparing CNI leading to increased disparity due to the difference in CNI and steroid dosing and heterogeneous diagnostic criteria. Risk factors for PTD have been outlined in Fig. 11.3.

An important feature of PTD is the amount of dynamic change in glucose metabolism – mostly related to large reductions in IST between 1–6 months post-transplant, or conversely the effect of additional steroid usage for rejection episodes. A state of the art article for PTD put together by Sharif and Coheny [28] outlines that pancreatic β-cell dysfunction in the presence of insulin resistance is the main defect in the pathophysiology of PTD. Insulin resistance and MTS (along with insulin resistance as an important pathophysiological defect) are prevalent in PTD. Use of IST is an additional risk factor.

Management of PTD should begin as part of pre-transplant evaluation to be vigilant, and watch for patients with high risk [45].

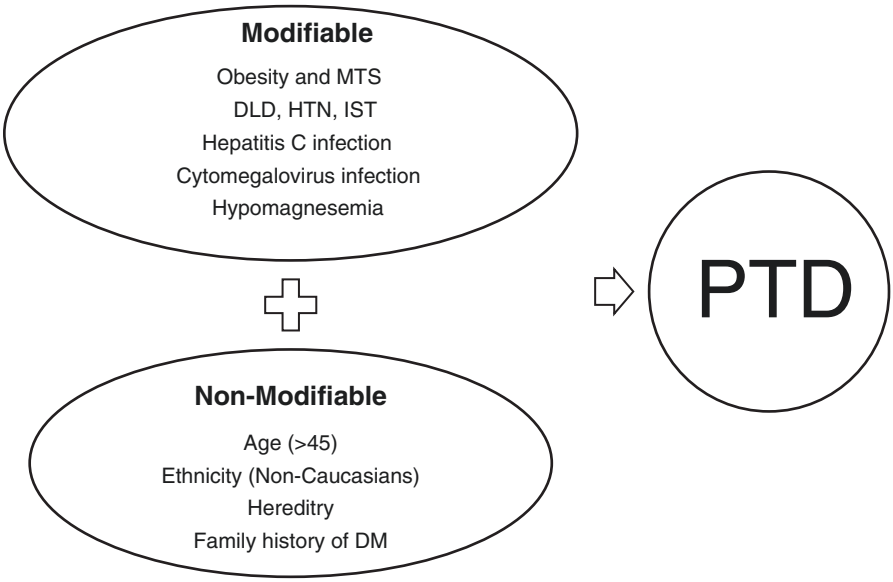

Fig. 11.3 Risk factors for PTD

Hypertension

HTN in KiTR is multifactorial. Donor and recipient can contribute via different factors specific to them. Recipient's weight gain after transplant, IST especially tacrolimus, cyclosporine and steroids, increased renin and sympathetic release from native kidneys along with genetic and hormonal interactions can cause hypertension. Donor factors like age (older), sex (female), DGF, episodes of rejection, anatomy, and vasculature can be contributing factors to HTN [50]. Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend BP goals of 125/75 mmHg for transplant recipients with proteinuria and 130/85 in the absence of proteinuria [51].

Morbidity and Mortality

A review and meta-analysis [52] showed that underweight, overweight and obese recipients had higher mortality. Transplantation among obese KiTR offered survival advantage compared with obese transplant candidates who remained on waitlist; mortality was half compared to those who remained on dialysis [53]. But beneficial effect of transplantation was lost when BMI was over 40 Kg/m^2 with lower survival advantage of transplant in these patients [53].

Management of Obesity in Post-transplant

Obesity management in the post-transplant period after a successful transplant is best managed by a multi-disciplinary team approach. Dietician, social worker, transplant coordinator, financial advisor, transplant surgeon, nephrologist and administrative staff constitute a typical transplant team.

Management should be geared towards employing strategies to prevent weight gain after transplant, as well as different options for treatment of obesity once it becomes established. Following strategies can be helpful to prevent excessive post-transplant weight gain.

Behavioral Changes

ESRD patients on dialysis have a multitude of causes for poor nutritional status, including poor appetite, poor exercise capacity, limited mobility in diabetic patients after limb amputations, feeling poorly right after dialysis, and from uremia. On the other hand, improvement in uremia after transplant along with discontinuation of dietary restrictions, and high-dose steroid induced hyperphagic state contribute to the development of obesity post-transplant as mentioned at the beginning of this chapter.

As patients feel relieved from the dietary restrictions after receiving a kidney transplant, it should be kept in mind that "letting loose" of these restrictions don't take away the responsibility of healthy eating in general after the transplant. This principle should be reinforced in the post-transplant period and during every clinic visit along with dietary counseling by a qualified dietitian.

Lifestyle Changes: Exercise and Physical Training

A recent study by A. J. Nastasi [54] found that pre - Kidney transplant physical impairment was independently associated with a 2.30-fold increased risk of post-transplantation mortality. Also, it was found that physically impaired recipients were significantly older, had higher BMI (28.3 vs. 26.7) were on dialysis for longer (3.4 vs.2.7 years), were more likely to be diabetic (36.0% vs. 18.0%,). As a result, advocating for early ambulation post-operatively, and counseling patients on starting an incremental exercise/physical training regimen after discharge is important in improving patient's endurance/functional status as well as preventing unwanted weight again.

Early Intensive Nutritional Counseling

Individualized dietary advice and implementation of structured weight reduction programs can be helpful in reducing weight gain.

Management of Nutrition in Post-transplant Period

In Immediate Post-transplant Period

In the immediate post-transplant period, especially the first 4–6 weeks after surgery, it is very important to keep up with increased nutritional needs, given increased catabolism from the stress of surgery and use of higher dose of steroids which are commonly employed as part of the initial immunosuppressive regimen. Also, with increased urine output in the immediate post-operative period, replacement of electrolytes especially potassium, calcium and magnesium is crucial along with management of intravenous fluids to keep up with increased urine losses. Patient's oral intake can be limited in the post-operative period after surgery due to nausea, ileus or pain. So, daily assessment for needs of enteral (tube feeds) or parental nutrition should be done while encouraging oral intake as tolerated. The main focus is to provide adequate protein (1.3–2 g/Kg body weight) and calorie intake (30–35 Kcal/Kg body weight) to help promote wound healing, counteract protein catabolism and maintaining a healthy weight [8].

Early Post-transplant Period

ESRD patients with chronic uremia have alterations in their metabolic processes and can have malnutrition from chronic uremia. As this is corrected post-transplant, it can contribute to weight gain due to improved appetite and nutritional status. Assessment of weight and nutritional needs should be done at each clinic visit and health providers should intervene at the earliest with counseling and dietician referral as needed.

Late (Long-Term) Post-transplant Period

Use of chronic low dose steroids as part of maintenance immunosuppression therapy in addition to intensified steroid regimen to treat any graft rejections during the lifetime of the graft can add to the cumulative steroid dose and is the primary determinant of weight gain after the first year [31] of transplant.

Role of Steroid-Free Immunosuppression Regimens

As per the recent literature, the trend has been towards steroid sparing and CNI sparing regimens for post-transplant immunosuppression. The most pronounced benefit of early steroid withdrawal appears to be on >20 pounds (lbs.) weight gain. More than 20 lbs. weight gain is defined as the difference of >20 lbs. when comparing pretransplant weight with post-transplant weight [55].

1. Early steroid withdrawal regimen was associated with improvement in diabetes, hypertension, hypercholesterolemia, weight gain and coronary artery disease rates post-transplant.
2. Lowering the dose of steroid or early steroid withdrawal after a Kidney transplant can help prevent insulin resistance.
3. Early steroid withdrawal resulted in less weight gain compared with 5 mg maintenance dose.
4. Reducing the dose or withdrawal of CS can reduce the risk of PTD and may actually reverse it and restore insulin sensitivity [26].

Treatment of Post-transplant Obesity

Recognizing high-risk patients at an early stage and timely counseling by dietician would be helpful in preventing obesity in the post-transplant period. Above strategies can be helpful in achieving weight loss in several patients but will take a coordinated and determined effort on part of the patient with help from the transplant team. However, if this fails, and patients have established obesity that is not amenable to above strategies, they can be treated with weight-loss medications or be referred for bariatric surgery in those with morbid obesity.

Medications

Pharmacological methods have not been studied much to treat obesity in transplant recipients unlike in general population. These are not routinely recommended. The US Food and Drug Administration (FDA) has approved few major weight loss medications including sibutramine, phentermine hydrochloride, liraglutide, and orlistat. Fenfluramine has been removed from the US market due to concern about pulmonary hypertension and valvular abnormalities. There are no controlled studies of these agents in transplant recipients. Many of these drugs are contraindicated in pregnant patients. There is limited experience with the use of these drugs in KiTR.

(a) Sibutramine may be safe for KiTR but is metabolized by the same enzyme as many of transplant anti-rejection medications in the P450 3A4 system. It may

interfere with the metabolism of cyclosporine [56], tacrolimus, or rapamycin. As with all serotonin uptake inhibitors, rare cases of pulmonary hypertension may occur. It is associated with HTN [57].

(b) Topiramate and combination of Phentermine/Topiramate: Topiramate is an inhibitor of cytochrome P450. Phentermine may also cause modest weight loss in transplant recipients.

(c) Orlistat – It may be effective, but it inhibits fat absorption and can reduce cyclosporine bioavailability [58].

(d) Liraglutide – is an incretin mimetic and has been approved for the treatment of type 2 diabetes. Its use in KiTR can delay gastric emptying, that could potentially affect absorption of co-administered IST. A case series [59] showed that tacrolimus trough concentrations were unaltered after co-administration with liraglutide. Stronger evidence is lacking.

Weight Reduction Surgery

(a) Use of bariatric surgery (BS) among morbidly obese KiTR was first described in 1996 [60]. BS has been uncommon among KiTR, due to uncertainty about outcomes of BS for weight loss. So, it is not routinely advised as a treatment option. A retrospective study using United States Renal Data System (USRDS) between 1991–2004, looked into the safety and efficacy of BS in total of 188 patients (72 pre-listing, 29 on waitlist, 87 post-transplant patients) with Roux-en-Y gastric bypass as the most common procedure and concluded that there was mean excess body weight loss of 61% and is lower than age-matched, non-ESRD patients undergoing BS [34].Effect on the pharmacokinetics of IST and risk of graft rejection are a theoretical concern for BS in KiTR. Close watch to keep IST levels in the desired range should be done in such patients.

(b) Laparoscopic adjustable gastric banding (LAGB) has also been described in Kidney transplant candidates and recipients; complications like band migration and erosion in transplant recipients were reported [34].

(c) Laparoscopic sleeve gastrectomy (LSG) has been described in KiTR and doesn't interfere with absorption of IST. Its irreversibility may potentially harm those who lose too much weight [34].

Conclusion

Kidney transplantation in ESRD patients improves long-term survival, quality of life, and is cost-effective. Obesity can be a challenge for kidney transplantation and may preclude it in some patients. Obesity contributes to the higher prevalence of CVD risk factors like HTN, HLD, DM and insulin resistance in both the pre-and post-transplant period.

Post-transplant obesity is a significant problem leading to adverse patient and allograft outcomes. In the care of post-kidney transplant recipients, prevention of obesity by focusing on the identification and optimization of modifiable risk factors while maintaining allograft function on minimum effective doses of IST is of utmost importance.

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Chapter 12
Post Kidney Transplant: Hematological Complications

Daniel C. Felix

Introduction

Though renal transplantation can provide life-saving benefits in patients with the end-stage renal disease, unfortunately, transplant recipients are at an increased risk for blood disorders. As these disorders are not uncommon in this patient population, understanding their pathophysiology and management is crucial in caring for transplant recipients. Here we discuss the causes, pathogenesis, clinical features, and treatment strategies for common disorders such as anemia, cytopenias, post-transplant lymphoproliferative disorders (PTLD), and erythrocytosis in addition to some uncommon disorders such as thrombotic microangiopathy (TMA) and hemophagocytic syndrome (HPS).

Post-transplant Anemia (PTA)

PTA is a common hematologic complication that can occur at any time post-transplant for a variety of reasons. Anemia is defined in patients with chronic kidney disease as a hemoglobin less than 13 g/dL in males and less than12 g/dL in females [1]. About 40% of renal transplant recipients develop anemia [2, 3]. Causes of PTA include medications, renal allograft dysfunction, infections, nutritional deficiency, and rejection [4]. Many renal transplant recipients had complications of anemia prior to transplantation with chronic kidney disease or while on dialysis and there are some similarities between them. Symptoms of anemia include fatigue, weakness, shortness of breath, and pale skin.

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There are many medications transplant recipients take that can cause anemia. Immunosuppressive agents, antimicrobials, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are a few of the more common culprits by suppressing erythropoiesis in the bone marrow. Antiproliferative agents such as azathioprine (AZA) and mycophenolate (MMF) along with induction agents anti-thymocyte globulin (ATG) and alemtuzumab are myelosuppressive agents that disrupt erythropoiesis by suppressing the bone marrow. Calcineurin inhibitors such as tacrolimus (TAC) and cyclosporine (CsA) can cause PTA indirectly by damaging the kidney as they are nephrotoxic. The mammalian target of rapamycin (mTOR) inhibitors, sirolimus, and everolimus effect erythropoietin binding to its receptor which inhibits intracellular signaling pathways disrupting erythropoiesis [5]. Agents that are used for infection prophylaxis such as ganciclovir, valganciclovir, and trimethoprim-sulfamethoxazole can also case PTA via marrow suppression. Anti-hypertensive agents such as ACEI and ARB can cause PTA through a few mechanisms. They can inhibit production of endogenous erythropoietin, inhibit stimulation of red blood cell precursors [6], and generate a protein that inhibits erythropoiesis [7]. When used in combination as they are in many transplant recipients, the effects of these agents can be synergistic.

Renal allograft dysfunction is another major cause of PTA since erythropoietin production is directly related to renal function. As creatinine increases and renal function worsens, erythropoietin production decreases. Similar to anemia of chronic kidney disease, there could be a component of erythropoietin resistance in addition to a decrease in endogenous erythropoietin production [8].

Transplant recipients are at a higher risk for certain viral infections that can cause PTA as they are on immunosuppressive medications. Infections such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19 (PVB19) can cause aplastic anemia in renal transplant recipients [9].

Nutrition and rejection can also affect PTA. Rejection of the renal allograft can lead to decreased erythropoietin production [10]. Erythropoietin secretion can be restored to normal levels once rejection is treated. Allograft rejection can also cause a systemic inflammatory response syndrome which disrupts the binding of iron and folic acid, blocking their transport and leading to PTA. Deficiencies in nutrients needed for erythropoiesis such as iron, folic acid, and vitamin B6/B12 can result in PTA [11]. Renal transplant recipients can develop iron deficiency anemia due to blood loss caused by surgery, dialysis, and lab collections in addition to postoperative complications such as gastrointestinal bleeding [10].

Treatment of PTA is important as it can prevent further complications such as worsening CKD [12, 13] and development of cardiovascular disease [8] while also providing symptomatic relief and improving quality of life in patients. Blood transfusions, while logically simple, are reserved for emergency situations due to the scarcity of the resource and the potential for sensitization in the patient due to antibody formation to the donor antigens. Erythropoiesis-stimulating agents (ESAs) such as epoetin alfa, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta stimulate the bone marrow to increase production of red blood cells. They are recommended for use in patients with CKD as they reduce the number of blood transfusions needed [1, 14].

Prior to initiating ESA therapy, iron studies should be assessed to ensure adequate iron stores for red blood cell production. If iron deficient, iron supplementation is recommended to ensure an adequate response to the ESA. Due to their risk for thromboembolic events, ESA therapy should not be initiated until the hemoglobin is less than 10 g/dL and should not be used to maintain a hemoglobin greater than 11.5 g/dL [1]. For this reason, patients on ESA therapy should be monitored closely.

Post-transplant Cytopenias (PTC)

In addition to anemia, other types of cytopenia, a disorder where one or more blood cell type production is greatly reduced or ceases altogether, that can occur in transplant recipients include leukopenia, thrombocytopenia, and pancytopenia. Medications and viral infections are often the cause of these disorders.

Leukopenia

Leukopenia, defined as a WBC count less than 3000–4000 cells/μL, occurs in about 20 t 63% of renal transplant recipients [15]. Neutropenia, the most common form of leukopenia, is defined as a low count of neutrophils, generally less than 1500 cells/μL. Renal transplant recipients usually experience this within the first 100 days post-transplant and it can persist for 1–4 weeks [16].

Multiple factors play a role in the development of leukopenia. Azathioprine has one of the highest incidences of leukopenia with 50% of transplant recipients developing leukopenia while on therapy [17]. Mycophenolate causes leukopenia if 13–35% of renal transplant recipients [18]. Dose reduction or drug discontinuation can reverse these effects. T cell depletionary agents such as anti-thymocyte globulin or alemtuzumab can also cause leukopenia by eliminating circulating lymphocytes. This effect is usually more profound and prolonged due to the nature of its mechanism. Anti-virals against CMV such as ganciclovir and valganciclovir cause leukopenia in 50% of patients due to their bone marrow suppressing effect [19]. Trimethoprim-sulfamethoxazole, amongst other antibiotics, can also cause leukopenia when used with other marrow suppressing drugs [20, 21]. Cessation of antimicrobial agents can reverse leukopenia but should be done with caution as viral infections can also cause myelosuppression. Infections such as CMV, PVB19, and influenza amongst others have been found to cause leukopenia [22].

Treatment of leukopenia is most effectively done through the removal of offending agent whether it be drug or pathogen. As previously mentioned, dose reductions or drug cessation can attenuate leukopenia, but this can increase the risk for rejection which often requires treatment with further leuko-depleting agents. Granulocyte-colony stimulating factors (G-CSF), such as filgrastim or TBO-filgrastim, can increase neutrophil counts in renal transplant recipients which may improve their leukopenia.

Thrombocytopenia

Defined as a total platelet count less than 50,000/μL, thrombocytopenia is quite prevalent during the first year after renal transplantation and can present as bleeding, bruising, weakness, and fatigue [23, 24]. Similar to other cytopenias, it can be caused by medications, infections, and rejection that cause bone marrow suppression [25]. Calcineurin inhibitors and mTOR inhibitors can cause thrombocytopenia through TMA, a condition where many thrombi form within a patient's microvasculature [26]. Other immunosuppressive medications that cause bone marrow suppression leading to thrombocytopenia include anti-thymocyte globulin, ganciclovir, and valganciclovir [27]. CMV and EBV infections have also been implicated in causing thrombocytopenia [28].

Treatment of thrombocytopenia includes removing the causative agent, stimulating platelet formation in bone marrow, and treating TMA [29]. Platelet transfusions can also be utilized but should be reserved for severe thrombocytopenia or abnormal bleeding. Thrombopoietin growth factors such as romiplostim and eltrombopag are also available but should be reserved as a second line treatment option due to limited data on transplant recipients. Rituximab and eculizumab, a complement inhibitor, might be effective in treating TMA in transplant recipients.

Pancytopenia

Patients unfortunately present with reduced cell counts in multiple blood cell lines. These pancytopenias can lead to several complications such as oxygen shortage and decreased immune function [30]. Certain systemic infections such as histoplasmosis, blastomycosis, herpesvirus-6 (HHV-6), and herpes virus-8 (HHV-8) can present themselves as pancytopenia [31]. These infections can be treated in a transplant recipient with decreased immunosuppression and appropriate antimicrobials which will reverse the pancytopenia. Medications can also be the cause of pancytopenia. Drug interactions, such as the combination of azathioprine and allopurinol, can be especially problematic in causing pancytopenia. Once the causative agents are removed, the pancytopenia is reversible.

Post-transplant Lymphoproliferative Disorders (PTLD)

PTLD is a group of well-recognized hematologic complications of renal transplantation. These disorders range from lymphoid hyperplasia to highly invasive malignant lymphoma and can occur in 1–5% of renal transplant recipients [32]. Around 80% of PTLD cases are caused by EBV infections in transplant recipients due to their immunosuppression [33, 34]. This herpes virus infects B cells, causing viral

replication inside the cells. Immunocompetent hosts can mount an innate immune response to suppress EBV replication and control proliferation of B cells infected with the virus. Transplant recipients on immunosuppressive drugs that deplete T cells or impair their function cannot mount a strong enough immune response to EBV leading to an uncontrolled proliferation of EBV infected B cells that lead to B cell lymphoma or lymphoid hyperplasia [35]. EBV causes genetic changes at the cellular level of infected cells resulting in the formation of malignant cells [36–38]. In a host environment with diminished immune function, these cells replicate faster then they are cleared and form tumors.

PTLD cases usually occur within 1–2 months of transplantation but patients are at highest risk within the first year of transplantation [39]. EBV seronegative patients are at higher risk for the development of PTLD compared to seropositive recipients, especially those receiving an organ from a seropositive donor. Pediatric transplant recipients are at a higher risk for PTLD compared to adults due to their lower rates of EBV seropositivity at the time of transplantation [40, 41]. Belatacept, a costimulation blocker used for maintenance immunosuppression in renal transplant recipients, has been found to increase the risk for PTLD in EBV seronegative recipients causing its use to be contraindicated in this population [42, 43]. PTLD can be life-threatening with mortality rates ranging from 25% to 26.6% due to its aggressive and rapid progression [44].

The approach to diagnosing PTLD includes a patient presentation, histopathological evidence, and serologic testing. When presenting with PTLD, patients usually develop symptoms like infectious mononucleosis such as enlarged tonsils and cervical nodes [45]. This can also spread outside lymph nodes and involve other organs and tissues such as the central nervous system, lungs, gastrointestinal tract, and allograft. The fulminant presentation includes widespread infiltration with multiple tumors and multi-organ involvement [46]. To assess for the presence of an active EBV infection, qualitative and quantitative EBV polymerase chain reaction (PCR) can be collected to monitor the viral load in peripheral blood of the recipient. EBV PCR can be used to monitor for EBV infections and be a diagnostic tool for PTLD. Patients at high risk for EBV can have their viral loads monitored to predict impending PTLD [47]. Confirmatory diagnosis of PTLD should be based on histopathological examination of biopsy tissue [48]. Presence of an increased number of B cells in lymphoid tissues with focal areas of necrosis could be indicative of PTLD [49]. Immunohistologic staining of tissue should be used to assess for the presence of EBV DNA, RNA, or protein which is crucial for accurately diagnosing PTLD [50].

The mainstay of treatment of PTLD is reduction or cessation of immunosuppression. This will allow for the host immune system to neutralize the infection and replication of malignant cells, leading to remission and symptom attenuation [51]. Unfortunately, reduction of immunosuppression does carry the risk of causing allograft rejection and should be done cautiously with close monitoring. If immunosuppression taper is not successful or not possible, other treatment options include chemotherapeutic agents such as rituximab, IVIG therapy, localized radiation, and tumor excision [52]. Rituximab, a monoclonal antibody that binds to CD20 found

on B cells causing apoptosis, has been successfully used in transplant recipients to treat PTLD, having response rates of 50–69% [53]. In certain cases with advanced disease or relapse, combination chemotherapy with rituximab followed by cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been shown to be superior to rituximab monotherapy [54].

Prophylaxis of EBV can prevent PTLD in transplant recipients. Matching seronegative recipients with seronegative donors can help reduce transmission of EBV, but the scarcity of organs available for transplantation does not always allow for this. Use of depletionary induction agents should be discouraged in patients at high risk for EBV infections. Antivirals such as acyclovir, valacyclovir, ganciclovir, and valganciclovir have been used for EBV prophylaxis but with minimal success [55]. These agents have been found to prevent EBV replication and infection of B cells but do not have activity against infected B cells, having no activity in active PTLD [56].

Post-transplant Erythrocytosis (PTE)

PTE is defined as a persistently elevated hemoglobin level greater than 17 g/dL for more than 6 months and is common after renal transplantation occurring in 10–20% of patients within 8–24 months of transplantation [57, 58]. Complications of PTE include hypertension, thrombosis, and even life-threatening complications such as cerebral vascular injuries due to the increased viscosity of the blood caused by the increased hemoglobin. The mortality of complications associated with PTE is about 1–2% [59]. Patients can present with headaches, weakness, fatigue, and thromboembolism.

Causes of PTE can be multi-factorial with evidence suggesting that erythropoietin, renin-angiotensin system (RAS), and endogenous androgens all play a role in its pathogenesis [59]. Erythropoietin is produced by the kidney in interstitial fibroblasts. New renal allografts can overproduce erythropoietin leading to overstimulation of erythropoiesis [60]. When the kidney senses decreased blood flow or ischemia, such as in chronic rejection, hydronephrosis, renal artery stenosis, and with calcineurin inhibitor use, it stimulates over-production of erythropoietin [61]. Erythropoiesis is also regulated by the RAS, a hormone system that also controls blood pressure. One of the hormones in this system, angiotensin II, might stimulate erythropoiesis by increasing production of erythroid progenitors or other erythropoietic factors within the bone marrow. Androgens cause men to be at increased risk for PTE since they enhance the sensitivity of primitive erythrocytes to erythropoietin [62].

The goal in treating PTE is to decrease the hemoglobin level below 17.5 g/dL. ACEI and ARB are effective at inhibiting the RAS, decreasing erythropoiesis [63]. Other agents such as theophylline, ketanserin, and sirolimus have been used to lower hemoglobin levels in patients with PTE [64]. If drug therapies are ineffective at treating PTE, phlebotomy should be performed to decrease risk for thromboembolic events [59].

Rare Disorders

In addition to common causes of hematologic complications, transplant recipients are at risk for rare conditions as well such as thrombotic microangiopathy (TMA) and hemophagocytic syndrome (HPS). These conditions can have more severe complications and worse prognosis for renal transplant recipients.

Thrombotic Microangiopathy (TMA)

TMA can occur in renal transplant recipients due to renal endothelial tissue damage caused by calcineurin inhibitor usage. Patients typically present with symptoms of anemia, thrombocytopenia, renal dysfunction, fever, increased lactate dehydrogenase, and decreased haptoglobin and schistocytes early posttransplant [65, 66]. The two major types of TMA are hemolytic uremic syndrome (HUS) and thrombocytopenic purpura (TTP) [67]. Calcineurin inhibitors, mTORs, CMV infection, antibody-mediated rejection (AMR), and antiphospholipid antibody syndrome are all risk factors for TMA. The first step in treating TMA posttransplant is tapering or removing the calcineurin inhibitor. In patients with systemic TMA, plasma exchange therapy should be initiated [66]. Eculizumab should be considered in a patient with recurrent TMA, antiphospholipid antibodies, or other known risk factors such as complement factor H mutations [68, 69]. Alternative immunosuppressant agents such as belatacept should be considered when TMA is caused by AMR. Patients receiving renal transplants for atypical hemolytic syndrome may benefit from prophylactic eculizumab.

Hemophagocytic Syndrome (HPS)

HPS is characterized by uncontrolled proliferation of nonneoplastic macrophages that ingest other blood cells caused by uncontrolled stimulation of IL-2 and tumor necrosis factor-α. Most cases of HPS are caused by opportunistic infections in transplant recipients including viral infections (CMV, EBV, adenovirus, PVB19, HHV-6, HHV-8, and BK polyomavirus), bacterial infections (*Escherichia coli,* tuberculosis, and *Bartonella henselae*), fungal infections (*Pneumocystis jirovecii* pneumonia), and protozoan infections (toxoplasmosis, babesiosis, and leishmaniasis) [70, 71]. To diagnosis HPS, a patient must meet five out of the eight criteria: [1] fever, [2] splenomegaly, [3] decreased counts of two blood cell lines, [4] elevated triglyceride and/or fibrinogen levels, [5] elevated ferritin levels, [6] hemophagocytosis, [7] decreased natural killer cell activity, and [8] elevated soluble CD25 (soluble IL-2 receptor) [72]. In 70% of cases, confirmation of diagnosis can be achieved with a bone marrow biopsy showing mature histiocytes consuming other blood cells.

Outcomes of HPS are poor posttransplant with a high mortality rate of 53% and high rates of graft loss associated with rejection and septic shock [73]. Treatment usually involves treating the underlying infection and reducing immunosuppression. Intravenous steroids and IVIG might be utilized to attenuate hemophagocytosis [70]. In cases resistant to supportive therapy, transplant nephrectomy may be a viable option for these patients [73].

Conclusion

After renal transplantation, blood disorders are not infrequent. As discussed, anemia, thrombocytopenia, leukopenia, pancytopenia, erythrocytosis, and PTLD are more common conditions in transplant recipients compared to TMA and HPS. Medications, infections, allograft dysfunction, nutrition, and rejection all play a role in the development of these disorders and is summarized in Table 12.1. If untreated, these blood disorders can cause significant harm to patients in the form of decreased quality of life and even death. Treatment often involves changes to immunosuppressive regimens with removal or discontinuation of drugs, often increasing the risk for allograft rejection. These disorders are often resistant to first-line interventions, requiring more aggressive treatment options such as antimicrobial or chemotherapeutic agents, drugs that come with their own set of risks and complications. Preventative strategies such as infection prophylaxis and preemptive monitoring can have benefits in decreasing the risk for these disorders. New immunosuppressive agents without myelotoxicity are needed to decrease the incidence of these hematologic complications in renal transplant recipients. These new agents will hopefully not only decrease the risk for blood disorders but also increase allograft and patient survival.

Table 12.1 Hematological complication

Hematologic complication			Causes	Mechanism	Incidence	Signs and symptoms	Treatment
Common disorder	PTA		Renal allograft dysfunction, immunosuppressive agents, viral infections, nutrition, rejection	Myelosuppression, nephrotoxicity	38–39%	Hb < 13 g/dL in males and <12 g/dL in females, fatigue, weakness, shortness of breath, pale skin	1. Adjusting medications 2. Treating viral infections 3. Iron therapy 4. Nutrient repletion 5. Treatment with ESAs 6. Blood transfusion
	PTC	Leukopenia	Immunosuppressive agents, viral infections, antibiotics, antivirals, nutrition	Myelosuppression	20–30%	WBC < 3000–4000 cells/μL, neutrophils <1500 cells/μL	1. Adjusting medications 2. Treating viral infections 3. Treatment with G-CSF
		Thrombocytopenia	Immunosuppressant agents, viral infections, acute rejection	Myelosuppression	15–25%	Total platelets <50,000/μL, bleeding, bruising, weakness, fatigue	1. Adjusting medications 2. Treating viral infections 3. Platelet transfusions 4. Treatment with thrombopoietin growth factors
		Pancytopenia	PVB19, HHV-6, HHV-8, histoplasmosis, blastomycosis, immunosuppressant agents	Myelosuppression	20–30%	Hb < 9 g/dL, WBC < 4000 cells/μL, platelet <100,000/μL, bleeding, bruising, weakness, fatigue, shortness of breath	1. Adjusting medications 2. Treating infections
	PTLD		Immunosuppressive agents, EBV	Myelosuppression, mutation of cell genes	20–30%	Mononucleosis infection, lymphadenopathy, malaise, fever, weight loss, night sweats, upper respiratory tract symptoms	1. Adjusting medications 2. Rituximab therapy IVIG therapy 3. Combination chemotherapy 4. Localized radiation 5. Tumor excision
	PTE		Over-production of erythropoietin, RAS activation, endogenous androgens	Increased erythropoiesis	10–20%	Hb >17 g/dL for >6 months, hypertension, headaches, weakness, fatigue, thromboembolism	1. RAS inhibitors (ACEI and ARB) 2. mTOR inhibitors 3. Phlebotomy

(continued)

Table 12.1 (continued)

Hematologic complication		Causes	Mechanism	Incidence	Signs and symptoms	Treatment
Rare disorder	TMA	Immunosuppressant agents, acute antibody-mediated rejection	Intervascular platelet aggregation leading to microvascular endothelial injury	0.6%	Anemia, thrombocytopenia, renal dysfunction, increased lactate dehydrogenase, decreased haptoglobin, schistocytes	1. Adjusting medications 2. Plasma exchange 3. Eculizumab therapy
	HPS	Viral, bacteria, fungal, or protozoan infections, immunosuppressant agents	Uncontrolled stimulation of IL-2 and tumor necrosis factor-α leading to an uncontrolled proliferation of macrophages	0.4%	Fever, splenomegaly, decreased counts of two blood cell lines, elevated triglyceride and/or fibrinogen levels, elevated ferritin levels, hemophagocytosis, decreased natural killer cell activity, elevated soluble CD25 (soluble IL-2 receptor)	1. Adjusting medications 2. Corticosteroids 3. IVIG therapy 4. Treating infections 5. Transplant nephrectomy

Adapted from (Ref. [23])

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Chapter 13
Post Kidney Transplant: Bone Mineral Disease

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Bone disease is a major cause of morbidity after kidney transplantation. Changes in bone quality and density as well as mineral metabolism differ after kidney transplantation compared to patients with chronic kidney disease and, therefore, the post-transplant bone disease is significantly different from the range of chronic kidney disease and mineral bone disorders seen pre-transplant. This Chapter aims to discuss the epidemiology, pathophysiology, and therapeutic strategies for managing bone disease after kidney transplantation.

Epidemiology

Early studies after kidney transplant revealed a rapid decrease in bone mineral density (BMD) of 4–10% in the first 6 months after transplant [1–3]. Progressive decline seemed to continue with further decreases of 0.4–4.5% in BMD of the lumbar spine between 6 and 12 months post-transplantation [4]. More recent studies with conventional immunosuppressive regimens have reported a bone loss of only 0.1–5.7% in the lumbar spine within the first year of transplantation with stable BMD thereafter [5]. The incidence of hip fracture in patients who underwent a kidney transplant in 2010 was 45% lower than in patients transplanted in 1997 [6].

Despite improvements over the past 2 decades, the reduction in BMD in kidney transplant recipients contributes to an increased incidence of fractures that is four times higher than the general population [7]. In the first 5 years after transplantation, up to 25% of kidney transplant recipients experience a fracture, and up to 45% of kidney transplant recipients experience a fracture over their lifetimes [7]. The most

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common fracture locations are the hip and ankle/foot. There is a 60% increased risk of mortality in kidney transplant recipients who sustain a fracture compared with the general population and a three-fold increase in mortality in those who sustain a hip fracture [8, 9].

Pathophysiology

Bone loss after kidney transplantation is due primarily to a reduction in trabecular bone mass secondary to the decreased bone formation as a result of glucocorticoid therapy [10]. In contrast, bone loss associated with chronic kidney disease-mineral and bone disorder (CKD-MBD) is primarily due to a reduction in cortical bone mass due to secondary hyperparathyroidism. The post-transplantation bone disease results from a combination of the evolution of preexisting CKD-MBD and the development or progression of osteoporosis. Risk factors for bone loss and fractures are summarized in Box 13.1.

Box 13.1 Risks Factors Associated with Post-transplantation Bone Loss and Fractures

Risk factors for osteoporosis
- General factors
  - Younger age at transplantation
  - Poor nutrition
  - Smoking
  - Alcohol abuse
- Endocrine/mineral factors
  - Hypogonadal status
  - Hypomagnesemia
- Biologic abnormalities
  - Functionally different alleles of the vitamin D receptor gene

Risk factors for fracture
- Skeletal factors
  - Lumbar osteoporosis or nonvertebral fractures
  - Preexisting history of fracture
  - Renal osteodystrophy
- Risk of falls
  - Postural instability
  - Decreased visual acuity
  - Peripheral vascular disease

Peripheral neuropathy
Orthostatic hypotension
Drugs (sedatives, antihypertensive agents)

Risk factors for both fracture and osteoporosis
General factors
Age ≥ 50 years
Women
Body mass index <23 kg/m^2
Diabetes
Time on dialysis

Transplantation factors
The cumulative dose of corticosteroids

Biologic abnormalities
Vitamin D deficiency
Parathyroid hormone >130 ng/L
High serum fibroblast growth factor 23 level

Adapted from reference [11]

Pre-existing renal osteodystrophy is a risk factor for fracture and adverse outcomes post-transplantation [12]. Renal osteodystrophy related to CKD-MBD refers to alterations in bone morphology associated with CKD, and is classified based on histological findings on bone biopsy. Bone pathology is assessed based on abnormalities in bone turnover, mineralization, and/or volume. Low bone turnover as a result of excessive suppression of the parathyroid gland is the most common factor in the development of CKD-MBD. Persistent hyperparathyroidism occurs in approximately 15–50% of patients after transplantation [13]. An elevated parathyroid hormone concentration >130 ng/L at 3 months post-transplantation is an independent risk factor for fractures with a 7.5-fold increase in fracture risk [14].

Osteoporosis is a serious public health issue affecting up to one in two women and one in five men over 50 years of age, with similar rates among transplant recipients as in the general population. Osteoporosis is defined as a reduction in bone mineral density (BMD). Glucocorticoid-induced suppression of bone formation is the most important risk factor for bone loss and is a key factor for the development of osteoporosis after transplantation. Glucocorticoids inhibit osteoblast proliferation and differentiation and stimulate apoptosis of osteoblasts. Glucocorticoids also have indirect effects on the skeleton through decreased calcium absorption in the gut, reduced gonadal and adrenal hormone production, and decreased sensitivity to parathyroid hormone (PTH). It is thought that the reduction in bone density is directly related to the cumulative dose exposure of glucocorticoids in kidney transplant recipients. The lower rates of bone loss following kidney transplantation

in recent years may reflect lower doses of glucocorticoids used to treat these patients. The addition of calcineurin inhibitors to glucocorticoids may further enhance bone disease due to increased PTH and decreased magnesium from calcineurin inhibitors [2].

Risk factors for the development of osteoporosis in the general population, such as age over 50 years, female gender, family history of osteoporosis, low body weight, sedentary lifestyle, tobacco use, excess alcohol ingestion, impaired nutrition, and previous fracture also apply to kidney transplant recipients [11]. Additional transplant-related factors that may increase the risk for osteoporosis include pre-transplant diabetes or end-stage renal disease caused by diabetic nephropathy, pretransplant dialysis, and pre-transplant glucocorticoid exposure.

Evaluating Fracture Risk

Measurement of BMD can be performed by a dual-energy x-ray absorptiometry (DEXA) scan of the hips and spine. Use of a DEXA scan provides an accurate, non-invasive, and cost-effective estimation of BMD without the need for bone biopsy and may help to predict fracture risk in kidney transplant recipients. Results of DEXA scans are classified according to the standard deviation difference between a patient's BMD and that of a young adult reference population (T-score). Osteoporosis is defined as a T-score of ≤ -2.5 and osteopenia is defined as a T-score of -1 and -2.5. Clinical data have shown that kidney transplant recipients with evidence of osteoporosis on DEXA scan have a significantly higher risk of fractures than patients who do not have osteoporosis [15]. It is generally recommended to obtain a DEXA scan of the hip and spine at baseline, either before transplant or in the immediate post-transplant period, and at 1–2 years post-transplant to evaluate progression of BMD. The Kidney Disease Improving Global Outcomes (KDIGO) recommendations also include evaluation of a DEXA scan at 3 months after transplantation in patients with an estimated glomerular filtration rate (eGFR) of more than 30 mL/min/1.73m^2, on corticosteroids, and who have risk factors for osteoporosis (see Box 13.1) [16].

The Fracture Risk Assessment Tool (FRAX) is an online screening tool that can be used as an assessment of fracture risk based on clinical risk factors, with or without the use of femoral neck bone mineral density. Clinical risk factors include age, sex, race, height, weight, body mass index, a history of fragility fracture, a family history of osteoporosis, use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking, and alcohol intake of three or more units daily. The FRAX tool calculates the 10-year probability of a major osteoporotic fracture. The FRAX tool has been shown to modestly predict fracture risk in kidney transplant recipients, however has not been validated for use in kidney transplant recipients in clinical trials [17].

A bone biopsy is the gold standard for the diagnosis of bone disease after kidney transplantation. However, bone biopsies are rarely performed due to their invasive nature and need for a specialist to interpret the results. Furthermore, there are no published studies looking at the predictive value of bone biopsies in identifying kidney transplant recipients at risk of fracture. The KDIGO CKD-MBD guideline states that it is reasonable to consider a bone biopsy to guide treatment in the first 12 months post-transplant [16]. More specifically, a bone biopsy may be considered in patients with severe osteoporosis, frequent fractures, or persistent bone pain to rule out adynamic bone disease prior to initiating treatment with a bisphosphonate.

Therapeutic Strategies for Managing Bone Disease

Lifestyle modifications that may help prevent bone disease after kidney transplantation include weight-bearing exercises, smoking cessation, increased sun exposure, and optimization of diet. All transplant recipients should be encouraged to perform regular weight-bearing exercises after transplant, which may help to prevent and/or treat osteoporosis in both the general population and in transplant recipients. All patients should also receive counseling regarding early mobilization and fall prevention after transplantation. Patients who use tobacco should also receive counseling regarding smoking cessation. Although sun exposure may help with the production of vitamin D3, prolonged exposure to the sun may increase the risk of skin cancer in kidney transplant recipients on immunosuppression, and therefore, should be minimized. Patients should have an adequate intake of calcium and vitamin D from their diet. Studies have also suggested that diets high in potassium, magnesium and vitamin K from fruits and vegetables can also improve BMD and reduce hip fractures. Alcohol consumption should be limited as excess alcohol consumption has a negative effect on bone health, both directly and indirectly by increasing the risk of falls.

Reducing glucocorticoid exposure can help to minimize bone loss and should be considered in patients with pre-existing osteopenia or osteoporosis. There is some evidence to suggest that early steroid withdrawal may reduce fracture risk by up to 30% and lower fracture-related hospitalization without an increased risk of rejection [18]. However, osteoporosis and bone loss can still occur with prednisone doses as low as 7.5–10 mg per day and with early steroid withdrawal, which may be related to concomitant use of other immunosuppressive medications such as calcineurin inhibitors [19].

Pharmacologic agents include calcium, vitamin D, calcimimetics, antiresorptive agents, and hormone therapy. These agents are summarized in Table 13.1 and discussed in the next section.

Table 13.1 Therapeutic strategies for management of bone disease after kidney transplantation

Therapeutic class	Effects	Toxicities
Calcium Calcium carbonate Calcium citrate Calcium gluconate Calcium chloride Calcium lactate Tricalcium phosphate	Directly incorporated into bone structure; Supplementation replaces glucocorticoid-induced urinary calcium excretion	Constipation, gas, bloating Calcium can decrease absorption of bisphosphonates
Vitamin D, metabolites, analogs Cholecalciferol Ergocalciferol Calcitriol Doxercalciferol Paricalcitol	Stimulate intestinal calcium absorption, bone resorption, renal calcium and phosphate resorption; Decrease parathyroid hormone; Promote innate immunity; Inhibit adaptive immunity	Hypercalcemia, hypercalciuria The vitamin D preparations have much longer half-life than the metabolites and analogs
Antiresorptive agents Bisphosphonates Alendronate Ibandronate Pamidronate Risedronate Zolendronic acid Denosumab	Inhibit bone resorption; indirect increase in bone mineral density	Adynamic bone disease; Possible renal failure with bisphosphonates; Rare osteonecrosis of the jaw with bisphosphonates; increased risk of urinary tract infections with denosumab
Hormones Teriparatide Calcitonin	Teriparatide stimulates bone turnover; Calcitonin suppresses bone resorption	Teriparatide may cause hypercalcemia and hypercalciuria

Calcium and Vitamin D

Calcium and vitamin D play an important role in maintaining adequate bone health and maintenance. Glucocorticoids decrease intestinal absorption of calcium and increase urinary calcium excretion. Vitamin D deficiency also leads to decreased absorption of calcium from the intestines, causing increased osteoclast production and enhances mobilization of calcium from the bone to plasma. Patients taking glucocorticoids should maintain a calcium intake of 1000–1200 mg per day and vitamin D intake of 600–800 international units per day through either diet and/or supplementation. Furthermore, the recommended vitamin D intake for healthy adults over age 50 is 800–1000 international units per day. Vitamin D levels should be assessed and supplementation should be adjusted to maintain a target serum 25-hydroxyvitamin D level of greater than 30 ng/mL. Although calcium and vitamin D supplementation is necessary, it is generally not sufficient to prevent bone loss and fracture in patients taking high-dose glucocorticoids and additional pharmacologic therapy is often required.

Table 13.2 Calcium supplements

Product	How supplied	Elemental calcium	Route
Calcium carbonate	Numerous forms (260–600 mg calcium per unit)	40% calcium (104–240 mg)	Oral
Calcium citrate	Tablets (200–500 mg calcium per tablet)	24% calcium (48–120 mg)	Oral
Calcium gluconate	500 mg tablet 650 mg tablet 975 mg tablet 1000 mg tablet 10% solution	45 mg 58.5 mg 87.75 mg 90 mg 9% calcium	Oral, Intravenous, or intramuscular injection
Calcium chloride	10% intravenous solution	27% calcium	Intravenous injection only
Calcium lactate	Tablets (650–770 mg calcium per tablet)	13% calcium (84.5–100 mg)	Oral
Tricalcium phosphate	1565 mg tablets (as phosphate)	38% calcium (600 mg)	Oral

There are several calcium supplements available as different salt forms with varying amounts of elemental calcium (Table 13.2). Calcium carbonate contains the highest percentage of elemental calcium of all the available salt forms. Calcium carbonate contains 40% elemental calcium compared to 24% found in calcium citrate, 13% found in calcium lactate, and 9% found in calcium gluconate. Absorption of oral calcium supplements is enhanced with food and therefore calcium supplements should be taken with meals. The gastrointestinal tract can only absorb 500–600 mg of calcium at one time; therefore, supplements need to be taken several times per day and should be spaced by at least 4–5 h to achieve the recommended intake. Calcium supplements are generally well tolerated with constipation, gas, and bloating being the most common side effects. Calcium can decrease absorption of bisphosphonates, therefore calcium and bisphosphonate should not be taken at the same time.

Vitamin D and vitamin D analogs suppress PTH synthesis and reduce PTH concentrations. Furthermore, vitamin D stimulates intestinal calcium absorption and promotes differentiation of osteoblast precursors into mature cells, resulting in increased bone resorption. These effects may lead to hypercalcemia, which may limit the use of vitamin D supplementation.

Vitamin D supplements come from plant sources (ergocalciferol, vitamin D2) or animal sources (cholecalciferol, vitamin D3). Vitamin D2 is less effective than vitamin D3 in maintaining adequate vitamin D levels. Vitamin D2 and D3 require processing first through the liver where they are converted to 25-hydroxyvitamin D, then through the kidneys where they are converted to the active form 1,25-dihydroxyvitamin D. Vitamin D supplements are available as inactive vitamin D2 and vitamin D3, active 1,25-dihydroxyvitamin D3 (calcitriol), and synthetic metabolically active vitamin D analogs (paricalcitol and doxercalciferol) (Table 13.3).

Table 13.3 Vitamin D and vitamin D analogs

Product	How supplied	Route of administration
Calcitriol (1,25-dihydroxyvitamin D3)	0.25 mcg, 0.5 mcg capsule 1 mcg/mL oral solution 1 mcg/mL intravenous solution	Oral or Intravenous injection
Cholecalciferol (D3)	400 international units per tablet 1000 international units per tablet	Oral
Doxercalciferol (analog)	0.5 mcg capsules 2.5 mcg capsules 2 mcg/mL	Oral Oral
Ergocalciferol (D2)	50,000 international units per capsule 8000 international units/mL drops	Oral Oral
Paricalcitol (analog)	1, 2, 4 mcg capsules 2, 5 mcg/mL	Oral Intravenous injection

Calcitriol is the pharmacologically active form of 1,25-dihydroxyvitamin D3, which does not require hepatic or renal activation. Calcitriol is not recommended as first-line therapy due to increased risk of hypercalcemia and hypercalciuria compared to other vitamin D supplements. Paricalcitol is a synthetic metabolically active vitamin D analog, which does not require hepatic or renal activation. Doxercalciferol is a vitamin D analog prodrug that requires hepatic activation but does not require renal activation. There is a lower incidence of hypercalcemia with paricalcitol and doxercalciferol compared with calcitriol [20]. The vitamin D analogs have been shown to prevent bone loss after a kidney transplant [21].

Calcimimetics

Cinacalcet is a calcimimetic that attaches to the calcium receptor on the parathyroid gland, which increases the sensitivity of receptors to serum calcium concentrations and reduces PTH. Despite the reduction in PTH, cinacalcet has not been proven to have a positive effect on BMD in kidney transplant recipients [22]. The initial dose is 30 mg daily, irrespective of PTH concentrations. Cinacalcet may cause hypocalcemia in approximately 5% of patients and should not be started if serum calcium concentrations are less than 8.4 mg/dL. Cinacalcet should be used with caution in patients with a seizure disorder which can be exacerbated by hypocalcemia. Cinacalcet may also result in significant hypercalciuria which may lead to nephrocalcinosis. The most common side effects include nausea and diarrhea. Cinacalcet inhibits cytochrome P450 (CYP) 2D6 metabolism, thereby inhibiting the metabolism of CYP2D6 substrates such that dose reductions in drugs with narrow therapeutic indices may be required (e.g., flecainide, tricyclic antidepressants, thioridazine). Cinacalcet is primarily metabolized by CYP3A4, so drugs that are potent inhibitors of CYP3A (i.e., ketoconazole) may increase cinacalcet concentrations up to two-fold.

Antiresorptive Agents

Bisphosphonates decrease the rate of bone resorption, leading to an indirect increase in bone mineral density. They accumulate at sites of active bone resorption, where they enter osteoclasts and induce osteoclast apoptosis, thereby inhibiting bone resorption. Since bisphosphonates may induce low bone turnover, long-term use has shown to increase the risk of adynamic bone disease in kidney transplant recipients. It is important to consider a bone biopsy before initiating therapy in those at high risk of adynamic bone disease, such as those who have had a previous parathyroidectomy.

Bisphosphonates are available as both oral and intravenous formulations, with dosing frequency ranging from once daily to once yearly (Table 13.4). Bisphosphonates have a short plasma half-life but elimination from the skeleton is slow with a half-life in the bone of over 10 years. The fraction not taken up by bone is renally cleared and therefore, impaired graft function can have a significant effect on the pharmacokinetics and half-life of bisphosphonates. Bisphosphonate therapy is contraindicated in patients with severe renal dysfunction and should not be used in patients with a creatinine clearance less than 30–35 mL/min. Oral bioavailability of bisphosphonates is very low and significantly decreased with food, therefore they should be taken at least 30 min before the first food, beverage, or medication of the day including calcium supplements or antacids.

The most common adverse effects of bisphosphonates are gastrointestinal including esophagitis and gastric ulcers. Therefore it is recommended to take the oral formulations with a full glass (6–8 ounces) of water while in an upright position and to avoid lying down for at least 30 minutes after the dose and until the patient eats food to help prevent esophageal damage. Patients should not take their dose at bedtime. Patients should be instructed to report any signs/symptoms of dysphagia, odynophagia, retrosternal pain, or new or worsening heartburn while taking bisphosphonates. Bisphosphonates may also cause osteonecrosis of the jaw and

Table 13.4 Bisphosphonates

Product (brand name)	How supplied	Route of administration	Dosage frequency
Alendronate (Fosamax)	5 mg, 10 mg, 35 mg, 40 mg, 70 mg tablets 70 mg/75 mL PO solution	Oral	Daily or weekly
Ibandronate (Boniva)	150 mg tablet 3 mg/3 mL IV solution	Oral or Intravenous injection	Monthly Every 3 months
Pamidronate (Aredia)	30 mg/10 mL IV solution 90 mg/10 mL IV solution	Intravenous injection	Every 3 months
Risedronate (Actonel)	5 mg, 30 mg, 35 mg, 150 mg tablet	Oral	Daily, weekly or monthly
Zolendronic acid (Reclast, Zometa)	4 mg/5 mL IV solution 4 mg/100 mL IV solution 5 mg/100 mL IV solution	Intravenous injection	Yearly

patients should be advised to report any signs/symptoms such as pain, swelling, infection of the jaw/gums, or gum loss.

Clinical studies with a bisphosphonate in kidney transplant recipients have shown that bisphosphonate therapy preserves or increases BMD in the lumbar spine and femoral neck in the early post-transplantation period [11, 23]. However, there is no evidence to support the ongoing use of bisphosphonates beyond the first year post-transplant. Several controversies around the proper use of bisphosphonates in kidney transplant recipients include whether continuous or intermittent therapy should be used, duration of therapy, and the level of renal impairment at which bisphosphonates should be avoided.

Denosumab is a humanized monoclonal antibody against the receptor activator of nuclear factor-kappa B (RANKL). Binding to RANKL inhibits the formation, function, and survival of osteoclasts resulting in decreased bone resorption and increased bone mass and strength. In turn, denosumab decreases the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis and in patients with impaired kidney function, including those with CKD stage 4 [24]. Denosumab has been shown to improve BMD at the lumbar spine and total hip at 12-months post-transplant in kidney transplant recipients; however data are limited [25]. The use of denosumab in kidney transplant recipients may be limited to patients with high fracture risk who have a progressive decrease in BMD despite adequate treatment with calcium and vitamin D.

Denosumab is administered as a subcutaneous injection of 60 mg every 6 months. Denosumab is not renally cleared, which makes it more attractive than bisphosphonates in kidney transplant recipients with significant graft dysfunction. Denosumab may increase the risk of infections, especially urinary tract infections, and diarrhea. Like bisphosphonates, denosumab may induce low bone turnover, and therefore, it is important to consider a bone biopsy before initiating therapy in those at high risk of adynamic bone disease, such as those who have had a previous parathyroidectomy.

Hormone Therapy

Teriparatide is an anabolic, recombinant PTH, which stimulates osteoblast activity and bone formation and has been shown to be effective at increasing BMD and lowering risk of vertebral fractures in patients with glucocorticoid-induced osteoporosis. Teriparatide may be beneficial in some patients who develop fragility fractures while receiving bisphosphonates as preventive therapy; however data in renal transplant recipients are lacking [26]. Teriparatide is given as a once-daily subcutaneous injection. Adverse effects include hypercalcemia, hypotension, and constipation.

Calcitonin is a hormone secreted by the thyroid gland which directly inhibits osteoclastic bone resorption. This results in a sustained reduction in bone turnover and increased BMD. Calcitonin also increases mineral stores in bone and promotes

renal excretion of calcium and phosphorus. Calcitonin is available as an intramuscular or subcutaneous injection as well as a nasal spray, both of which are administered once daily. Adverse effects include hypocalcemia, hypophosphatemia, local nasal irritation with the nasal spray, or irritation at the injection site with the intramuscular or subcutaneous injections.

The effectiveness of calcitonin in preventing bone loss in kidney transplant recipients remains uncertain. When compared to bisphosphonates, kidney transplant recipients had significantly higher BMD with bisphosphonates than with calcitonin in the early post-transplant period; however those effects were no longer seen at 18 months after transplant [21]. Calcitonin may be a good option in conjunction with calcium and vitamin D in patients who are unable to tolerate bisphosphonates.

Conclusion

The post-transplantation bone disease results from a combination of the evolution of preexisting CKD-MBD and the development or progression of osteoporosis with numerous modifiable and non-modifiable risk factors. There is significant morbidity associated with post-transplantation bone disease and all transplant recipients should be evaluated for mineral bone disorder and monitored for ongoing bone loss. Management of post-transplant bone disease should include both lifestyle changes and pharmacologic management of the bone mineral disorder. Steroid minimization may be most beneficial and supplementation with calcium and vitamin D should be part of standard management to prevent bone loss after a kidney transplant. Cinacalcet seems to be effective in reducing PTH, however has no effect on BMD. Bisphosphonates have a positive effect on BMD after a kidney transplant, however there is no evidence to support the ongoing use of bisphosphonates beyond the first year post-transplant. Antiresorptive therapy, such as bisphosphonates or denosumab, should be reserved for patients at high risk of fracture with evidence of significant bone loss, despite optimal supportive therapy. Due to lack of data in kidney transplant recipients, hormone therapy should be reserved for use in patients who develop fragility fractures while receiving bisphosphonates or in patients who are unable to tolerate bisphosphonates.

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Chapter 14
Transplant and Pregnancy

Catherine A. Moore

Introduction

Greater than half of female kidney transplant recipients are of childbearing age, thus, preconception counseling, contraceptive management, and family planning are of great importance in the routine care of the female transplant recipient. Chronic kidney disease occurs for many reasons including hypertension, diabetes, autoimmune diseases, and various forms of glomerulonephritis. All ages can be affected, and some cases progress to end-stage renal disease (ESRD, or renal failure) early in life. Chronic kidney disease adversely affects female sexual function and fertility, with a reported fertility rate in women with ESRD on dialysis of less than 1% per year [1]. However, fertility rates improve significantly after kidney transplantation compared with during dialysis, often within months of transplantation. The first documented successful pregnancy with a live birth in a kidney transplant recipient in 1958 marked a new era in the quality of life improvements after transplantation.

Fertility in Transplant Recipients

End Stage Renal Disease leads to complex dysfunction of the Hypothalamic-Pituitary-Gonadal axis and resultant secondary amenorrhea [2, 3]. Renal replacement therapy does not restore fertility, and successful pregnancy with a live birth in a patient with ESRD is rarely reported. Furthermore, fetal outcomes in this setting are poor, with an estimated infant survival rate of 40–50% [1].

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Fertility rates are thought to significantly improve following kidney transplantation, although exact data are unclear, mainly relying on volunteer registries. One US-based study using Medicare claims data of more than 16,000 women in the first 3 years following kidney transplantation reveals pregnancy and live birth rates of 33 per 1000 and 19 per thousand female transplant recipients, significantly lower than the general American population over the time period studied [4].

In a study comparing 63 female kidney transplant recipients of childbearing age to 50 healthy women, there was no significant difference between groups in rates of regular menstruation or in the percentage of women with observed ovulatory cycles [3]. Menstrual regulation and ovulation rates are correlated with normalization of allograft function [2, 3, 5]. Circulating sex steroids are initially suppressed immediately following kidney transplantation but return to normal levels within 1 year [6].

Given the reliance on volunteer registry data and small case series, the rates of infertility or use of assistive reproductive technology following kidney transplantation are not clear [2]. mTOR inhibitors such as sirolimus do have an adverse effect on male fertility, although the impact on female reproductive function is unknown [7].

Pre-conception Counseling

Optimal timing of pregnancy is at least 1–2 years after transplantation [2, 8–12]. This recommendation is supported by data showing an increased risk of nonviable outcomes in the immediate post-transplant period (47% nonviable pregnancies less than 6 months after transplant, compared with 28% in the 6–24-month interval after transplant, and 19% after 24 months) [10]. A transplantation-to-conception interval greater than 5 years is associated with longer gestational ages and higher mean birth weights without an increased risk of pregnancy-related allograft loss [10].

The contraceptive choice is determined based on the general medical condition of the patient as well as the potential risks of additional sex hormone delivery. Women with uncomplicated solid organ transplants, in general, are classified as having an acceptable risk to benefit ratio for all forms of contraception. In contrast, in high-risk solid organ transplant recipients, oral contraceptives are ill-advised [13]. Combined oral contraceptives may impair hepatic metabolism of calcineurin inhibitors, corticosteroids, and sirolimus [14]. In addition, hypertensive patients and women over the age of 35 are advised to avoid oral contraceptives.

Long-acting reversible contraception with intrauterine devices may provide a more favorable option for transplant recipients, with minimal risks and high efficacy [14].

Recommended Criteria for Considering Pregnancy in Transplant Recipients

Maternal allograft survival and fetal outcomes are related to maternal renal function at the time of conception; thus, stable and adequate allograft function is a critical part of the prenatal assessment. Serum creatinine should optimally be less than 1.5 although some groups accept a creatinine of 2.0 or less, and there should be no recent history of allograft rejection. In addition, blood pressure should be less than 140/90 mmHg, proteinuria should be stable and less than 500 mg daily, comorbidities such as diabetes mellitus or systemic lupus erythematosus (SLE) should be medically optimized, and the patient should be on a stable immunosuppression regimen [8–11]. Rhesus (Rh) factor compatibility of patient and transplant, as well as cytomegalovirus (CMV), hepatitis B, herpes simplex virus (HSV), and toxoplasmosis status, should be established prior to conception [15]. Rubella vaccination should be done before transplantation but can be provided at the time of preconception counseling if necessary [10]. Potential teratogens including ACE-inhibitors, statins, mycophenolate mofetil, and mTOR inhibitors should be discontinued at least 6 weeks prior to planned conception [12]. Patients may transition to azathioprine and prednisone. Calcineurin inhibitor therapy may be essential to prevent allograft rejection in many patients, and the use of cyclosporine or tacrolimus is not a barrier to planned conception [2].

The pre-existing disease may influence maternal and fetal outcomes, and this should be considered in addition to the clinical parameters noted above [16]. Patients with SLE are at higher risk for complications in pregnancy, including preeclampsia, preterm labor, and maternal death, and risk is higher with active disease [17]. A minimum of 6 months of disease quiescence is therefore recommended prior to conception [18]. In addition, patients with lupus nephritis should be offered screening for Ro and La Antibody, which impart risk for fetal heart block and neonatal cutaneous lupus [16]. Patients with known genetic disorders such as Alport Syndrome and Polycystic Kidney Disease should be counseled regarding risk of inheritance. Case reports of onset of atypical HUS in pregnancy and the post-partum period, with a high incidence of complement abnormalities, raises concern that pregnancy carries a risk for disease reactivation in aHUS [19].

Pregnancy Outcomes in Transplant Recipients

Although most pregnancies following renal transplantation are successful, these are still classified as high-risk. Compared to control subjects, kidney recipients have a significantly higher risk of hypertension, preeclampsia, gestational diabetes, preterm delivery, intrauterine growth restriction (IUGR), low birth weight, and

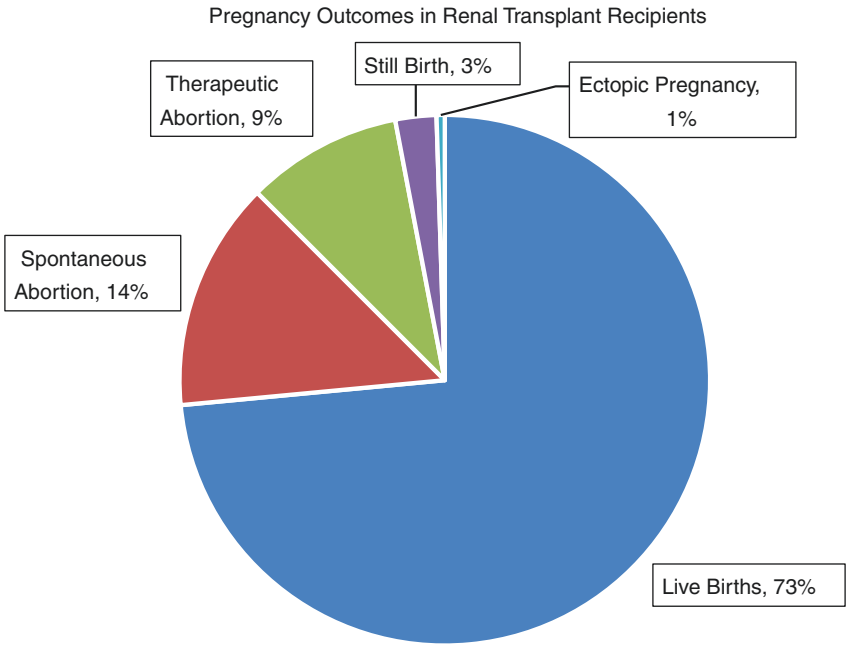

Fig. 14.1 Pregnancy outcomes in kidney transplant recipients. (Retrieved data from a meta-analysis of 50 studies worldwide published by Deshpande and colleagues, 2011 [21])

cesarean section [5, 16, 20–22]. Over 50% of pregnant transplant recipients are hypertensive, and the incidence of preeclampsia approaches 30% [21]. The incidence of preterm delivery is 47% with mean gestational age of 35.6 weeks [21]. Pregnancy outcomes are outlined in Fig. 14.1.

Effect of Pregnancy on Allograft Function

Pre-pregnancy allograft function is the most prominent factor influencing long-term post-pregnancy renal function. Although data are limited to case-control studies, most evidence suggests that antepartum graft function is unlikely to be adversely affected by pregnancy in women with serum creatinine less than 1.5 mg/dL who are treated with prednisone and azathioprine (AZA) [2, 15, 22].

The impact of pregnancy on long-term graft survival, particularly in women using calcineurin inhibitors, is unclear and remains an area of controversy. The increased glomerular filtration rate seen during pregnancy may damage allograft glomeruli, leading to progressive glomerular sclerosis [23]. Ten to fifteen percent of women with good allograft function before pregnancy will experience a decline in renal function during pregnancy that may be permanent [2]. Additionally, 11% of

transplant recipients develop new long-term medical problems postpartum, although it is unclear if pregnancy plays a causative role in this [24]. To date most case-control studies suggest that there is no significant difference in graft survival between pregnant and non-pregnant kidney transplant recipients [2, 10].

Medical and Obstetric Management of The Pregnant Kidney Transplant Patient

Given the multiple potential complications kidney transplant patients face, including rejection, infection, and immunosuppressant intolerance and dosing changes, a suggested management scheme is outlined in Table 14.1.

Table 14.1 Management scheme during pregnancy for the renal transplant recipient

Test/visit	When	Rationale
Before conception		
Rubella vaccine	Pre-transplantation	Live virus vaccine not recommended post-transplantation due to immune suppressants.
Rh compatibility of patient and allograft	Pre-pregnancy	If the patient is Rh negative but the kidney is Rh positive, there is a risk of maternal sensitization to Rh
Hepatitis B, C, HSV, CMV, HIV, toxoplasmosis, and rubella titers	Pre-pregnancy	Counsel regarding the risk of transmission. Hepatitis B vaccine can be given. Cervical cultures should be checked if HSV positive.
Stop mycophenolate, sirolimus, everolimus, and ACE-inhibitors 6 weeks prior to conception.	Pre-pregnancy	These agents are contraindicated in pregnancy due to the risk of fetal anomalies.
Stop statins 6 weeks prior to conception	Pre-pregnancy	Fetal risk of first-trimester statin use is not clear.
Urine culture	Pre-pregnancy	Risk of ascending asymptomatic bacteriuria and pyelonephritis
Consultation with a high-risk obstetrician	Pre-pregnancy	High-risk pregnancy with the likelihood of preterm delivery.
During pregnancy		
Blood pressure	Twice daily	High risk of hypertension in the transplant population.
Start low dose aspirin	Daily, beginning at 12 weeks gestation.	High risk of preeclampsia in the transplant population.
Allograft ultrasound	First trimester	Baseline to assess for hydronephrosis prior to significant uterine enlargement.

(continued)

Table 14.1 (continued)

Test/visit	When	Rationale
Clinic visits	Every 2–3 weeks up to 20 weeks; every 2 weeks until 28 weeks; every week after this	High-risk pregnancy with the likelihood of preterm delivery.
Fetal ultrasound	First trimester: Dating 20 weeks: Targeted scan for anomalies After 24–25 weeks: Every 3–4 weeks for growth	No increased risk of fetal anomalies with most immunosuppressive regimens (cyclosporine, tacrolimus, azathioprine, corticosteroids)
Antenatal testing: Nonstress test or BPP, Doppler if growth restricted	Weekly at 30–32 weeks	Increased risk of placental dysfunction
Liver function tests	Every 6 weeks (if on azathioprine)	Screen for azathioprine hepatotoxicity
CBC	Every 2–6 weeks	Decreased WBC may predict neutropenia in the newborn. If anemia present and iron deficiency excluded, erythropoiesis-stimulating agents (ESA) may be used.
Calcium and phosphorous	At start and PRN	May have tertiary hyperparathyroidism or history of subtotal parathyroidectomy
Glucose tolerance test	Each trimester Depending on which immunosuppressants Are used.	Many patients are on steroids and tacrolimus, and insulin resistance is common.
Serum BUN, creatinine, calculated clearance, and proteinuria.	Every 2–4 weeks	Screening for rejection and preeclampsia
Calcineurin inhibitor levels	Every 1–2 weeks	The volume of distribution changes with increased maternal blood volumes
IgM to toxoplasmosis	Each trimester if seronegative	Risk of congenital infection
IgM to CMV	Each trimester if seronegative	Risk of congenital infection
Examine for HSV lesions	At labor	May affect the approach to delivery
Urine dipstick	Each visit, with cultures every month	Risk of ascending asymptomatic bacteriuria and pyelonephritis
Kidney biopsy	Unexplained decrease in allograft function	Rarely done during pregnancy
Postpartum		
Blood pressure	Twice daily for 6 weeks	Screening for gestational hypertension
Serum BUN, creatinine, calculated clearance, and proteinuria.	1 month and 6 months postpartum	Screening for rejection and preeclampsia

Adapted from Josephson and McKay, 2007 and Hou, 2013, the European Best Practice Guidelines for Transplantation, 2002, and the US Preventative Services Task Force [2, 9, 25, 26]

Immunosuppressant Selection and Monitoring

Selection of immunosuppressant agents in pregnant patients requires balancing the risks of allograft rejection with fetal injury or loss. Most immunosuppressive agents cross the placenta, resulting in fetal exposure and possible risk. In practice, there is extensive experience with most agents in pregnancy. Standard immunosuppression generally consists of two to three agents: a calcineurin inhibitor that primarily inhibits T cell activation, an anti-proliferative agent that hinders T and B cell division, and/or corticosteroids that prevent a variety of lymphocyte activation steps. There is a "privileged immunologic status" of pregnancy that allows for maternal tolerance of her "fetal allograft" [27]. Pregnant women are not, however, systemically immunosuppressed. This mechanism, which prevents fetal rejection, is not active in the renal allograft and, therefore, does not translate into a lower requirement for systemic immunosuppression or risk of rejection during pregnancy.

Corticosteroids

If already being taken, corticosteroids should be continued during pregnancy. Both prednisone and prednisolone cross the placenta, but placental metabolism converts them to less active forms. There are case reports of fetal adrenal insufficiency and thymic hypoplasia with high-dose corticosteroid treatment, but this is rare when the total daily dose is kept at 15 mg or less [15, 25]. In the setting of acute rejection, however, high-dose steroids should be used [9].

Calcineurin Inhibitors

Calcineurin inhibitors (cyclosporine (CSA) and tacrolimus) prevent T cell activation and should be continued during pregnancy. CSA crosses the placenta with fetal exposure similar to maternal drug levels, and tacrolimus crosses less readily, with cord blood tacrolimus levels less than 50% of maternal serum levels [28, 29]. Cyclosporine has not been associated with congenital malformations but carries a small risk of fetal growth restriction [15, 25, 30]. Tacrolimus is associated with less hypertension and hyperlipidemia compared to CSA [20, 30]. Cyclosporine and tacrolimus levels usually decrease during pregnancy due to the increased volume of distribution, although hepatic metabolism may slow due to high levels of sex steroids [2, 25]. Higher doses may be needed to prevent allograft rejection during pregnancy [31]. Current recommendations are to adjust dosing to maintain pre-pregnancy therapeutic levels [9, 18].

Inhibitors of Purine Synthesis

All antiproliferative agents are classified by the FDA as category D, but azathioprine (AZA) is the safest and most widely used in pregnant transplant patients. Azathioprine is a pro-drug whose active form inhibits purine metabolism. The fetal liver lacks the enzyme necessary for conversion of AZA to the active metabolite [15, 25]. Azathioprine is reported to cause rodent fetal abnormalities and rare case reports of birth defects in human fetuses [25]. There has been no evidence of fetal anomalies with dosing less than 2 mg/kg/day [9]. AZA also has been associated with dose-related fetal myelosuppression (suppression of blood-forming elements), but clinically relevant leukopenia is rare.

Mycophenolate mofetil (MMF) is a purine synthesis inhibitor that largely has replaced AZA in non-pregnant patients. Because MMF used during pregnancy is associated with a higher incidence of fetal structural malformations compared to other agents, the FDA and international guidelines have contraindicated MMF in pregnancy [20, 32, 33]. MMF should be stopped 6 weeks prior to conception and substituted with AZA [2, 9].

mTOR Inhibitors

Sirolimus is a newer anti-proliferative agent that also is contraindicated in pregnancy because fetal toxicity is reported in animals. Due to serious concerns regarding fetal risk, there are limited human data. Existing registry data and case reports regarding the use of sirolimus or everolimus during early pregnancy do not reveal a clear risk of congenital abnormalities [2]. Sirolimus generally is substituted with CSA or tacrolimus during pregnancy.

Biologic Agents

Belatacept is a novel soluble fusion protein that blocks the co-stimulation of T cells. This protein is closely related to Abatacept, which has been studied more extensively in patients with rheumatoid arthritis. To date, there are no studies evaluating the safety of belatacept in pregnancy, although the National Transplant Pregnancy Registry in the US is extending efforts to collect data on belatacept use [2]. Animal studies have not revealed a risk of congenital abnormalities with abatacept or belatacept exposure, although there is a possible risk of autoimmunity in murine offspring. Studies of abatacept in pregnancy have revealed no pattern of congenital abnormalities associated with either maternal or paternal drug exposure [34]. Use of these agents in pregnancy should only be considered in cases where the potential maternal benefit justifies the potential fetal risk.

Rituximab is a monoclonal antibody directed against CD-20 positive B cells. Immunoglobulin G crosses the placenta, with increasing efficiency as pregnancy progresses. Although there is limited information regarding the safety of rituximab in pregnancy, given concerns regarding infection risk (particularly maternal susceptibility to CMV), conception should be delayed for at least 1 year following Rituximab exposure [2, 35].

Common Complications

Hypertension

Hypertension is seen in one of every two to five pregnant transplant recipients [21, 25]. Hypertension during pregnancy increases the risk of preterm delivery, growth restriction, and *abruptio placentae*. Target blood pressure levels for pregnant renal transplant recipients are the same as for non-pregnant patients with renal insufficiency; the goal is less than 140/90 mmHg [36]. All kidney transplant recipients should monitor their blood pressures daily during pregnancy, (Table 14.1) [2, 9, 25]. The preferred agent for treatment of hypertension during pregnancy is alpha methyldopa; however, labetalol, calcium channel blockers, alpha blockers, thiazide diuretics, clonidine, and hydralazine, all are considered safe during pregnancy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are absolutely contraindicated given their association with fetal congenital defects. They should be discontinued prior to conception or promptly upon confirming pregnancy. In transplant recipients with volume expansion, diuretics may be required for adequate blood pressure control [9, 23, 27].

Preeclampsia

The incidence of preeclampsia is approximately 27% in kidney transplant recipients [16, 21], which is significantly higher than the general population. The diagnosis of preeclampsia, however, is challenging given the common occurrence of pre-existent hypertension and proteinuria in kidney transplant recipients. Calcineurin inhibitors also raise uric acid levels, making the uric acid level a less useful serum marker for preeclampsia. Therefore, there should be a low threshold to hospitalize for hypertension in pregnant kidney transplant recipients [15]. Current guidelines support the use of low dose aspirin starting at 12 weeks gestation in patients at high risk for preeclampsia [2, 26]. Pregnant transplant recipients with preeclampsia should be delivered expeditiously. Progression to eclampsia in a transplant recipient, as in any other pregnancy, is an obstetric emergency.

Bacterial Infections

Pregnant kidney transplant recipients are at higher risk for bacterial infections, particularly of the urinary tract due to the pregnancy-related alterations in physiology. The incidence of urinary tract infection in pregnant kidney transplant recipients may be as high as 40%, and uncommon organisms must be considered [37]. The current recommendation is monthly screening urine cultures [2, 9, 25, 37]. If asymptomatic bacteriuria is diagnosed, these patients should receive two weeks of antimicrobial therapy; they may require suppressive antibiotics if this recurs.

Progressive Kidney Injury

Pregnant transplant recipients are at risk for renal insufficiency from pyelonephritis, preeclampsia, calcineurin inhibitor toxicity, obstruction, acute or chronic rejection, and recurrent disease. Some of these etiologies may present similarly, posing a diagnostic challenge to the clinician. It is most important to distinguish between preeclampsia and acute rejection as causes of acute kidney injury in the pregnant patient because the former is treated with delivery and the latter with high-dose steroids. Unfortunately, progressive proteinuria, increased uric acid levels, and hypertension can occur in the setting of renal insufficiency of any cause and it, therefore, can be difficult to distinguish between preeclampsia and acute rejection. An ultrasound-guided kidney biopsy may be necessary in these settings, particularly when delivery poses a significant risk to the fetus.

Ureteral obstruction of the transplanted kidney by the gravid uterus is uncommon, but it has been reported [15]. Furthermore, interpretation of hydronephrosis in the transplanted kidney is difficult, because there often is mild baseline hydronephrosis following transplant or during pregnancy. A baseline allograft ultrasound in the first trimester is recommended for this reason.

The incidence of reported acute rejections during pregnancy or within 3 months postpartum is about 10–15%, which is similar to the reported rate in non-pregnant women [2, 9, 25]. There is concern that rejections are under-diagnosed because of the expected drop in serum creatinine that occurs during pregnancy [25], and transplant recipients are at risk for acute rejection in the postpartum period. Acute rejection should be confirmed by allograft biopsy and is treated with high-dose steroids [11]. Data regarding anti-thymocyte globulin (ATG) use is limited to case reports, with limited evidence of successful and safe outcomes in pregnancy [18].

Labor and Delivery

The anatomic location of the renal allograft in the postero-lateral pelvis does not interfere with normal vaginal delivery, and a decision to perform cesarean section is based on usual obstetric indications [25]. It is advisable for pregnant transplant

recipients to have a formal consultation with a transplant surgeon with a surgical plan for cesarean section should it become necessary. If felt indicated, a transplant surgeon can be present in the operating room if a cesarean section is to be done, although a transplanted kidney normally is not in the obstetrician's operative field. There may be an increased risk of ureteral injury with a low-transverse incision, but this is rare.

Breastfeeding

Breastfeeding in the setting of immunosuppression has been controversial, and prior guidelines recommended against breastfeeding, citing the risk of drug exposure. More recent literature notes that, in women taking prednisone, azathioprine, and cyclosporine or tacrolimus, there have been no evident adverse effects on their breastfed infants [12, 38]. In addition, fetal exposure to these same medications exceeds the potential exposure in breastmilk [38]. Considering the many potential benefits of breastmilk in neonates, particularly those at risk for low birth weight and premature delivery, there is a trend towards acceptance of breastfeeding as an option for mothers using the above immunosuppressive agents. As of 2012, 36% of women participating in the National Pregnancy Transplant registry, a US-based volunteer registry, reported breastfeeding, increased from <5% in 1995 [38].

In contrast, alternative agents including MMF, sirolimus, or belatacept, do not carry sufficient clinical safety data, and breastfeeding should be avoided when using these medications.

Summary

In summary, the return of fertility is a benefit of kidney transplantation in women of childbearing age. Pregnancy in a kidney transplant recipient is considered high risk and requires a multidisciplinary approach with frequent monitoring. However, with careful assessment of maternal renal function, immunosuppression, infection surveillance, and fetal growth, the likelihood of a favorable perinatal outcome can be optimized.

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