Solid Organ Transplantation

17

Heather Stewart and Eva Waite

Case Presentation

O.T. is a 21-year-old patient, status post-renal transplantation, presenting for evaluation in the process of transitioning to an adult primary care provider (PCP). Her general pediatrician is located in a nearby suburban practice. The patient does not bring any records with her to the appointment but is accompanied by her mother, who is a single parent with one other child. When the patient is asked what her concerns are, she denies any. When addressed, the patient's mother states that she is concerned about her daughter transitioning to a new doctor and also that her daughter has been missing her periods recently.

O.T.'s history is significant for renal transplantation at the age of 6 years. The primary diagnosis necessitating the transplantation is unknown by the patient and her mother. She has been underweight "since before her transplantation" and has a gastrostomy tube (G-tube) in place for nutritional supplementation. She has hypertension for which she takes amlodipine and labetalol. Additionally, she is taking tacrolimus as her chronic immunosuppressive agent. She also has a history of depression for which she is not currently receiving any treatment. Her review of systems is remarkable for irregular menses for the last several months. Her social history is remarkable for no toxic habits. She does have a boyfriend at college but denies having been sexually active. O.T. is currently in her last year of college, pursuing a degree in graphic art design, though she is not sure what she will do when she graduates. Her family history is negative for hypertension and kidney disease.

Her physical exam is remarkable in that the patient makes limited eye contact and is poorly engaged, having deferred to her mother throughout the entire collection of her medical and social history. Her blood pressure (BP) is 126/72, and body mass index (BMI) is low at 16.8 kg/m^2. Her head, eyes, ears, nose, and throat (HEENT) exam is remarkable for jaw opening that is limited but with no associated discomfort. Cardiopulmonary exam and peripheral pulses are normal. She has an intact G-tube in her left upper quadrant and a palpable pelvic kidney in the right lower quadrant. Her skin exam is normal with a few healed surgical scars

H. Stewart
Division of Pediatric Nephrology and Hypertension, Department of Pediatrics, University of South Carolina School of Medicine - Palmetto Richland Children's Hospital, 9 Medical Park, Suite 270, Columbia, SC 29203, USA

E. Waite
Departments of Internal Medicine and Pediatrics, Mount Sinai Medical Center, 17 East 102 St, Seventh Floor, New York, NY 10029, USA
e-mail: eva.waite@mountsinai.org

H. Stewart (✉)
17 East 102 Street, Box 1087, New York, NY 10029, USA
e-mail: heather.stewart@uscmed.sc.edu

M. Pilapil et al. (eds.), *Care of Adults with Chronic Childhood Conditions*,
DOI 10.1007/978-3-319-43827-6_17

but no abnormal nevi. Her musculoskeletal exam is normal and her neurologic exam is non-focal.

Case Discussion

In caring for a patient with a solid organ transplant, it is critical to monitor for and treat the sequelae of the medications used for immunosuppression. In addition, it is important to monitor for the recurrence of the underlying disease that necessitated transplantation. Initially after the transplant procedure, the greatest concern is for infection due to surgical complications or viral infections. As the patient becomes further removed from the transplant, as in this case, the risk for infection is less of an issue. Though the transplant patient is at risk for the usual bacterial or viral infections typically experienced by the general population, the infections can become more serious due to the immunosuppression. More importantly, the immunosuppressant medications required to maintain the transplanted organ often result in a number of metabolic sequelae. These include an increased risk for diabetes mellitus, hyperlipidemia, hypertension, and gout and, as a result, an increased risk for cardiovascular disease as the patient ages. Patients also often develop chronic kidney disease (CKD) over time due to the effect of calcineurin inhibitors (CNIs) on the kidney. The PCP's goal will be to monitor for these adverse affects in comanagement with the transplant team. Additionally, the PCP typically assumes the primary management of secondary hypertension, diabetes, or gout. Providers should always consider possible drug interactions with the patient's transplant regimen and to avoid medications that can decrease the effectiveness of the immunosuppressant or increase its toxicity to the patient. In addition, the PCP will need to monitor the effects of the immunosuppressant medications on continuing development of bone and reproductive health. Finally, the PCP will be responsible for routine health maintenance with increased vigilance for the special screening recommendations for solid organ transplant patients, such as skin cancer screening.

In this particular case it will be beneficial for the PCP to engage with both the patient and the parent. A primary goal should be to encourage the patient to become a more active participant at future visits. Her limited eye contact may be due to shyness but might also be a sign of underlying developmental delay or depression. Screening with the patient health questionnaire-2 (PHQ-2) would be appropriate at this initial visit. Her irregular menses might be attributable to undernutrition as indicated by her low body mass index, an unplanned pregnancy, or hormonal dysfunction. It would be prudent to evaluate with a pregnancy test at the initial visit, and if negative, discuss appropriate forms of contraception. She would benefit from consultation with a nutritionist to evaluate her feeding regimen and to ensure that she is receiving adequate calories from oral intake and supplementation with her G-tube feeding regimen. Her limited jaw mobility should also be addressed as it could also be limiting her ability to chew and consume adequate calories. Finally, given her nutritional status and irregular menses, it would be appropriate to check serum thyroid, androgen, and prolactin hormone levels.

If O.T. is interested in contraception it will be important to choose the method that is safest for her in the context of her medical conditions. Since O.T. has hypertension, she should probably avoid agents containing estrogen, leaving progesterone-only agents as her lone option for hormonal contraception. Initially, one might consider the use of depot medroxyprogesterone acetate (DMPA), as it is a reliable form of contraception and is associated with weight gain. However, it is associated with osteopenia and should probably be avoided in an undernourished patient with a likely history of metabolic bone disease from kidney dysfunction. For this reason oral progesterone pills alone might be the best option. She could also be counseled on the risks and benefits of an intrauterine device (IUD), since she is more than 2 years post transplant, as well as the appropriate use of barrier methods.

Overview

Prevalence and Epidemiology

The optimal treatment for eligible patients with end-stage kidney disease (ESKD) that offers improved patient survival, reduced morbidity, improved quality of life, and economic savings compared to dialysis is kidney transplantation. Pediatric kidney disease affects children of all ages, and with the various renal replacement therapies available, including dialysis and transplantation, these patients are expected to survive into adulthood. Advances in the medical and surgical care of kidney transplant recipients including the judicious use of antibiotics, the improved understanding of the immunobiology of rejection, and advances in immunomodulatory medications for the treatment of rejection and use in maintenance immunosuppression have undoubtedly played a role in the success of patient and allograft survival.

In the United States, the incidence of ESKD in children has been slowly decreasing. As of 2012, there were 7522 children between the ages of 0 and 19 with prevalent ESKD [1]. Of these children, kidney transplant was the most common modality of renal replacement therapy (5485 [72.9 %]), followed by an essentially equal distribution of hemodialysis (1138 [15.1 %]) and peritoneal dialysis (899 [12.0 %]). The number of pediatric patients living with a kidney transplant has more than doubled since 1988, with 5485 children transplanted in 2012. The first-year deceased- and living-donor transplant outcomes have steadily improved over the last 20 years. In 2011, the most recent reporting year, the first-year mortality rates for both deceased-donor (probability of graft failure 0.05 and death 0.01) and living-donor (probability of graft failure 0.04 and death 0.01) pediatric transplant recipients were the same [1].

Kidney transplantation is not a cure. The Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients Annual Data Report notes that the conditional 1 year graft half-life for deceased-donor (DD) kidneys is estimated at 12 years and for living-donor (LD) kidneys it is estimated at 16 years [2]. Overall, the number of pediatric kidney transplants peaked in 2005 at 899 and remained steady at approximately 750 over the subsequent 3 years [2]. Since 2006, the number of DD transplants has exceeded the number of LD transplants; in 2013 there were 474 DD transplants and 279 LD transplants [2]. This is partly due to the implementation of allocation policy known as Share 35. This policy was implemented September 2005 and awarded pediatric priority for donors less than 35 years of age.

Pathophysiology, Risk Factors, and Transplantation Complications

The major indications for kidney transplantation in childhood are congenital abnormalities of the kidney and urinary tract (CAKUT), congenital nephrotic syndrome, polycystic diseases, and neonatal kidney injury/cortical necrosis due to thrombosis.

More than one-third of pediatric patients with ESKD have comorbidities, including cerebral palsy, heart disease, chromosomal abnormalities, a syndromic diagnosis, and developmental delay, which may adversely impact the patient's quality of life and overall prognosis following kidney transplant [1].

Post-transplantation patients are at an increased risk of allograft dysfunction, rejection, infection, bone metabolic problems, cardiovascular disease, dyslipidemia, type II diabetes, growth delay, malignancies, alteration in neurocognitive development, poor adherence to medication, and decreased quality of life. The major cause of graft loss is patient death, mainly due to complications related to cardiovascular disease, infection, and malignancy. The patient's transplant status and long-term immunosuppression can impact routine primary care issues and recommended algorithms.

Conditions Associated with Solid Organ Transplant

Hypertension

Hypertension (HTN) is quite common in kidney transplant recipients and is associated with an increased risk of graft failure. Epidemiologic studies indicate that 50–90 % of kidney transplant patients either have hypertension or are on antihypertensive medications [3]. Most recipients require two or more antihypertensive medications to achieve target BP goals. The major goals of antihypertensive therapy after transplant are to preserve kidney function and to decrease cardiovascular risk. After kidney transplantation, poorly controlled blood pressure has been shown to be an independent risk factor for cardiovascular disease (CVD) and is also associated with an increased risk of graft failure [4].

There is no universal agreement as to the optimal BP goals in kidney transplant recipients. However, the kidney disease outcomes quality initiative (KDOQI) clinical practice guidelines on hypertension and antihypertensive agents in CKD recommend reduction of blood pressure in kidney transplant patients to less than 130/80 mmHg, with lower targets in patients with proteinuria [5]. The kidney disease: improving global outcomes (KDIGO) clinical practice guidelines for the care of the kidney transplant recipient include guidelines for the management of hypertension. These guidelines emphasize that target BPs in kidney transplant recipients should be similar to those provided by "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" [6].

The KDIGO guidelines acknowledge that different targets should be set according to the method of BP readings—home readings versus office versus ambulatory blood pressure monitoring [7]. Home readings are usually 5–10 mmHg lower than office readings; night-time readings often 10 to 15 mmHg lower [7]. Loss of the nocturnal systolic BP dip is associated with higher left ventricular mass index, increased cardiovascular events, lower allograft function, and increased risk of allograft failure after kidney transplantation [8, 9].

Post-transplantation hypertension arises from a variety of factors. Some of these factors may have originated pre-transplant while others are related to immunosuppressive medication effects or post-transplant complications. Pre-transplant factors include increased vascular stiffness and vascular calcification. Dialysis patients have functional and structural alterations in their arterial walls leading to increased vascular stiffness. Vascular calcifications also develop in the ESKD population due to deranged calcium-phosphorus metabolism/secondary renal hyperparathyroidism. Post-transplant factors include delayed or poor allograft function, volume overload, presence of native kidneys, and transplant renal artery stenosis. Delayed graft function (DGF) is a risk factor for post-transplant hypertension. DGF results in the kidney's decreased ability to excrete sodium, which contributes to a lag in daily sodium excretion, salt and water retention, rightward shift of the pressure natriuresis curve, and an increase in blood pressure [10, 11]. Native kidneys induce hypertension via renin secretion or through increased sympathetic nerve activity. The overall prevalence of hypertension associated with native kidneys is unknown. Studies have noted that bilateral native nephrectomies in patients with resistant hypertension can lead to the improvement in BP control in most but not all patients. Native nephrectomies are not commonly performed in the recent decades, likely due to improved antihypertensive drug therapies [10, 11]. Transplant renal artery stenosis (TRAS) increases BP by activation of the renin-angiotensin-aldosterone system (RAAS), leading to systemic vasoconstriction and increase in sodium and water retention. Significant TRAS can be refractory to medical management and can contribute to unexplained worsening of allograft function [10, 11].

The immunosuppressive medications most often used in transplant, especially CNIs and prednisone, can potentiate hypertension. CNIs, the mainstay in the prevention of allograft rejection, cause widespread arterial vasoconstriction, thereby

increasing systemic vascular resistance. CNIs also cause vasoconstriction of the afferent arteriole leading to a reduction in glomerular filtration rate (GFR), thereby leading to an increase in tubular sodium reabsorption. Prednisone-induced hypertension has been attributed to the activation of free mineralocorticoid receptor promoting sodium and water retention.

All classes of antihypertensive agents can be used to lower blood pressure in kidney transplant patients. Due to the paucity of data favoring any particular antihypertensive class, both KDOQI and KDIGO guidelines do not specify any individual class of antihypertensive medication for the treatment of post-transplant hypertension. When selecting a particular class of antihypertensive as the initial treatment of post-transplant hypertension, it is practical to consider the presence or absence of proteinuria, diabetes mellitus, allograft dysfunction, volume overload, and risk factors for cardiovascular events. It is also important to become familiar with the interactions between antihypertensive and immunosuppressive agents. While calcium channel blockers are useful, it is important to avoid the non-dihydropyridine group, such as diltiazem and verapamil. These drugs are potent inhibitors of the cytochrome p450 system and increase CNI levels. The dihydropyridine class, nifedipine XL, amlodipine and isradipine, are often used since they do not affect GFR or electrolyte balances. They can, however, potentiate gum hyperplasia. Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are useful if a patient has proteinuria, but renal function and electrolytes must be monitored as they can decrease GFR and cause significant hyperkalemia. Beta blockers such as labetalol and carvediol can be useful in diminishing headaches caused by CNIs. Diuretics are particularly effective in volume-dependent hypertension and can be useful in the setting of hyperkalemia. Alpha blockers are less commonly used due to problems with hypotension. Central agents, such as clonidine, can be used as second-line therapy, especially when compliance may be improved with use of the weekly transdermal patch form [12].

New-Onset Diabetes After Transplant (NODAT)

New-onset diabetes after transplantation (NODAT) refers to the occurrence of diabetes in previously nondiabetic persons after organ transplantation. NODAT occurs in an estimated 30 % of patients within the first 3 years after transplantation. The majority of NODAT cases appear during the first 6 months after transplantation, when patients are treated with high doses of immunosuppression. International Consensus Guidelines on NODAT were published in 2003, recommending that NODAT be diagnosed based on the American Diabetes Association (ADA) criteria for type 2 diabetes [13]. Criteria are namely hemoglobinA1C (HgA1c) $\geq$6.5 %; or fasting plasma glucose of $\geq$126 mg/dL; or 2 h plasma glucose level of $\geq$200 mg/dL after an oral load of 75 g of anhydrous glucose; or random plasma glucose level of $\geq$200 mg/dL plus the presence of symptoms.

NODAT is associated with increased morbidity, mortality, and healthcare costs. Besides the traditional risk factors for type 2 diabetes mellitus (age, obesity, family history, and ethnicity), hepatitis C virus infection and the exposure to immunosuppressive agents, specifically CNIs and corticosteroid, increase the risk for NODAT [14]. Recipients that develop NODAT are not only at risk for the complications associated with diabetes itself but they are also at an increased risk for graft-related complications such as rejection, graft loss, infection, and vascular complications [4, 14, 15]. Current immunosuppressive regimens rely heavily on the use of agents that have been identified as being diabetogenic, such as corticosteroids, CNIs, and mammalian target of rapamycin inhibitors (mTOR) [4]. Corticosteroids increase hepatic gluconeogenesis, the development of insulin resistance, and defective insulin secretion. CNIs, which have been shown to be superior to cyclosporine in regards to patient and graft-survival, impose a higher risk of promoting the development of diabetes in solid organ transplant recipients. CNIs reduce glucose-stimulated insulin release in a dose-related and reversible manner, without affecting insulin resistance. Data

also suggest that CNIs are directly toxic to the pancreatic β(beta)-cells [16, 17]. It should be noted that mTOR inhibitors are also diabetogenic, especially if combined with CNIs [18]. Although the mechanism is not yet completely understood, the use of mTOR inhibitors leads to hypertriglyceridemia-related peripheral insulin resistance and impaired pancreatic β(beta)-cell response [19]. Based on animal and human data, rapamycin appears to induce an insulin secretion defect and impairs β(beta)-cell survival and proliferation [20].

The management of a transplant recipient with NODAT is best accomplished with a multidisciplinary team approach among the PCP, transplant subspecialist, endocrinologist, and dietician. The targets for treatment are the same as for all diabetic patients with sufficiently intensive treatment to maintain normal or near-normal glycemia with a HgA1c lower than 7.0 %. The choice of glucose-lowering agent should take into account the desired level of glucose control, potential drug–drug interactions, and renal function. It is important to note that the majority of kidney transplant recipients with a well-functioning allograft have some degree of CKD. A stepwise approach to the treatment of NODAT is recommended. In consultation with the transplant subspecialist, consideration should be given to modifying the patient's immunosuppressive regimen to reverse or ameliorate diabetes, after weighing the potential adverse effects including the risk of rejection. It is also critical to address modifiable risk factors including weight control, diet, and exercise. For those patients still not at target after such interventions, it is appropriate to initiate medical therapy: initially monotherapy with an oral hypoglycemic agent taking into account patient-specific factors, renal function, side effects, and potential drug–drug interactions with the patient's immunosuppressive regimen. If monotherapy is insufficient in achieving glucose control, one should proceed to combination therapy, adding another hypoglycemic agent with different mechanisms of action. When oral hypoglycemic medications fail to reach glycemic control targets, insulin therapy should be considered.

When selecting the medications used to treat NODAT, it is always important to take into account the patient's renal and hepatic function and assess for possible drug interactions with the patient's immunosuppressants and other medical therapies. Concern for lactic acidosis has limited the use of metformin in kidney transplant recipients. However, there are recent reports suggesting benefit from metformin therapy in patients with mild to moderate CKD. Caution is recommended in using metformin with appropriate dose adjustment based on the estimated GFR (eGFR) and close laboratory monitoring of renal function and electrolytes. There are various recommendations regarding metformin dosing in renal impairment. The ADA proposes the following: For those patients whose renal function has decreased below an eGFR of 45 mL/min/1.73 m^2, metformin must be avoided and that other classes of oral agents should be considered; for those with an eGFR greater than 45 mL/min/1.73 m^2, metformin can be used but renal function must be monitored closely—the interval depending on the level of renal dysfunction [12, 21]. Of the sulfonylureas, glipizide is the preferred agent in patients with impaired renal function; it is primarily converted to inactive metabolites and less likely to cause hypoglycemia than other sulfonylureas. Other classes such as DDP-4 inhibitors can be used in adjusted doses for patient with eGFR less than 30 mL/min/1.73 m^2. Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone can be used without need for renal clearance adjustment. However, they must be avoided in patients with heart failure. In addition, TZDs have been linked to decreased bone formation, accelerated bone loss, and increased risk for fractures. They must be used with caution in patients with CKD and metabolic bone disease. Other agents such as α(alpha)-glucosidase inhibitors, amylin analogs, and meglitinides can be used at somewhat lower levels of renal function but have less potent blood sugar lowering effect. Liraglutide is a popular GLP-1 agonist injectable that has been associated with weight loss. It is currently not listed as having recommendations for renal or hepatic adjustment. However, when combined

with CNIs it can increase risk of renal toxicity. Finally, one should remember that insulin is the safest of the medications used for transplant-associated diabetes with the fewest drug interactions [12, 22].

Cardiovascular Disease and Dyslipidemia

Atherosclerotic cardiovascular disease is the leading cause of mortality and death-censored graft loss after transplantation. The annual rate of fatal or nonfatal CVD events is 3.5–5.0 % in kidney transplant recipients, a rate 50-fold higher than the general population [7]. Kidney transplantation is known to reduce mortality compared with dialysis; studies suggest that this effect may be due to the reduction in cardiovascular risk associated with the improvement in kidney function. The reason for this observation is unknown. Specific risk factors for post-transplantation CAD include age, male gender, hypertension, cardiovascular event prior to transplantation, longer pre-transplant time on dialysis, post-transplant diabetes mellitus, use of corticosteroids, lower serum albumin post-transplant, and higher triglyceride levels post-transplant [23].

Dyslipidemia is often a complication of the use of immunosuppressive drugs. Patients treated with corticosteroids and CNIs can have adverse lipid profiles with elevated LDL and reduced HDL. Sirolimus can also contribute to moderate-to-severe hypercholesterolemia and hypertriglyceridemia. Dyslipidemia can contribute to the patient's preexisting elevated cardiovascular risk profile. In 2009, the KDIGO Working Group did not find new guidelines or systematic reviews since the KDOQI Dyslipidemia Guidelines were published in 2004 [24]. Therefore, the KDIGO working group recommendations include screening with a serum lipid panel for all adult and adolescent kidney transplant recipients, 2–3 months after transplantation, 2–3 months after change in treatment or onset of other conditions known to cause dyslipidemia, and at least annually thereafter. The working group further recommends treating adults to a goal LDL <100 mg/dL and non-HDL <130 mg/dL and adolescents to a goal LDL <130 mg/dL and non-HDL <160 mg/dL.

HMG-CoA reductase inhibitors (statins) are widely used in kidney transplant recipients given their established benefits in the general population. A 2009 systematic review noted that statins did not decrease all-cause mortality but were associated with a significant reduction in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides levels [25]. Although there are drug–drug interactions that must be monitored in kidney transplant recipients, the use of statins is generally safe. All statins appear to be effective in lowering LDL and total cholesterol with little evidence to support recommending one agent over another. Atorvastatin, simvastatin, pravastatin, and fluvastatin have all been used in studies of kidney transplant recipients. In the assessment of lescol in renal transplantation (ALERT) study, a large placebo-controlled trial, fluvastatin effectively lowered LDL cholesterol to a goal of <100 mg/dL and also demonstrated a 30 % decreased risk in fatal and nonfatal cardiac events [26].

Certain drug interactions should be taken into consideration when using statins in kidney transplant recipients. The hepatic metabolism of statins is affected by concurrent use of CNIs, which increases the risk of rhabdomyolysis. It is important to remain mindful of additional medications that can increase CNI levels (azole antifungals, macrolides, and diltiazem) and magnify the risk of liver toxicity and rhabdomyolysis. Serum transaminase levels and CNI drug levels should be monitored closely when initiating a statin, and serially monitored once stable drug dosing has been achieved.

Bone Mineral Density and Osteoporosis

While many complications of ESKD may be reversed by transplantation, bone and mineral disturbances may persist. Bone disease is

common in transplant recipients with multiple factors involved in its pathogenesis. Rates of bone loss are greatest in the first 6–18 months after kidney transplantation and range from 4–9 % at the spine and 5–8 % at the hip [27, 28]. There are numerous contributing factors, but the main factors include preexisting renal osteodystrophy at the time of renal transplantation, transplant-specific therapies, and reduced GFR. In kidney transplant recipients, osteopenia can also be influenced by long-term hemodialysis, age, heredity, gender, exercise habits, and the presence of diabetes mellitus.

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is the most complex pre-transplant bone disease. One or more types of bone disease may be present including low-turnover bone disease states (osteomalacia or adynamic bone disease), osteitis fibrosa cystica due to secondary hyperparathyroidism, osteoporosis, and mixed bone disease (see Table 17.1) [27].

Bone biopsy studies have revealed that the low-turnover bone conditions osteomalacia and adynamic bone disease are the two most common bone disorders seen in kidney transplant recipients.

The risk for fracture after kidney transplant is approximately 2–3 % per patient per year with 7–10 % of all renal transplant patients suffering 1 or more fractures over their lifetime [29, 30]. Hypercalcemia is also common post-kidney transplant and is considered to result from parathyroid hormone (PTH)-induced osteoclast activation and bone resorption. The dominant clinical adverse bone events following transplantation include bone loss, fractures, osteonecrosis, and bone pain. An analysis of 68,814 patients reported to the United States renal data system (USRDS) revealed that 22.5 % of kidney transplant recipients developed a fracture within 5 years [31]. Given the extent of the problem, various screening tools have been suggested to mitigate risk. Strategies include routine measurement of parathyroid hormone, 25-hydroxy vitamin D, and bone mineral density (BMD) assessment by dual-emission X-ray absorptiometry (DEXA).

BMD screening with DEXA is currently recommended for all women who are older than 65 years of age and postmenopausal women who are younger than 65 years of age with one or more additional risk factors for osteoporosis. Densitometry testing is recommended for transplant recipients on the basis of the assumption

Table 17.1 Different types of bone disease seen in kidney transplant recipients

Type of bone disease	Characteristics
Low turnover	
Adynamic	Reduced bone volume and mineralization is paralleled by a decrease in bone formation Few osteoid seams and few osteoblasts Osteoclasts can be low, normal, or high
Osteomalacia	Accumulation of unmineralized matrix Decrease in mineralization precedes or is more pronounced than the inhibition of collagen deposition
High turnover	
Hyperparathyroid	Marked increase in bone turnover Irregularly shaped trabecules with numerous abnormal remodeling sites Unusually high number of bone cells with irregular arrangement and shape
Mixed renal osteodystrophy	Caused by defective mineralization with or without increased bone formation and increased parathyroid hormone (PTH) activity in bone Bone volume is variable and depends on dominant pathogenic cause Increased numbers of heterogeneous remodeling sites Typically an increase in osteoclasts

that data from the general population are pertinent to this cohort. Fractures resulting from osteoporosis typically involve the lumbar spine or hip. However, fractures in the transplant population frequently include the non-axial skeleton (hips, long bones, ankles, feet), supporting the hypothesis that post-transplant bone disease is not a simple form of osteoporosis.

The kidney disease improving global outcomes (KDIGO) Working Group summarizes key observations about the utility of various screening strategies. KDIGO notes: (1) no randomized clinical trials in kidney transplant recipients have examined bone-specific therapies on patient-level outcomes, including mortality or fractures; (2) low bone mineral density in non-kidney transplant recipients predicts fractures but data are scant for kidney transplant recipients; (3) there are insufficient data to suggest any bone-specific therapies after the first year of transplant; (4) treatment with calcium, calcitriol, or vitamin D analogs and/or bisphosphonates has been suggested to improve bone density in kidney transplant recipients; (5) reports of the use of bisphosphonates indicate therapy is associated with improvements in bone density without being adequately powered to note improvements in patient survival or fracture [7].

A major factor in the pathogenesis of post-transplant bone disease is immunosuppressive therapy. Glucocorticoids are commonly used in most maintenance immunosuppressive regimens and in the event of allograft rejection. The highest glucocorticoid-associated rates of bone loss are in the first 6 months after transplantation. Glucocorticoids reduce bone formation by decreasing osteoblast replication, differentiation, and increasing apoptosis [32]. They also promote osteopenia and calcium loss. Additional mechanisms include reduced gonadal hormone production, decreased calcium absorption from the gut, decreased insulin-like growth factor 1 (IGF-1) production, and diminished PTH sensitivity [32–35]. The CNIs cyclosporine and tacrolimus have also been linked to osteoporosis. Both direct and indirect effects of these medications influence bone resorption. Cyclosporine is thought to cause bone loss through direct effects on osteoclasts and by indirectly acting on T-cell function. Tacrolimus inhibits T-cell activation and proliferation and cytokine gene expression. Though rat studies have demonstrated that tacrolimus leads to bone loss, skeletal effects in humans are not well studied [36]. Less intense bone loss has been noted in patients on tacrolimus, probably due to the fact that tacrolimus allows for lower doses of glucocorticoids to be used.

Therapeutic options for post-transplantation bone disease focus on glucocorticoid avoidance or withdrawal, as well as use of vitamin-D analogs, calcium supplementation, calcimimetics, and bisphosphonates. The rational for minimizing glucocorticoid use relates to its established risks of osteoporosis and avascular necrosis. Studies have noted beneficial effects on BMD after early tapering of prednisolone. A 2012 study analyzed both the USRDS and scientific registry of transplant recipients (SRTR) databases to assess whether early corticosteroid withdrawal after kidney transplant would result in lower fracture risk [37]. With adjustment for multiple covariates, investigators found that corticosteroid withdrawal was associated with 31 % fracture risk reduction while fractures requiring hospitalization were also significantly reduced. For patients with persistent hyperparathyroidism, options include vitamin D analogs, cinacalcet, and surgery. PTH levels usually decline rapidly during the first 3–6 months post-transplantation due to the reduction in functional parathyroid gland mass. Persistently elevated levels of serum PTH can lead to complications such as soft tissue calcification, hypophosphatemia, and hypercalciuria. During the first months following transplantation 1,25-dihydroxy vitamin D levels are low due to the action of glucocorticoids, reducing the 1-alpha-hydroxylase activity. In this case, it is recommended to administer cholecalciferol to replace the substrate to calcitriol. Cinacalcet is a calcimimetic drug licensed for the treatment of secondary hyperparathyroidism in patients with ESKD. It is often used off label in patients with persistent hyperparathyroidism after

transplantation. It has been demonstrated that this drug is effective in mitigating high PTH levels post-kidney transplantation with no adverse effects on renal function [38]. In a 2004 blinded study, transplant recipients who received calcium and the vitamin D analog calcitriol were shown to have attenuation of bone loss and an increase BMD when compared to transplant recipients receiving calcium alone [39]. There was also no hypercalcemia or decrease in renal function in either study group, though the study did not evaluate for the beneficial or harmful effects of therapy on fracture rate, hospitalization, or mortality [39]. Numerous studies have shown that bisphosphonates are effective in preventing bone loss when used early after transplantation. They may also help improve bone density when used late in the setting of established bone loss. Despite the positive effect on bone density, there are concerns with the use of bisphosphonates, particularly given the issues regarding renal safety, the unknown effects on fracture rates, and the potential exacerbation or induction of adynamic bone disease. Most transplant nephrologists agree that bisphosphonate therapy should be limited to patients who have a particularly high risk of fracture. Ideally in these kidney transplant patients, adynamic bone disease should be excluded by bone biopsy prior to the administration of bisphosphonate therapy. Several different treatment regimens have been shown to improve bone density, including daily or weekly oral therapy, or even intermittent intravenous administration. An individualized approach is necessary for the prevention of post-transplantation bone loss.

Hyperuricemia and Gout

In the general population, hyperuricemia is defined as >6 mg/dL. The risk of developing gout increases twofold for every incremental increase in serum uric acid of 1 mg/dL. Because of gender differences and the absence of detailed information in kidney transplant recipients, KDIGO defines hyperuricemia as >6 mg/dL in women and >7 mg/dL in men. Monitoring and management of hyperuricemia in kidney transplant patients is important due to the increased incidence of gout in addition to the association with loss of kidney function and cardiovascular disease. Hyperuricemia is a common metabolic problem in kidney transplant recipients and is exacerbated by the use of CNIs that impair renal uric acid secretion, use of diuretics, and impaired renal function. Cyclosporine has been associated with an even greater risk of hyperuricemia and gout than the CNI tacrolimus. The annual incidence of gout is 0.5 % for patients with hyperuricemia (7–8.9 mg/dL) and increases exponentially to 4.9 % for patients with serum uric acid levels of >9 mg/dL [40]. The American College of Rheumatology (ACR) guidelines recommend a target serum uric acid level of <6 mg/dL at a minimum in all patients and <5 mg/dL in more severe or complicated cases [41]. KDIGO guidelines reiterate the recommendation of a treatment threshold of <5 mg/dL in kidney transplant patients. In the general population, there is evidence that modifications that decrease risk include weight loss, low purine diet (reduced meat and alcohol consumption), and avoidance of diuretics. Some antihypertensive drugs such as amlodipine and losartan are reported to have a uricosuric effect.

Treatment of asymptomatic hyperuricemia is not generally recommended in the general population or in kidney transplant recipients. However, it is advocated in patients with recurrent symptomatic episodes of gout, tophi, uric acid stones, or radiographic changes of gout. Several therapeutic classes are available. Xanthine oxidase inhibitors, including allopurinol and febuxostat, reduce the production of uric acid by inhibiting xanthine oxidase. Allopurinol dosing is dependent on renal function and should not be used in conjunction with azathioprine due to the risk of severe myelotoxicity. This potentially life-threatening adverse drug–drug interaction results from an increased concentration of 6-mercaptopurine (the active metabolite of azathioprine), which is metabolized by xanthine oxidase [40]. If used together, azathioprine should be reduced by at least 50 %, and frequent complete blood counts should be used to monitor

the interaction. Febuxostat has the same mechanism of action as allopurinol. However, since it is a nonpurine analog, it can be used in patients who have had hypersensitivity reactions to allopurinol [29]. While febuxostat does not require renal dose adjustment, caution is advised when used in the presence of severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2) or hepatic disease. Uricosuric agents, such as probenecid and sulfinpyrazone, are not recommended in transplant recipients due to their ineffectiveness in patients with poor renal function (eGFR < 30 mL/min/1.73 m^2) and reports of drug–drug interactions with cyclosporine and mycophenolate mofetil. They are also contraindicated in patients with a history of renal calculi and low urine volume <1500 mL/day.

The ACR recommends the use of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids for acute gout in patients without significant renal impairment [41]. These agents are to be used cautiously in kidney transplant patients. Acute gout flares respond to increased doses of oral steroids and colchicine, NSAIDs, and cyclooxygenase-2 inhibitors, however, high doses of these agents are required for uricosuric effect. At high doses these agents can lead to impaired glomerular perfusion, hyperkalemia, and increased sodium retention contributing to hypertension. In conjunction with CNIs there can be additional escalation in acute kidney injury, hyperkalemia, and hypertension due to vasoconstriction. Colchicine is an effective and rapidly acting anti-inflammatory agent. However, it may be poorly tolerated due to the increased likelihood of diarrhea when used in conjunction with immunosuppressant drugs. Toxic effects on muscle tissue have been reported in patients with decreased renal function <50 mL/min/1.73 m^2. Without dose adjustment, kidney transplant recipients are at high risk of experiencing adverse drug effects of colchicine, including myelotoxic effect and myopathy in patients receiving a combination of cyclosporine and colchicine [40]. Serum levels of colchicine are increased by several drugs such as clarithromycin, voriconazole, fluconazole, diltiazem, verapamil, ritonavir, grapefruit juice, and cyclosporine. Corticosteroids' primary anti-inflammatory mechanism of action is the inhibition of nuclear factor xB (NF-xB) via tumor necrosis factor-α(TNF-alpha) or interleukin 1b (IL-1beta) [40]. Corticosteroids are commonly used in kidney disease and kidney transplant patients for the treatment of acute gout attacks. Issues to consider when using them are exacerbation of hypertension, hyperglycemia, impaired wound healing, and rebound gout attack when tapering dosages to prior maintenance immunosuppressive dose.

In summary, as a result of overproduction and undersecretion of uric acid, hyperuricemia and gout are common conditions in the kidney transplant population. Important considerations in the implementation of treatment are impaired organ function and the numerous drug interactions. It is reasonable to consider implementing treatment for asymptomatic hyperuricemia with a serum uric acid level >9 mg/dL. However, the standard prophylactic regimen recommended by the ACR utilizing NSAIDs and colchicine may not be feasible in kidney transplant recipients. The choice of prophylaxis and treatment regimens should be made in consultation with the patient's transplant nephrologist.

Special Transplant Drug Interactions and Long-Term Adverse Effects

During the first-year post-transplant, a typical drug regimen for a recipient consists of 8–10 medications on average. The necessity for polypharmacy increases the potential for serious drug interactions. Interactions affecting drug metabolism are common and typically involve the cytochrome P-450 system. With the increasing number of new agents on the market, it remains challenging for physicians to recognize potential drug interactions without the assistance of pharmacists. Therefore, the information in this section should by no means be considered all-inclusive. We recommend the provider consider discussing the addition of any new medication in a transplant recipient with the transplant center. A list of commonly used classes of

Table 17.2 Common maintenance immunosuppressive medications in transplantation [4, 12, 13, 42]

Class	Agent	Mechanism of action	Adverse side effects
Calcineurin inhibitors (CNI)	Tacrolimus, cyclosporine	Inhibit calcineurin phosphatase and T-cell activation ***Metabolized by cytochrome P450 IIA (CYP3A)***	Tacrolimus: pancreatic islet cell toxicity, neurotoxicity (insomnia, tremor, delirium), alopecia, hyperkalemia, hypomagnesemia Cyclosporine: gingival hyperplasia, hirsutism, tremor, hypertension, hypercholesterolemia, hyperkalemia, hypomagnesemia, hyperuricemia/gout
Mammalian target of rapamycin (mTOR) inhibitors	Sirolimus, everolimus	Inhibit Interleukin-2 induced T-cell proliferation ***Metabolized by cytochrome P450 IIA (CYP3A)***	Nephrotoxicity when used in combination with CNIs; de novo proteinuria, impaired wound healing and dehiscence, hypertriglyceridemia, mucositis, leukoencephalopathy, embryotoxic and fetotoxic
Antimetabolites	Mycophenolate mofetil (MMF), mycophenolic acid (MPA), azathioprine (AZA)	Prevents proliferation of both T & B cells	MMF and MPA: Diarrhea, Leukopenia, Teratogenic AZA: Myelosuppression, hepatic dysfunction, pancreatitis

immunosuppressive medications used in solid organ transplant patients is found in Table 17.2 [4, 12, 13, 42].

A number of drugs interact with immunosuppressants either pharmacodynamically or pharmacokinetically, potentially altering the efficacy and safety of immunosuppressive drugs (see Table 17.3) [12, 14, 21, 42]. Drugs that induce or compete with the cytochrome P450 enzyme system can dramatically increase or decrease the blood concentrations of immunosuppressants. Such alterations place the transplant recipient at risk of under-immunosuppression and rejection or enhanced side effects due to drug toxicity.

Reproductive Health and Fertility

Most female patients have a rapid recovery of normal menstrual cycles after receiving their solid organ transplant. Thus, it is important to discuss the need for contraception and planning for a healthy pregnancy when the time is right to conceive as well as protection from sexually transmitted infections.

Contraception

When selecting contraceptive methods, one should generally consider the effectiveness of the method, relative contraindications in relation to the timing of patient's transplant, and any other comorbidities, such as hypertension or diabetes [43]. The most effective contraceptives are in the long-acting reversible contraceptives (LARC) group, which consist of intrauterine devices (IUDs) and sub-dermal implants. The second most effective class includes the combined hormonal contraceptives (oral contraceptive pills [OCPs], transdermal patch, or intravaginal ring), and injectable DMPA, followed by the progestin-only pill. The final tier consists of barrier methods such as condoms, diaphragm, cervical caps, fertility awareness, and withdrawal [43].

When discussing the relative safety of a contraceptive method, it should be compared to the risks of an unplanned pregnancy. One can refer to the US Centers for Disease Control (CDC) adaptation of the World Health Organization (WHO) United States medical eligibility criteria (USMEC) for contraceptive use (see Table 17.4).

Table 17.3 Selected medications and their interactions with calcineurin inhibitors and mTOR inhibitors [12, 14, 21, 42]

Class	Agent	Major interactions	Side effects
Calcineurin Inhibitors (CNI)	Tacrolimus, Cyclosporine	Drugs that INCREASE blood levels by inhibition of cytochrome P450: • Antibiotics: clarithromycin, erythromycin, azithromycin[a] • Antifungals: ketoconazole, fluconazole, itraconazole, voriconazole • Antiretrovirals: protease inhibitors, especially ritonavir • Calcium channel blockers: verapamil, diltiazem, nicardipine, nifedipine, Amlodipine[a] • Histamine blockers: ranitidine, cimetidine • Hormones: oral contraceptives, anabolic steroids, testosterone analogs, danazol • Others: amiodarone, allopurinol, bromocriptine, carvedilol, cisapride, conivaptan, HMG-CoA reductase inhibitors, metoclopromide, theophylline • Herbals: grapefruit juice, goldenseal, herbal teas (e.g., camomile), Pomegranate juice, schisandra Drugs that DECREASE blood levels by induction of cytochrome P450: • Antibiotics: cephalosporins, imipenem • Antituberculous drugs: Rifabutin, Rifampin, Oxcarbazepine, Isoniazid • Anticonvulsants: Barbiturates, Carbamazepine, Phenytoin • Others: Bosentan, Cholestyramine, Cinacalcet, Sevelamer, Ticlopidine • Herbals: St. John's Wort	Acute Kidney Injury Hypertension Vasoconstriction Thrombotic microangiopathy (TMA) Sodium retention Edema Hyperkalemia Hypomagnesemia Hyperuricemia Hyperlipidemia New-onset diabetes Alopecia Gingival hyperplasia Rhabdomyolysis/Myotoxicity when used in conjunction with HMG-CoA reductase inhibitors
Mammalian target of Rapamycin (mTOR) Inhibitors	Sirolimus, Everolimus	Use of the following are Contraindicated: Clarithromycin, Ketoconazole, Mifepristone, Rifabutin, Rifampin, Voriconazole Share the same metabolism by CYP450 system as CNIs, therefore mTORs have similar interactions with calcium channel blockers,	Potentiation of CNI nephrotoxic effects De novo proteinuria/Nephrotic syndrome Impaired healing Hypertriglyceridemia Interstitial pneumonia Teratogenic

(continued)

Table 17.3 (continued)

Class	Agent	Major interactions	Side effects
		antifungals, anticonvulsants, antituberculous agents, noted above.	
Antimetabolites	Mycophenolate mofetil (MMF), Mycophenolic acid (MPA)	Major interactions • Hematologic/Myelosuppressive—Azathioprine (hematologic toxicity), Hydroxychloroquine, Acyclovir, Ganciclovir • Increase drug level of MMF and MPA—Amoxicillin • Reduce Absorption of MMF and MPA—Antacids, cholestyramine, sevelamer	Diarrhea Nausea/emesis Leukopenia Progressive multifocal leukoencephalopathy (PML) Congenital malformations
	Azathioprine (AZA)	Major interactions Hematologic/Myelosuppressive—Allopurinol	Myelosuppression Nausea/emesis Hepatic dysfunction Pancreatitis

Cautions This table is not a complete list of potential drug interactions. Interaction data refers to systemic drug forms of immunosuppressants. Refer to drug references and transplant pharmacist for assistance on specific agents and for further details on potential interactions

[a]The interaction with these medications is usually minimal

This was adapted in 2010 and includes recommendations for patients who have been solid organ recipients within the last 2 years, when they are at highest risk for complications [44, 45]. The guidelines were developed in four different categories based on the balance of potential risk of pregnancy and benefits of contraception.

For women with uncomplicated transplants, in the first 2 years following their transplant, every contraceptive method is considered a Category 2, indicating that the benefits of contraception generally outweigh the risks [45]. A complicated transplant, defined as graft failure, graft rejection, or cardiac allograft vasculopathy, places the patient in the higher risk Category 4. For these women, estrogen-containing contraceptives that increase the risk of coagulation and thromboembolism are effectively contraindicated. IUD initiation, in the first 2 years following transplant, is considered a category 3 (risks outweighs benefit but still safer than pregnancy), whereas continuation of an IUD is considered Category 2 and can remain safely in place. Estrogen-containing agents remain contraindicated in conditions such as venous thromboembolic disease, hypertension, or diabetic nephropathy. In these conditions, progesterone-only agents are the safest option. Previous concerns about IUDs being contraindicated in transplant patients have been disproven. In a review of >200 solid organ transplant patients who used an IUD, only two had report of method failure and there were no cases of increased risk of pelvic infection

Table 17.4 United States medical eligibility criteria for contraceptive use

United States medical eligibility criteria for contraceptive use	
Category 1	Condition for which there is no restriction for the use of contraceptive method
Category 2	A condition for which the advantages of using the method generally outweighs theoretical or proven risks
Category 3	A condition for which the theoretical or proven risks usually outweighs the advantages of using the method
Category 4	A condition that represents an unacceptable risk if the contraceptive method is used

or tubal infertility [45]. In addition, concerns about increased risk for infection due to IUD have not been born out with other immunocompromised populations, such as women with human immunodeficiency virus (HIV). Combined OCPs are reasonable contraceptive choices and tend to offer good menstrual cycle control. Several small studies in renal and liver transplant patients have not shown increased risk for rejection, although some women require adjustment to their antihypertensive regimen. The fact that OCPs are easily available and familiar to most women must be weighed with their higher failure rate compared to LARC.

DMPA carries a black box warning concerning the bone effects of this agent with long-term use. When counseling transplant patients regarding DMPA, the benefits of decreased bleeding and efficacy should be balanced with theoretical risk to bone health, especially in women younger than 25 years of age who may still be building bone. Emergency contraception is considered a Category 1 in all medical conditions since it is a 1-time dose of hormonal contraception. The current methods of emergency contraception consist of the progestin levonorgestrel (LGN), the selective progesterone receptor modulator (SPRM) ulipristal, and the urgent placement of a copper IUD.

Pregnancy

The recommended time interval between transplant surgery and conception should be at least 12 months and individualized according to the patient's general health, completion of antiviral prophylaxis, and establishment of stable immunosuppression level and graft function [44]. The patient should not be taking teratogenic medications such as mycophenolate, azathioprine, or other Category D medications. Although transplant pregnancies are generally successful, outcomes differ from the general population in terms of prenatal survival rates, indicating that these pregnancies remain high risk in spite of good allograft function. Pregnancy outcomes after kidney and liver transplantation in the United States show a significant increase in the risk of major obstetrical complications including pre-eclampsia, preterm delivery, and low birth weight. Data from a 2014 study revealed the mean gestational age at birth was 35 weeks in transplant recipients, shorter than the national average of 39 weeks. The mean live birth weight for recipients was less at 2485 grams versus 3358 grams [46]. For lung and cardiac transplant recipients, the risk of pre-eclampsia was 18 % (higher than the 7 % in healthy nulliparous women). Lung transplant patients have a high rate of rejection during and after pregnancy and a 5 year mortality rate of 50 %. A number of associated factors such as age, parity, chronic hypertension, or renal disease determine the risk of pregnancy complications, including miscarriage and gestational diabetes, and are probably more important factors than the type of transplant [46].

Cancer

Solid organ transplant recipients have a twofold to threefold increased risk of developing cancer compared to the general population [47]. The risk of developing cancer is most likely multifactorial due to the type of organ transplanted, the immunosuppressant regimen, exposure to oncogenic viruses—Epstein–Barr virus (EBV), human papillomavirus (HPV), and human herpesvirus-8 (HHV-8)—and environmental factors. There are three proposed oncogenic mechanisms by which immunosuppression can increase cancer risk: direct pro-oncogenic property of the immunosuppressant, increased risk of oncoviral driven malignancy, and impaired immune surveillance of neoplastic cells [47]. Cyclosporine, tacrolimus, and azathioprine exert direct effects on cells that promote cancer while mTOR inhibitors and MMF show anti-proliferative effect and decrease cancer risk [47]. Post-transplant cancers can be arbitrarily divided into de novo, donor-related, and recurrent cancers. De novo cancers include non-melanoma skin cancer, post-transplant lymphoproliferative disorder (PTLD), and anogenital cancers, as they are new tumors that develop away from the transplanted organ. Donor-related cancers may be transmitted by the donor organ or may originate within the transplant graft. Recurrent cancers recur

from pre-transplant malignancies such as hepatocellular carcinoma and cholangiocarcinoma [47].

Non-melanoma skin cancer is the most common post-transplant malignancy, with an increased incidence up to 250-fold compared to non-transplanted individuals [47]. Squamous cell carcinoma (SCC) is the most common, followed by basal cell, Merkel cell, and Kaposi sarcoma. Post-transplant SCCs are biologically aggressive and often multicentric with a tendency to recur locally in >10 % of patients and leading to metastatic disease in 5 % of patients. PTLD is the second most common malignancy in adults. It is predominantly B cell in origin, accounting for 85–90 % of cases, with many of these being associated with EBV. The remaining 10–15 % are T cell in origin and are usually EBV negative [47]. The greatest risk is in the first-year post-transplant and is affected by host risk factors such as degree of immunosuppression, viral infections, age of the recipient, and type of allograft. PTLD is highest among individuals receiving intestinal transplants (20 %) and lowest for individuals receiving liver/kidney transplants (1–5 %). The relative risk of non-Hodgkin lymphoma (NHL) is elevated eightfold compared to the general population. It can be divided into early disease (a gift from the donor) or late disease, which occurs beyond the second year of transplant. Use of cyclosporine and azathioprine increases risk for NHL.

Hodgkin lymphoma is raised fourfold in transplant recipients. Both Hodgkin lymphoma and NHL are more aggressive than in immunocompetent patients [48].

The next most common group of cancers are the anogenital cancers, which make up <3 % of cancers but again are 100-fold more common in the immunosuppressed population [47]. They are twice as common in females as male patients and have about a 7 year latency from transplant. HPV-related lesions can arise despite a pre-transplant HPV-negative status. HPV-positive renal transplant recipients have 14-fold higher risk for cervical cancer, 50-fold higher risk for vulvar cancer, and 100-fold greater risk for anal carcinoma [47]. Patients with predisposing chronic conditions are at increased risk for developing cancer. Patients with primary sclerosing cholangitis and ulcerative colitis with liver transplants are at an increased risk for cholangiocarcinoma and colon cancer. Patients with renal, liver, and heart transplants are at greater risk of developing renal cell carcinoma, though they are typically small asymptomatic lesions with a favorable surgical prognosis.

Due to the significant increased risk of skin and anogenital cancers, it is recommended that transplant patients have annual skin examinations. Immunosuppressed females should have annual cervical/pelvic examination and not be liberalized to an every 3 or 5 year pap testing strategy [45].

Except for patients with history of ulcerative colitis, there is no change in the recommendations for screening for breast, colon, or prostate cancer in the transplant population. Although lung cancer is increased from 1.4- to 5.4-fold compared to the general population, there is currently no change in the selection criteria of patients to screen for lung cancer.

Conclusion

Solid organ transplant recipients represent a growing population of medically complex patients for whom outcomes are optimized through a well-coordinated plan of care delivered by a multidisciplinary team ("Appendix"). Though much of this care is directed by transplant subspecialists, PCPs have several critical roles to fulfill. PCPs should be familiar with the diagnosis and treatment goals of common comorbid conditions associated with solid organ transplant as well as commonly used immunosuppressive agents and their associated toxicities and drug–drug interactions. PCPs should also address the sexual and reproductive health of patients and be familiar with cancer screening guidelines for transplant patients. Finally, PCPs should help support young adults with solid organ transplants navigate challenges while transitioning to adult-centered care systems.

Appendix

Solid organ transplant fact sheet	
Definition	The replacement of a nonfunctioning solid organ such as kidney, liver, or heart with an organ obtained by donation from another individual. It can be either cadaveric or living donor. The individual must remain on immunosuppressant regimen in order to avoid rejecting the organ
Epidemiology	The number of pediatric patients living with a kidney transplant has more than doubled since 1988 with 5485 children transplanted in 2012. The first-year deceased- and living-donor transplant outcomes have steadily improved over the last 20 years
Pathophysiology	The type of solid organ, and whether it is a first or second transplant, often predicates the intensity of the immunosuppressant regimen used The immunosuppressants are from several classes: • Calcineurin inhibitors (tacrolimus, cyclosporine) • Mtor inhibitors (sirolimus, everolimus) • Steroids (prednisone) • Anti-metabolite (mycophenlic acid, mycophenolate and azathioprine) • Costimualtory blocker (Belatacept)—kidney transplantation only
Sequelae of original disease	Poor growth Metabolic bone disease Association with syndromes affecting other organ systems: • Alagille syndrome • Alport syndrome May have some degree of developmental delay associated with underlying disease or complicated treatment course Recurrence of original disease (systemic lupus erythematosus)
Sequelae of immunosuppressant regimen	Infection Increase risk of metabolic disorders: • Diabetes • Hyperlipidemia • Gout • Osteoporosis Hypertension Increased risk for cardiovascular disease Increased risk for kidney dysfunction Increased risk for cytopenias Increased for malignancies: • Dermatologic • Aerodigestive • Vulvar • Post-transplant lymphoproliferative disorder
Medication interaction	Must always adjust for decreased function of the transplanted organ Always evaluate interaction with immunosuppressant regimen
Challenges in transition	Some centers have reported increased risk of graft rejection and loss when transitioning from pediatric to adult providers Adult providers are less familiar with some of the underlying pediatric syndromes
Helpful Resources	CDC contraception 2010 application (app) download for smartphones

CDC Centers for Disease Control

References

1. US Renal Data System (USRDS). USRDS 2014 Annual Report: Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014.
2. Matas AJ, Smith JM, Skeans MA, Thompson B, Gustafson SK, Stewart DE, et al. OPTN/SRTR 2013 annual data report: kidney. Am J Transplant. 2015;15 (Suppl 2):1–34.
3. Kasiske BL, Anjurn S, Shah R, Skogen J, Kandaswamy C, Danielson B, O'Shaughnessy E, et al. Hypertension after kidney transplantation. Am J Kidney Dis. 2004;43(6):1071–81.
4. Pedraza F, Roth D. Medical management of the kidney transplant recipient. Prim Care Clin Office Pract. 2014;41(4):895–906.
5. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004;43:S1–S290.
6. Chobanian AV, Bakris GL, Black HR, Cushman W, Green L, Izzo J, Jones D, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA. 2003;289:2560–72.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. Am J Transplant. 2009;9(Suppl 3):S1–S157.
8. Toprak A, Koc M, Tezcan H, Ozener IC, Oktay A, Akoglu E. Night-time blood pressure load is associated with higher left ventricular mass index in renal transplant recipients. J Hum Hypertens. 2003;17:239–44.
9. Ibernon M, Moreso F, Sarrias X, Grinyo J, Fernandez-Real J, Ricart W, Seron D. Reverse dipper pattern of blood pressure at 3 months is associated with inflammation and outcome after renal transplantation. Nephrol Dial Transplant. 2012;27:2089–95.
10. Lakkis J, Weir MR. Treatment-resistant hypertension in the transplant recipient. Semin Nephrol. 2014;34 (5):560–70.
11. Wadei HM, Textor SC. Hypertension in the kidney transplant recipient. Transplant Rev. 2010;24:105–20.
12. Lexicomp Online®. Hudson, Ohio: Lexi-Comp, Inc.; April 04, 2016.
13. Davidson J, Wilkinson A, Dantal J, Dotta, F, Haller, H, Hernandez, D, Kasiske, B, et al. International Expert Panel. New-onset diabetes after transplantation: 2003 international consensus guidelines. Proceedings of an international expert panel meeting Barcelona, Spain, 19 February 2003. Transplantation 2003;75(10, Suppl):SS3–SS24.
14. Padiyar A, Akoum FH, Hricik DE. Management of the kidney transplant recipient. Prim Care Clin Office Pract. 2008;35(3):433–50.
15. Schaefer HM. Long-term management of the kidney transplant recipient. Blood Purif. 2012;33:205–11.
16. Soleimanpour SA, Crutchlow MF, Ferrari AM, Raum JC, Groff DN, Rankin MM, et al. Calcineurin signaling regulates human islet (beta)-cell survival. J Biol Chem. 2010;285:40050–9.
17. Ajabnoor MA, El-Naggar MM, Elayat AA, Abdulrafee A. Functional and morphological study of cultured pancreatic islets treated with cyclosporine. Life Sci. 2007;80:345–55.
18. Flechner SM, Glyda M, Cockfield S, Grinyó J, Legendre Ch, Russ G, et al. The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. Am J Transplant. 2011;11:1633–44.
19. Galindo RJ, Fried M, Breen T, Tamler R. Hyperglycemia management in patients with post-transplantation diabetes. Endocr Pract. 2016;22 (4):454–65.
20. Barlow AD, Nicholson ML, Herbert TP. Evidence for rapamycin toxicity in pancreatic β-cells and a review of the underlying mechanisms. Diabetes. 2013;62:2674–82.
21. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. 2011;34(6):1431–7.
22. Ghisdal L, Van Laecke S, Abramowicz MJ, VanHolder R, Abramowicz D. New-onset diabetes after renal transplantation: risk assessment and management. Diabetes Care. 2012;35(1):181–8.
23. Vanrenterghem YF, Claes K, Montagnino G, Fieuws S, Maes B, Villa M, et al. Risk factors for cardiovascular events after successful renal transplantation. Transplantation. 2008;85:209–16.
24. Kasiske B, Cosio FG, Beto J, Bolton BM, Chavers R, Grimm R, Levin A, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the managing dyslipidemias in chronic kidney disease work group of the national kidney foundation kidney disease outcomes quality initiative. Am J Transplant. 2004;4(Suppl 7):13–53.
25. Navaneethan SD, Perkovic V, Johnson DW, Nigwekar SU, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. Cochrane Database Syst Rev. 2009;2: CD005019.
26. Holdaas H, Fellstrom B, Jardine AG, Holme I, Nyberg G, Fauchald P, Gonhagen-Riska C, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicenter, randomized, placebo-controlled trial. Lancet. 2003;361(9374):2024–31.
27. Ebeling PR. Approach to the Patient with Transplantation-Related Bone Loss. J Clin Endocrinol Metab. 2009;94:1483–90.
28. Ebeling PR. Transplantation osteoporosis. Curr Osteoporos Rep. 2007;5:29–37.
29. Nisbeth U, Lindh E, Ljunghall S, Backman U, Fellstrom B. Increased fracture rate in diabetes mellitus and females after renal transplantation. Transplantation. 1999;67(9):1218–22.

30. Abbott KC, Ogelsby RJ, Hypolite IO, Kirk AD, Ko CW, Welch PG, et al. Hospitalizations for fractures after renal transplantation in the United States. Ann Epidemiol. 2001;11(7):450–7.
31. Nikkel LE, Hollenbeak CS, Fox EJ, Uemura T, Ghahramani N. Risk of fractures after renal transplantation in the United States. Transplantation. 2009;87(12):1846–51.
32. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18(10):1319–28.
33. Kuroki Y, Kaji H, Kawano S, Kanda F, Takai Y, Kajiwaka M, et al. Short-term effects of glucocorticoid therapy on biochemical markers of bone metabolism in Japanese patients: a prospective study. J Bone Miner Metab. 2008;26(3):271–8.
34. Guistani A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. Endocr Rev. 2008;29(5):535–9.
35. Mazziotti G, Giustina A. Glucocorticoids and the regulation of growth hormone secretion. Nat Rev Endocrinol. 2013;9(15):265–76.
36. Epstein S. Post-transplantation bone disease: the role of immunosuppressive agents and the skeleton. J Bone Miner Res. 1996;11(1):1–7.
37. Nikkel LE, Mohan S, Zhang A, McMahon DJ, Boutroy S, Dube G, et al. Reduced fracture risk with early corticosteroid withdrawal after kidney transplant. Am J Transplant. 2012;12:649–59.
38. Bergua C, Torregrosa JV, Fuster D, Gutierrez-Dalmau A, Oppenheimer F, Campistol JM. Effect of cinacalcet on hypercalcemia and bone mineral density in renal transplanted patients with secondary hyperparathyroidism. Transplantation. 2008;86:413–7.
39. Josephson MA, Schumm LP, Chiu MY, Marshall C, Thistlethwaite JR, Sprague SM. Calcium and calcitriol prophylaxis attenuates post transplant bone loss. Transplantation. 2004;78:1233–6.
40. Sullivan PM, William A, Tichy EM. Hyperuricemia and gout in solid-organ transplant: update in pharmacological management. Prog Transplant. 2015;25(3):263–70.
41. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, Pillinger MH, et al. 2012 American College of Rheumatology guidelines for the management of gout. Arthritis Care Res. 2012;64(10):1431–61.
42. Danovitch GM. Handbook of kidney transplantation. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.
43. Krajewski CM, Geetha D, Gomez-Lobo V. Contraceptive options for women with a history of solid-organ transplantation. Transplantation. 2013;95(10):1183–6.
44. Josephson MA, McKay DB. Women and Transplantation: fertility, sexuality, pregnancy, contraception. Adv Chronic Kidney Dis. 2013;20(5):433–40.
45. Krajewski C, Sucato G. Reproductive health care after transplantation. Best Pract Res Clin Obstet Gynaecol. 2014;28:1222–34.
46. Brosens I, Brosens J, Benagiano G. The risk of obstetrical syndromes and solid organ transplantation. Best Pract Res Clin Obstet Gynaecol. 2014;28:1211–21.
47. Katabathina V, Menias CO, Pickhardt P, Lubner M, Prasad S. Complications of immunosuppressive therapy in solid organ transplantation. Radiol Clin N Am. 2016;54:303–19.
48. Grulich AE, Vajdic CM. The epidemiology of cancers in human immunodeficiency virus infection and after organ transplantation. Semin Oncology. 2015;42(2):247–57.