Renal Transplant

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Summary

- Over 90,000 patients are on the waitlist for a kidney transplant
- Renal transplant improves duration of life and quality of life compared to dialysis
- Thorough evaluation of transplant candidates is warranted to identify occult cardiovascular disease, infections, and malignancy
- Urologists are well suited to assist transplant teams in risk assessment and management of urologic diseases in both the pre-transplant and post-transplant settings

1. Introduction

End stage renal disease (ESRD) affects close to 750,000 Americans and resulted in $36 billion in Medicare paid claims, representing 7.2% of all Medicare spending. Without life-saving renal replacement therapy, the outlook for ESRD patients would remain bleak. In 2017, 87% of all incident cases began renal replacement therapy with hemodialysis, 10% started with peritoneal dialysis, and 3% received a preemptive kidney transplant. On December 31, 2017, 63% of all prevalent ESRD cases were receiving hemodialysis therapy, 7% were being treated with peritoneal dialysis, and 30% had a functioning kidney transplant.[1] Chronic dialysis prolongs the ESRD patient's lifespan, but it does not sufficiently replace a normal functioning kidney. The milieu of chronic renal insufficiency leads to accelerated cardiovascular disease, increased infections and diminished survival. **Five-year adjusted survival rates for patients initiating dialysis in 2012 were 43% for hemodialysis and 51% for peritoneal dialysis**. Overall mortality rates among ESRD (dialysis and transplant) patients have declined in the past decade, with rates leveling in more recent years.[1]

In comparison to chronic dialysis therapy, renal transplantation presents a survival benefit. In a landmark study, Wolfe and colleagues analyzed mortality rates in cohorts of all dialysis patients, patients on the transplant waiting list and recipients of primary deceased-donor renal transplants.

Relative to patients on the waiting list, deceased-donor renal transplantation was associated with lower mortality rates across all ages, genders, races and ESRD causes.[2] In addition to improvements in mortality, the restoration of normal kidney function from successful renal transplantation also improves patients' overall well-being and quality of life and is cost-effective compared to dialysis.

Solid organ transplantation is life saving for many patients. Living organ donation is possible in the case of some kidney and liver transplant recipients, but the majority come from deceased organ donors. In 2020, there were over 109,000 patients on the United Network for Organ Sharing (UNOS) waiting list **(Table 1)**. They are waiting for a kidney (84%), liver (11%), heart (3%), pancreas, lung, intestine, or a multivisceral transplant. Pediatric recipients (age less than 18 years) make up 1.7% while 68% are over the age of 50 years.[3]

Table 1. Approximate number of solid organ transplant candidates listed with UNOS	
Kidney	92,500
Liver	12,250
Pancreas	880
Kidney and pancreas	1,730
Heart	3,500
Lung	1,080
Heart and lung	50
Intestine	240

The waiting time until transplantation can vary widely by allocation policies that take into account disease severity, equity and outcomes. Currently, there can be significant differences among organ type and geographical region. Urologic interventions in “preparation” for transplant must take into account the availability of a living donor, or the expected waiting time until transplantation.

2. Patient Selection for Kidney Transplantation

Table 2 Indications for Renal Transplantation
End-stage renal disease requiring chronic dialysis
Chronic kidney disease stage V
Chronic kidney disease stage IV with calculated or estimated glomerular filtration rate (GFR) ≤ 20 ml/min

Table 3 Contraindications for Renal Transplantation
Absolute Contraindications
Severe or advanced vascular (cardiac, cerebral, peripheral) or pulmonary disease such that transplantation would pose a significant risk for morbidity/mortality
Active, untreated bacterial, fungal or viral infections
Intermediate or high-stage malignancy within the past 3 years (excluding non-melanoma skin cancer). An acceptable disease-free waiting period may be needed prior to transplantation depending on the cancer type (stage/grade) and treatment modality
Major ongoing psychiatric illness
Relative Contraindications
Projected life expectancy < 5 years independent of renal disease.
Medical nonadherence, substance abuse or behaviors leading to a failure to achieve a therapeutic physician-patient alliance
Body mass index (BMI) > 40 kg/m^2
Poor functional status independent of renal disease.

The improved outcomes with transplantation are contingent upon selecting patients who will do well with a transplant. By doing so, efforts are directed toward the best use of scarce donor organs. Patients should be selected such that they are likely to receive a benefit from the organ for at least three years. The evaluation process therefore is designed to identify candidates for whom the benefits of transplantation justify the risks. [4]

The primary indication for renal transplantation is irreversible, advanced-stage, chronic renal insufficiency. The specific indications and contraindications are listed in **Table 2** and **Table 3**. ESRD patients referred for transplant evaluation undergo a multidisciplinary evaluation with input from medical, surgical, psychosocial, nutritional and pharmacological professionals. The focus of this review is directed towards the role of the renal transplant surgeon.

2.1 Clinical evaluation

Clinical assessment of the kidney transplant candidate begins with a detailed history and physical exam. The history should include the primary cause and duration of renal disease, dialysis requirement and modality (peritoneal versus hemodialysis) and any significant urologic and vascular operations. Attention should be directed towards identifying cardiovascular, pulmonary and neurologic comorbidities as these conditions can result in significant peri-operative morbidity and mortality. The physical examination should identify patient issues that may influence the technical success of the renal transplant operation. These factors include extreme obesity (body mass index >40 kg/m ^{2}), a history of previous abdominal and/or pelvic surgery including organ transplants, and presence and severity of peripheral vascular disease. Identification of risk factors is important not only at the initial patient assessment but in subsequent assessments, particularly in high-risk patients, who should be evaluated at least annually when they are likely to receive a donor kidney.

2.2 Laboratory evaluation

The laboratory evaluation of renal transplant candidates includes general laboratory studies such as a complete metabolic panel, complete blood count, coagulation studies, urinalysis, urine protein/creatinine, and quantitative HCG in women < 50 years of age. Infectious screening includes determination of antibodies to cytomegalovirus (CMV), Epstein-Barr virus (EBV) and varicella zoster virus (VZV), hepatitis B, hepatitis C, human immunodeficiency virus (HIV) and syphilis. Tuberculosis screening should be performed in all patients via purified protein derivative (PPD) skin test (or QuantiFERON®-TB gold test) and chest X-ray. Patients with a history of mycobacterial disease and/or positive skin test should be considered for pre- and post-transplant isoniazid prophylaxis.[4]

Blood and tissue type determination are integral to renal transplantation. ABO blood type and antibody screen are necessary prior to surgery. Tissue typing involves identification of recipient human leukocyte antigens (HLA), which are necessary for registration on transplant waiting lists and for immunologic testing with potential donors.

2.3 Radiographic evaluation

A baseline abdominal and pelvis ultrasound, or computerized tomography (CT) scan, screens for evidence of abnormal masses, gallstone disease, and kidney problems (stones or chronic pyelonephritis). A non-contrast CT scan has the additional advantage of outlining areas of calcification in the aorto-iliac vessels to pre-operatively plan for safe sites of arterial anastomosis. The location of an abdominal reservoir for a penile prosthesis or artificial urinary sphincter should be documented to facilitate exposure of the bladder.

2.4 Cardiovascular evaluation

ESRD patients are at high risk of developing cardiovascular disease (CVD), therefore screening for CVD remains an important component of the pre-transplant evaluation. At present there is no consensus for screening asymptomatic ESRD patients and coronary revascularization has not been shown to clearly prevent cardiac events. Notwithstanding these limitations, screening should be considered for patients with CVD risk factors, such as age > 60, smoking, hypertension, dyslipidemia, diabetes mellitus (DM), prior CVD, more than one year on dialysis, and left ventricular hypertrophy. Patients with active cardiac conditions (unstable coronary syndromes, unstable angina, severe angina or recent myocardial infarction [MI] decompensated congestive heart failure, significant arrhythmia or severe valvular heart disease) are likely not candidates for transplant until these conditions have been resolved.

CVD screening should include a baseline electrocardiogram (ECG) in all patients. Noninvasive stress testing (dobutamine echocardiography or myocardial perfusion scanning) should be considered in asymptomatic candidates with ≥ 3 coronary artery disease (CAD) risk factors and no active cardiac conditions.[5] Patient with active cardiac conditions or abnormal noninvasive screening test results should be referred for cardiology consultation and considered for coronary angiography.

2.5 Malignancy evaluation

Screening for pre-existing cancers is a vitally important aspect of the pre-transplantation evaluation. Guidelines from major cancer preventative organizations should be considered. A five-year disease-free waiting period is often recommended for patients with treated invasive or metastatic malignancy. Localized and/or low-grade malignancies may only require an observation period of a year or less. The prognosis for many cancer patients continues to improve so an oncology consultation should be obtained to determine the risk for recurrence, long-term prognosis, and impact of immunosuppression for the specific malignancy being addressed. A diagnosis of ESRD can have an impact on the risk of some urologic malignancies. Additional discussion regarding evaluation and assessment of urologic malignancies in the transplant candidate is reported in the following section.

3. Urology Consultation in Renal Transplantation

3.1 Consultation Prior to Transplant

The transplant team may refer a transplant candidate with a history of urologic disease to determine the impact on post-operative care and long-term survival. In some cases, they may request

“clearance for transplant”. The role of the consultant is to evaluate the patient for current evidence of disease including infection and malignancy. Based on the evidence one should provide an estimate of the risks of recurrent infection, renal dysfunction, disease recurrence, and patient survival. Urologic interventions in “preparation” for transplant must take into account the availability of a living donor, or the expected waiting time until transplantation. The impact of immunosuppression on the progression of disease should be estimated if possible. The transplant team must then decide if these risk factors preclude transplantation.

Evaluation of voiding dysfunction using prostate symptom scores, prostate US, or urodynamic studies is not routinely performed prior to transplant and likely are only necessary in those with urological causes of ESRD, recent urinary tract infections, or previous urological interventions. For instance, in patients with a history of high pressure voiding secondary to bladder outlet obstruction, and bilateral hydronephrosis and renal cortical atrophy, determination of bladder capacity and voiding pressures can aid in the management of the allograft following transplant. Specifically, patients with high pressure bladders may need pharmacologic or procedural approaches to maintain normal filling pressures. Similarly, in patients with a history of vesicoureteral reflux causing ESRD, voiding cystourethrography (VCUG) may confirm bilateral reflux, thus favoring reconstruction of the allograft ureter without use of the native ureter. It is important to note that among the causes of ESRD, obstructive uropathy from bladder outlet obstruction and chronic pyelonephritis from vesicoureteral reflux are uncommon; therefore, these particular studies are generally not routinely obtained. Pre-transplant surgical intervention for voiding symptoms in patients with minimal urine output is discouraged given the risk of urethral stricture and bladder neck contracture in addition to possible improvement post-transplant. These patients should be advised that urethral catheterization and additional procedures might be necessary after transplant. Patients with bothersome voiding symptoms and normal urine volume should undergo evaluation and treatment similar to the general population.

A baseline abdominal and pelvic ultrasound, or computerized tomography (CT) scan, screens for evidence of abnormal masses, gallstone disease, and kidney problems (stones or chronic pyelonephritis). A non-contrast CT scan has the additional advantage of outlining areas of calcification in the aorto-iliac vessels to pre-operatively plan for safe sites of arterial anastomosis. The location of an abdominal reservoir for a penile prosthesis or artificial urinary sphincter should be documented to facilitate exposure of the bladder.

Asymptomatic urolithiasis is generally not a contraindication to transplantation. However, it may be a risk factor for infection including pyelonephritis. Stones associated with infection should be treated prior to the initiation of immunosuppression. Risk factors for recurrent stone formation should be identified and treated if possible.

3.2 Consultation Prior to Kidney Donation

For a living kidney donor, there is no direct benefit, but a significant benefit to the recipient. Laparoscopic surgery has reduced the recovery time from surgery, but there may be long-term risks

to having a solitary kidney. International consensus has been published for the generally acceptable risks, but each case must be evaluated independently.[6] An asymptomatic solitary unilateral stone may not be a contraindication to donation of that kidney if there is no prior history of stone passage and a metabolic risk for recurrent stones has been excluded. These stones can frequently be removed during the benchwork preparation of the kidney.

Potential donors should be screened for malignancy using age-appropriate tests as recommended by the AUA. Small renal masses may be detected as part of the evaluation imaging. Benign lesions such as angiomyolipoma can be excised at the time of organ donation. Some centers are willing to accept living kidney donors with small renal masses that are excised at the time of donation.[7] With all organ donors the risk of disease transmission must be evaluated.

3.3 Consultation Post Organ Transplantation

Urinary tract infections (UTI) are one of the most common medical complications of transplantation and are associated with substantial health care costs and antibiotic overuse. With rapidly growing antimicrobial resistance patterns, opportunity exists for improvement in antimicrobial stewardship, even in immunosuppressed populations. Risk factors for UTI include female sex, older age, prior history of UTI, diabetes, obesity, vesicoureteral reflux (VUR), urethral catheterization, urinary stasis, indwelling ureteral stent, delayed graft function, and polycystic kidney disease.[8,9] Use of ureteral stent during transplant has been associated with higher rates of UTI and the risk of systemic infection and calcification can be reduced by removal within a month.[10]

Immunosuppressed patients have great variability in presentation and all UTIs should be considered complicated. BK polyoma viruria can mimic typical UTI symptoms, may have associated constitutional symptoms, and can occur 1 week post-transplant to several years later. BK viral nephropathy does not produce graft tenderness. BK virus is most commonly detected by polymerase chain reaction analysis in blood or urine, yet diagnosis of BK nephropathy requires renal biopsy.

In renal transplants with systemic symptoms or recurrent UTI (rUTI), evaluation for an anatomical or functional abnormality is warranted. Initial investigation should include a PVR to assess for urinary stasis. Incomplete emptying should be further evaluated with uroflowmetry or urodynamics to assess for voiding dysfunction and bladder outlet obstruction. Ultrasound or CT can be used to assess for obstruction, abscess, urolithiasis, and complex cysts. Inclusion of the native kidneys during US in those with a history of PCKD is prudent. If there is suspicion of VUR, or a non-revealing initial radiographic evaluation, an appropriate next step is VCUG. A subset of patients with high grade VUR will become symptomatic and commonly present with rUTI. Cystoscopy is not routinely indicated in the evaluation of rUTI.

The management of transplant recipients with rUTI is challenging for the clinician as well as patient and should focus on non-antibiotic preventative strategies when feasible. Unlike BK virus, most bacterial UTIs do not improve with a reduction in immunosuppression. Recurrent UTIs associated with high grade VUR may improve following ureteral reimplant or ureteroureterostomy to the native

ureter. Additional common urologic consultations post-transplant including ureteral complications, the evaluation of hematuria, and post-transplant malignancies are discussed in more detail in the **December 2018 AUA Update: Urology Consultation in Renal Transplantation**.

3.4 Evaluation of Urologic Malignancy

Immunosuppressive medications and the resulting compromised immune system are currently necessary parts of a successful post-transplant outcome. The immune system plays an important role in both the surveillance and clearance of abnormal cells and therefore malignancies occur with a higher frequency in immunosuppressed patients. Large registry studies have compared the relative risk of developing certain cancers in transplant recipients compared to that of the general population using a standardized incidence ratio (SIR). Significantly increased risks of nonmelanoma skin cancer (SIR 13.9), lymphoma (SIR 7.5-12.5) and kidney cancer (SIR 4.7) were noted with a slightly increased risk of bladder cancer (SIR 1.5) and decreased or unchanged risk of prostate cancer (SIR 0.9). [11,12,13,14] Fortunately, only a small minority (5%) of transplant recipient deaths are due to malignancy, with the largest portion of deaths (50%) attributable to cardiovascular disease.[15,16] Screening and management of urologic malignancies in transplant candidates are guided by the above data.

PSA screening is recommended based on the **AUA guidelines** with careful attention paid to the life expectancy of the patient being screened. Total PSA is not affected by hemodialysis although free PSA is increased by 10-30%.[17] MRI and biomarkers can be used in a fashion similar to the non-transplant population. A diagnosis of clinically localized prostate cancer should rarely preclude an otherwise acceptable candidate for renal transplantation. In low risk and very low risk prostate cancer the risk of death associated with organ failure is probably greater than the risks associated with prostate cancer. [18] Men who qualify should be offered active surveillance and may continue this approach following transplantation. Patients with intermediate or high-risk prostate cancer who are otherwise transplant candidates may be treated with either radiation or surgery and often require little or no additional delay prior to transplantation. In transplant recipients who subsequently develop prostate cancer all therapeutic options have similar outcomes to the general population.[19] The only significant change is avoidance of pelvic lymph node dissection on the side of the allograft.

The great majority of patients with prolonged dialysis utilization develop acquired cystic kidney disease (ACKD), and 1.6-20% of patients with ACKD develop renal cell carcinoma (RCC), with a slight predominance of papillary RCC subtype. Given this increased risk of RCC, such patients are recommended for renal imaging in the pre-transplant setting. The ideal frequency of screening is unknown. Surveillance or treatment are considered based on the stage of the mass, current renal function, and anticipated timing of transplant. When evaluating pre-transplant patients with renal masses it is critical to consider the renal function implications of treatment as a transition to dialysis typically results in a much worse survival curve compared to active surveillance with avoidance of dialysis. A period of post-treatment surveillance is typically required only for those at high risk for recurrence. [20] In the post-transplant setting, renal cell carcinoma is the most common urologic

malignancy. More than 90% of RCCs in renal transplant recipients are incidentally detected and the great majority are low grade and stage tumors. Annual or biannual US screening is advocated by some, however a cancer specific or overall survival benefit has not been established. When a small native kidney renal mass is identified, it is reasonable to consider **surveillance analogous to recommendations for the general population** . If treatment is pursued, native kidney RCC should be treated with radical nephrectomy. For tumors identified in the renal allograft biopsy should be performed and strong consideration should be given to partial nephrectomy or ablative therapies as appropriate. Immunosuppression modification is usually not necessary for localized RCC.

Urothelial cell carcinoma in renal transplant candidates is uncommon and few data exist to guide management. Patients appear to present with more aggressive disease and experience worse disease specific survival than the nontransplant population.[21,22] A study by Penn et al found that approximately one-third of previously treated bladder cancers recurred following renal transplant. Unfortunately, no tumor stage or grade was reported in the study, limiting its applicability. [23] In general, transplant candidates with low and intermediate risk non-muscle invasive bladder cancer are probably safe for transplantation with close observation, whereas those with high risk non-muscle invasive bladder cancer or previously treated muscle invasive bladder cancer should remain disease free for a period of time (2 – 5 years) prior to transplantation.

Risk based treatment and surveillance **protocols outlined by the AUA** should be followed. Intravesical bacillus Calmette-Guérin (BCG) can be safely used in transplant recipients, although may be less effective due to diminished immune response.

In summary, a tailored approach should be pursued for transplant candidates and recipients presenting with urologic malignancies. In many cases, the benefit of a transplant may far outweigh the risks of immunosuppression and progression of urologic disease. In all cases, indications for treatment should be driven by life expectancy, aggressiveness of disease, and patient priorities.

4. Selection of Kidney Transplant Donors

The rate limiting step of kidney transplantation is identification of a suitable donor kidney. The donor kidney may come from the deceased, or from a living patient. The source of donor organs varies significantly around the world depending on societal values and support for transplantation. It is critical that all organ donation activities be continuously monitored to ensure ethical practices. [24] The supply of suitable deceased donor kidneys is frequently not adequate to meet the needs of appropriate transplant candidates. National media campaigns may increase deceased donation by encouraging registration as a deceased donor. Renal transplant outcomes are generally better with a living compared to a deceased donor and recipients are encouraged to introduce potential living donors to educational seminars to improve the decision-making process for all those involved. Ultimately, the selection of a kidney donor for each recipient is a complex process that involves both immunologic and non-immunologic factors.

4.1 Deceased Donor Allocation and Selection

The Organ Procurement and Transplantation Network (OPTN) (**https://optn.transplant.hrsa.gov**) was established by the United States Congress under the National Organ Transplant Act (NOTA) of 1984. The act called for the network to be operated by a private, non-profit organization under federal contract. All U.S. transplant centers must be members of the OPTN to receive funds through Medicare. Other members of the OPTN include organ procurement organizations (OPO), independent histocompatibility laboratories, and relevant medical, scientific, and professional organizations. Members of the OPTN must report data to the Scientific Registry of Transplant Recipients (SRTR) (**www.srtr.org/**). All suitable candidates in the United States must be registered and are usually consented for kidneys from deceased donors. The primary goals of the OPTN are to: 1) increase the effectiveness and efficiency of organ sharing and equity in the national system of organ allocation, and 2) to increase the supply of donated organs available for transplantation. The United Network for Organ Sharing (UNOS) (**www.unos.org**) administers the OPTN under contract with the Health Resources and Services Administration of the U.S. Department of Health and Human Services.

4.2 Declaration of Donor Death

All hospitals must report potential deaths to the local OPO. Organ procurement personnel screen all eligible donors and assign a staff member to discuss organ donation with the next of kin. There is a clear difference between severe brain damage and brain death. The physician must understand this difference, as brain death means that life support is futile, and brain death is the principal prerequisite for the donation of organs for transplantation. The declaration of donor death must be made by two physicians who are not part of the organ recovery or transplantation team in order to avoid any conflict of interest. Donors may be declared dead by neurological criteria or cardiorespiratory criteria. Neurologic criteria for brain death include coma, irreversibility, known brain damage, and absence of brain stem reflexes. [25] In donors who are dead by neurologic criteria, cardiopulmonary function can be supported through the organ recovery process to minimize warm ischemia to the potential allografts.

Donation after circulatory death (DCD) can occur when a potential donor does not meet neurologic criteria despite being comatose and ventilator dependent. When the decision to withdraw care is made, ventilator support is discontinued. Death is declared by absence of spontaneous respiration and sustained asystole for 5 minutes before organ recovery begins. All DCD donor organs are subject to a period of warm ischemia and have a higher rate of delayed graft function.

4.3 Kidney Preservation

The renal tubular sodium-potassium pump maintains a high intracellular concentration of potassium and is dependent on adenosine triphosphate (ATP). Ischemia leads to a depletion of ATP, loss of cellular potassium and magnesium, increased calcium, anaerobic glycolysis with acidosis, and activation of lysosomal enzymes. Following kidney reperfusion oxygen delivery recovers. Hypoxanthine, a product of ATP metabolism, is oxidized to xanthine resulting in the formation of free

radicals and cell damage. Cellular swelling reduces perfusion which leads to delayed function of the allograft and increased immunogenicity.

The goal of organ preservation is to maintain intracellular physiology. Simple cold storage is inexpensive and facilitates the transportation of the donor kidney. Pulsatile preservation pumps may reduce vascular spasm, extend the preservation time, and reduce the need for dialysis after transplant. [26] A randomized trial in 2009 demonstrated an absolute reduction in delayed graft function of 5.7% and an improvement in 1-year graft survival of 4% in the machine perfusion group compared to cold storage. Three year follow up data of this trial confirmed improved graft survival (91% vs 87%) of machine perfused kidneys.[27,28] In general, both the warm and cold ischemia times should be minimized to promote recovery of the allograft.

4.4 Allocation

More than 90,000 patients are waiting for deceased donor kidney transplants, and with about 12,000 deceased donor kidney transplants performed annually, there are many ESRD patients waiting for many years to get a transplant. The inadequate supply of deceased donor kidneys is one of the factors that have increased the use of 1) “marginal” organs and 2) living donor kidneys in the past decade. The increase in living kidney donation has been further facilitated by the widespread adoption of minimally invasive donor nephrectomy techniques; acceptance of living, biologically unrelated renal donors; and the widespread adoption of kidney paired donation.

The organ allocation policies continue to be revised based on analysis of data collected by the SRTR and approval of the UNOS Board of Directors. In December 2014, a new kidney allocation system was implemented (**https://unos.org/wp-content/uploads/unos/Kidney_Brochure.pdf**). Multi-organ transplant recipients, pediatric candidates, and former living-kidney donors receive priority. For most kidney transplant candidates, however, the most important factor in receiving an organ offer is time spent on the waiting list. Additional factors that may give a potential recipient more points include the quality of the HLA-DR match, and high levels of HLA antibodies (>80% PRA).

The relative risk of kidney graft survival varies based on donor age, state of health, ethnicity, and determination of death and social history. The category of donor organs any recipient is willing to accept must be decided by the patient and transplant physician. A goal of the new policy is to allocate kidneys with the longest expected graft survival, estimated by the “kidney donor profile index” (KDPI) (**https://optn.transplant.hrsa.gov/resources/allocation-calculators/kdpi-calculator/**), to patients with the longest “estimated post-transplant survival” (EPTS) (**https://optn.transplant.hrsa.gov/media/1512/guide_to_calculating_interpreting_kdpi.pdf**). Ethnicity as a variable within the predictive model is currently under review.

In June 2020, The Centers for Disease Control (CDC) and the Public Health Service (PHS) released updated guidelines for assessing the potential for certain viral infections in solid organ donors and monitoring for these infections in recipients. The implementation of universal nucleic acid testing of solid organ donors for HCV, HBV, and HIV has reduced the risk of viral transmission between donor

and recipient to 1 in a million or less. Advances in treatments for these infections has helped to significantly reduce the morbidity and mortality should a viral transmission occur. These updated guidelines no longer require separate consent for organs from donors previously determined to be "increased risk". Consent is now recommended to occur as part of a broader discussion of infectious transmission risk in solid organ transplantation (**https://www.cdc.gov/mmwr/volumes/69/rr/rr6904a1.htm**). In most cases the risk of ESRD is far greater than the risk of infection.

4.5 ABO Blood Group Compatibility

The ABO blood groups are determined by cell surface carbohydrate antigens expressed on red blood cells. Within the first two years of life, most individuals have been exposed to the non-inherited antigen (probably via the digestive tract).[29] An individual who is blood type B, will have anti-A antibody, and reacts to blood type A. If a kidney is transplanted between ABO-incompatible individuals, antibodies will bind to the non-inherited carbohydrate antigens expressed on endothelial cells leading to activation of the complement cascade, coagulation, thrombosis, and rapid graft loss. However, if these antibodies have a low titer at the time of transplantation, and production of antibody can be limited with immunosuppressive medications, then ABO incompatible renal transplants can be achieved. [30] Most of these recipients develop "accommodation" to the donor antigen, despite persistent donor specific blood type antibody. The graft endothelial antigen expression appears to be down regulated and chronic complement activation is minimal.

4.6 Histocompatibility

The human major histocompatibility complex (MHC) is a cluster of more than 200 genes on chromosome 6p21.31 and is responsible for the human leukocyte antigens (HLA) that are expressed as cell surface proteins on the renal allograft. These donor glycoprotein HLA molecules are recognized by the recipient's leukocytes, and then activate the immune response. While the MHC is required to protect the host from pathogens, it creates the major immunologic barrier to transplantation. All nucleated cells express HLA class I. Antigen presenting cells (dendritic cells, monocytes, macrophages, and B-lymphocytes) and inflamed tissues including endothelial cells have both HLA class I and II.

Most recipients have some mismatched (unshared) HLA antigens compared to the donor. HLA antibodies may be formed by the recipient prior to transplantation as a result of pregnancies, previous transplants, blood transfusions, and possibly some infections. Individuals with antibodies directed at more than 20% of the population are said to be sensitized. Sensitized transplant candidates, particularly those who are highly sensitized may face extreme difficulty in finding a donor to whom they will have a negative crossmatch.

4.7 Crossmatch Techniques

Rejection is the destruction of organs transplanted between genetically different individuals by

immune cells and antibodies. Immunosuppression protocols have been developed to allow graft acceptance. Predicting the risk of rejection by a particular recipient from a given donor is needed to determine the appropriate drug therapy. [31,32] The least sensitive test is the complement-dependent lymphocytotoxicity (CDC) assay in which donor T (class I antigens) or B-lymphocytes (class I and II antigens) are combined with recipient serum, complement is added, and cell lysis is detected by dye exclusion after a period of incubation. Since the CDC crossmatch detects only high levels of HLA antibodies, a positive CDC crossmatch is generally considered a contraindication to transplantation with that donor.

The percentage of donors with whom the recipient is likely to have a positive crossmatch can now be determined with solid-phase assays that use purified HLA single antigen beads (SAB). Since a given donor's HLA-typing will be known, the recipient's SAB testing may be employed to identify any donor-specific antibodies (DSA) without having the donor cells. For example, if a potential recipient is found to have strong DSA to HLA-A2 and HLA-DR17, a center may choose to consider A2 and DR17 "unacceptable" in the UNOS database and kidneys from donors with this HLA phenotype will not be offered to the patient. This same information can be used at the time of an organ offer to perform a "virtual crossmatch". Exclusion of recipients with donor specific antibodies can help expedite organ allocation and minimize cold ischemia time. The frequency and ethnic distribution of the HLA antigens in the donor population is also regularly monitored. Based on the results of specific HLA antibodies a percentage of antibodies reactive to a panel can be calculated (cPRA) (**https://optn.transplant.hrsa.gov/resources/allocation-calculators/cpra-calculator/**). Antibodies reactive to common antigens can significantly prolong the waiting time to find a suitable donor.

4.8 Living Donor Evaluation

Table 4. Laboratory Evaluation of the Live Kidney Donor
General
Complete metabolic panel
Transaminases, alkaline phosphatase
HbA1c, lipid profile
Complete blood count with differential
Coagulation studies
HCG - for all female patients
Type and screen
Infection Screening
CMV, EBV, HSV immunoglobulin levels
Hepatitis B, C RNA
HIV antibody determination
RPR with titer
Strongyloides IgG
Trypanosoma cruzi IgG (patients from Mexico, Central and South America)
Renal Function Screening
Urinalysis with microscopic examination
Random urine albumin/creatinine ratio Urine culture and sensitivity

24-hour urine for total protein and creatinine clearance
24-hour urine for metabolic evaluation for patients with nephrolithiasis (> 3 mm) identified on radiographic imaging (Ca2+, oxalate, uric acid, citrate, creatinine, Na+)

Healthy adults (>18 years of age) can be considered for live kidney donation if they are willing, without coercion, and without valuable compensation. Potential living donors go through a rigorous screening prior to a comprehensive medical, surgical and psychosocial evaluation. Donors should be healthy individuals, without diseases that would increase the risk of kidney failure, acute symptomatic infections, ongoing substance abuse and/or psychiatric disorders. In addition to a complete history and physical, living donor candidates undergo laboratory screening (**Table 4**), age and gender appropriate cancer screening, 24-hour ambulatory blood pressure monitoring, cardiac testing (based on patient history and examination) and contrast enhanced CT scan of the abdomen.

Living kidney donor renal function or GFR should be determined by nuclear medicine, iothalamate clearance methods, or by 24-hour urine for creatinine clearance. In addition to satisfying the previously stated criteria, living kidney donors should have a GFR > 80 ml/min.

Contrast enhanced CT scan remains the standard radiographic evaluation of living kidney donors. The size and shape of the kidneys, presence of any anatomic abnormalities, number, length and location of arteries and veins as well as assessment of other abdominal organs is possible with a CT scan.

Surgical consideration in live donor nephrectomy should always aim to follow the principle of leaving the “better” kidney with the donor. In most cases neither kidney is particularly “better” than the other; thus, kidney selection is based on vessel number and length. If the right and left kidney are similar in size and both have a single renal artery, the left kidney is preferred due to the longer renal vein. In the setting of multiple renal arteries, a general approach is to select the kidney with fewer arteries as this is associated with a lower risk of recipient vascular complications.

Live donor nephrectomy can be performed via laparoscopic, hand assisted, and open approaches. With any of these approaches the risk of peri-operative mortality is approximately 3 in 10,000 and long-term outcomes following kidney donation are very similar to age-matched healthy adults.[33] A clinician who is independent of the transplant team should act as an advocate for the potential donor. There is no upper limit for donor age, but donors who are quite young (<25 years) have a much greater life time risk of complications. In recent years, some transplant centers have accepted donors who have hypertension that is well controlled with a single antihypertensive medication. Ideally, living donors should have a body mass index (BMI) that is less than 30, but some transplant centers do accept individuals with BMI above 30. It is critical to council all donors to maintain a healthy weight as a preventative measure for developing diseases such as diabetes mellitus and/or hypertension that may subsequently contribute to renal damage.

The risks of living donor nephrectomy are generally considered acceptable for fully informed donors, given the considerable benefit of a living donor transplant for the recipient.

4.9 Managing Incompatible Living Donor/Recipient Pairs

Due to blood-type incompatibility, or HLA antibodies from prior blood transfusions, transplants, or pregnancy; approximately 35 percent of medically suitable donors are found to be incompatible with

their intended recipient.[34] Until recently, patients in this situation were told not to proceed with living donor transplantation, but to wait for a compatible deceased donor organ because of a high risk of rejection. The prolonged waiting time and inferior outcomes have made this a poor choice for many patients.

Given the lack of deceased donors in Japan, ABO blood-type incompatible transplantation was pursued with acceptable graft and patient survival, but longer-term results are not equivalent to blood-type compatible living donor transplants.[35] Protocols for such transplants may include plasmapheresis, intravenous immune globulin (IVIG), rituximab, and/or splenectomy to reduce anti-ABO titers to acceptable levels. In general, ABO-incompatible transplants also require more intensive immunosuppressive regimens.

Kidney transplantation with lower levels of donor specific antibodies (DSA) may be performed if a higher risk of antibody-mediated rejection (AMR) is acceptable. Depending on the strength of cross-match positivity being caused by HLA antibody, patients may require treatments such as IVIG and/or plasmapheresis prior to proceeding with transplantation.

4.10 Kidney Paired Donation (KPD)

An alternative strategy to facilitate living donor kidney transplantation for incompatible donor /recipient pairs is kidney exchange. The initial protocols were a simple swap of incompatible donors at a single center.[36] Computer programs were written to include incompatible pairs based on “desensitization” and virtual cross match techniques to avoid high levels of antibody. The inclusion of “non-directed donors” (NDD), who are remarkable individuals who seek to donate a kidney to a complete stranger in need, dramatically increased the power of these programs. Currently, there are several large multicenter databases of incompatible pairs to maximize the chances of finding compatible matches for participants (e.g. Alliance for Paired Donation, National Kidney Registry, UNOS). The most successful KPD programs utilize transcontinental shipping of living donor kidneys via commercial airline to facilitate transplants without compromising results. [37]

4.11 Living Kidney Donor Operation

Laparoscopic donor nephrectomy (LDN) has a low complication rate (6% minor, <2% major) and is the preferred technique for living donors. Many centers use a hand-assisted laparoscopic, fully laparoscopic, or robot-assisted technique. Open donor nephrectomy is rarely performed at this point but is typically accomplished through an extraperitoneal flank approach. Conversion to an open nephrectomy is uncommon, but all donors should be consented for this possibility prior to donation. The ureter is mobilized to the point at which it crosses the iliac vessels. The renal vessels should be ligated with a vascular stapling device. In the United States, Hem-o-Lock clips are not approved in LDN, since living donor deaths were reported due to delayed bleeding from the donor renal artery. The extracted graft is quickly placed in a basin of iced saline, the renal arteries are cannulated, and the kidney is flushed with ice-cold heparinized (5000 units per liter) Ringer’s lactate or an organ preservation fluid (if shipped).

5. Kidney Transplantation Surgery

The kidney transplant procedure involves preparation of the kidney graft, preparation of the recipient vessels, implantation of the kidney, reperfusion and hemostasis, and ureteroneocystostomy.

Preparation of the kidney may vary depending on the donor source. For living donor kidneys anatomic information is well known prior to surgery and much of the preparation can be done by the donor surgeon. In contrast, deceased-donor kidneys are removed with variable amounts of peri-nephric tissue and are often minimally prepared by the recovering teams. In these situations, it is prudent to inspect the kidney for anatomic abnormalities, evidence of surgical damage, and number and quality of blood vessels. The allograft should be prepared in a basin containing ice cold saline or preservation solution. The excess perinephric fat should be removed so that the entire parenchymal surface is visible. The renal vein is freed from the surrounding tissue and all extra-renal tributaries (gonadal, lumbar, adrenal veins) should be ligated and divided. In the setting of multiple renal veins, at least 50% of the venous drainage should be preserved in order to avoid outflow compromise and potential thrombosis. The renal vein should be mobilized to the level of segmental renal venous branches. The right renal vein tends to be much shorter than the artery; to facilitate reconstruction with a deceased donor the vena cava is frequently used as an extension graft. The renal artery is similarly mobilized and with a deceased donor, a cuff of aorta (Carrel patch) is often kept on the artery to minimize chances for narrowing of the arterial anastomosis. Attention should be directed toward preserving all accessory renal arteries and renal artery branches. Lastly the ureter should be identified and maintained with an abundant amount of peri-ureteral tissue. The kidney should be kept in cold preservation solution until the time of implantation.

After induction of general anesthesia, the recipient is kept in the supine position and a urethral catheter placed for continuous urine drainage. The catheter should enable sterile fluid infusion in order to distend the bladder for ureteroneocystostomy. Following standard prep and drape, a lower quadrant extraperitoneal incision is used to access the external and common iliac vessels. The lymphatic tissue overlying the external iliac artery is divided between ties and the artery is circumferentially mobilized from its origin to the inguinal ligament. Similarly, the external iliac vein is isolated to the level of the first major hypogastric (internal iliac) branch. If the external iliac vessels are felt to be unsuitable for kidney implantation, the common iliac vessels and subsequently more proximal vessels should be explored. Retraction of the surrounding structures is accomplished with the aid of a self-retaining retractor.

Once the vessels are suitably exposed, the kidney is brought into the field and proposed targets for anastomosis verified. The external iliac vein is clamped, an appropriate-sized venotomy made on its anterior aspect, the lumen is flushed with a heparin-containing saline solution and the anastomosis to the renal vein completed with fine (#5-0 or #6-0) non-absorbable suture. Anastomosis of the renal artery (or multiple renal arteries) to the external iliac artery is conducted in a similar fashion. Once the arterial anastomosis is completed, the venous clamp is released, and any areas of significant venous bleeding are controlled. The arterial clamps should be released in the direction of retrograde flow

(lower pressure) to antegrade flow (higher pressure). With the allograft re-perfused meticulous hemostasis should be obtained along the anastomotic sites, renal hilum and parenchymal surface. Following achievement of hemostasis, vascular patency and parenchymal turgor should be inspected and verified.

In general, either kidney (right or left) can be placed in either iliac fossa (right or left) as long as there is satisfactory mobility in the renal vessels and, if needed, the iliac vessels. As the iliac vein is deeper (more posterior) in comparison to the iliac artery, placement of the kidney often depends on the length of the renal vein. The right iliac vein tends to follow a more superficial course than the left iliac vein and is therefore more commonly selected as the side for kidney placement. In a similar sense, the left donor kidney has a longer vein and is more commonly selected for living donor procurement. Given these 2 factors, the left kidney is often placed in the right iliac fossa. Lastly, and equally important, placement of the kidney in the contralateral iliac fossa orients the renal pelvis (the posterior-most structure) anteriorly, which can facilitate future urinary tract procedures should they be necessary. These factors notwithstanding, the right iliac fossa is most commonly selected as the side for placement of a primary renal allograft.

Ureteroneocystostomy is most commonly done in an extra-vesical manner regardless of non-refluxing or refluxing methods. For the non-refluxing technique, the detrusor musculature is divided for 2-3 cm until only the bladder mucosa is visible. The ureter is trimmed and spatulated along a healthy segment, the bladder mucosa is opened and a mucosal anastomosis is completed with fine (#5-0) absorbable suture. In a refluxing anastomosis the full thickness ureter is anastomosed to full thickness bladder with fine absorbable suture. ESRD patients often have thick-walled, poorly compliant bladders and full thickness ureteroneocystostomy may be associated with a lower leak or stricture rate, but increased risk of urinary tract infection.[38]

Whether routine ureteral stent placement for transplant ureteroneocystostomy reduces urological complications has been the subject of study for many years. Numerous single center cohort studies have shown low complication rates with routine stent placement as well as with selective stent placement. Randomized trials examining this same question are plagued by significant heterogeneity. These trials were reviewed by Mangus and Haag in 2004 and by Wilson and colleagues in 2013.[39,40] Both of these meta-analyses, which reviewed 5 and, subsequently 7 randomized trials, respectively, found a lower risk of urological complications in patients with routine stent placement. On closer inspection however, this difference is almost entirely due to the randomized study by Pleass and colleagues in which the urological complication rate in selective stent patients was 17.3%, an extraordinarily high number.[41] When this study is excluded, and as indicated by Wilson et al., when a single experienced surgeon performs or supervises the ureteroneocystostomy, there is likely no advantage to routine stent placement.

Prior to wound closure it is imperative to position the kidney in a manner that maintains perfusion and avoids renal vessel compression. Typically, the kidney allograft can be positioned with the parenchymal surface on the psoas muscle and the renal hilum oriented medially. A temporary Blake

or JP drain is often placed to permit egress for serous or lymphatic fluids and minimize the risk of these fluids causing allograft or ureteral compression. Muscular, fascial and skin layers are closed in a standard manner.

6. Post-operative Care of the Transplant Recipient

Following the transplant operation, graft function is determined by urine output and change in GFR, as detected by serum creatinine level. Significant electrolyte imbalances can occur with diuresis; therefore, on a daily basis, electrolyte, renal function, and blood counts should be monitored.

Foley catheter drainage is maintained for 3 days or longer, depending on the intraoperative determination of detrusor muscle quality. The remainder of the post-operative care involves standard analgesic regimens, intravenous fluids to compensate for urine output and other fluid losses. Given the extraperitoneal nature of the procedure, oral intake can be resumed within 1 to 2 days following surgery and the typical length of hospitalization following an uncomplicated procedure is 3 to 7 days.

6.1 Post-operative Radiographic Testing

Renal allograft ultrasonography (US) should be performed in the postoperative setting if there is clinical suspicion of vascular compromise. US can be performed on an immediate basis and at the patient's bedside. Satisfactory US image quality may be limited in obese patients and in these cases, clinicians may prefer nuclear renography. Nuclear renography eliminates the operator dependence associated with US but cannot generate results in as timely a manner due to the need to prepare the radionuclide. In general, when there is clinical evidence of graft function, specifically adequate urine output (>1500-2000 ml/24 hours) and a declining serum creatinine, radiographic assessment is not critical.

6.2 Immunosuppressive Medications

The immunosuppressive management is defined pre-emptively based on patient immunologic risk factors and center-specific strategies. In general, immunosuppression for renal transplantation is comprised of 3 categories of agents: induction immunosuppression (intense immunosuppression given at the time of engraftment), maintenance immunosuppression (given long-term following transplantation) and therapy for rejection. Current induction immunosuppression protocols utilize lymphocyte depleting antibodies (rabbit antithymocyte globulin, alemtuzumab) or non-depleting, interleukin-2 receptor blocking antibodies (basiliximab). These agents are administered intravenously around the time of the transplant procedure (generally within the first week), with the idea being to provide maximum immunosuppression at the time of engraftment thereby minimizing the possibility of early rejection.

Maintenance immunosuppression protocols in the United States most often utilize 3 classes of medications in order to gain synergistic effects while minimizing toxicities by decreasing dosages. Most US protocols use calcineurin-inhibitor (CNI)-based drug (tacrolimus, cyclosporine), an antiproliferative agent (mycophenolic acid, enteric-coated mycophenolic acid, azathioprine), and

corticosteroids (prednisone). These orally administered medications are commenced within a few days after the transplant and are continued through the course of allograft function.[42] Having been discovered and brought to the field of organ transplantation only within the last 10 to 15 years, inhibitors of 2 additional pathways of cellular immunity are used to a lesser extent as maintenance immunosuppressants. These medications include agents that provide co-stimulatory blockade (belatacept) and mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus).

Lastly treatment of rejection first requires determination whether the rejection is T-cell mediated (cellular) or antibody-mediated (humoral). Since cellular rejection is lymphocyte mediated, corticosteroids and lymphocyte depleting agents comprise the first 2 lines of anti-rejection medications. If the rejection also has an antibody mediated component, strategies to modulate and/or reduce recipient antibody production are undertaken. These include administration of intravenous gamma globulin (IVIG), antibodies against B-cells (rituximab), proteasome inhibitors (bortezomib), complement inhibitors (eculizumab), and plasmapheresis.

7. Complications of Renal Transplantation

7.1 Surgical Complications

Surgical complications following kidney transplantation can involve the vascular, urinary and lymphatic systems. Immediate vascular complications that impair perfusion to the kidney or to the distal extremity must be addressed promptly as the limb or kidney may be lost. Restoration of flow may require repair of an intimal flap or dissection, thrombectomy and/or vascular bypass. Late complications of transplant renal artery stenosis are successfully treated with angioplasty and stent placement.

Urological complications include urinary fistula and ureteral strictures. Urinary fistulas or urine leaks typically occur from necrosis of the distal ureter, usually at the site of ureteroneocystostomy. Urine leaks most often present within the first 2 weeks following surgery and are manifest as a decline in urine output, rise in serum creatinine, worsening pain, swelling or leakage along the incision. Urine leaks typically do not resolve without return to the operating room, excision of the devitalized segment of ureter and re-anastomosis to the bladder.

Strictures at the ureterovesical anastomosis can develop several months following transplantation and are felt to be secondary to ischemia. In addition to technical causes, infectious and possibly immunologic factors may play a role in the occurrence of an anastomotic stricture. Most often strictures present with graft dysfunction leading to imaging that demonstrates hydronephrosis proximal to the stricture. In selected cases with narrowing of 1 cm or less, endourologic approaches may be effective; however, durable repair of ureterovesical stricture often requires open revision of the ureterovesical anastomosis.

Lymphocele formation is a common complication following renal transplantation, occurring at rates from 1% to 26%. The incidence of symptomatic lymphocele is approximately 5% and treatment of these may be required when there is associated hydronephrosis from obstructive uropathy or iliac

vein compression leading to deep venous thrombosis. Therapeutic options for symptomatic lymphoceles include external treatment via percutaneous approaches (aspiration, sclerotherapy, drainage) and internal drainage via surgical approaches (laparoscopic and open). In general, intraperitoneal drainage of a lymphocele offers the lowest recurrence rates. [43]

The prevalence of post-transplant acute urinary retention (AUR) resulting in discharge with an indwelling catheter or readmission varies from 6%-46%. BPH related AUR is typically discovered immediately after or within a few months of renal transplant. Therapy with alpha blocker, 5-alpha reductase inhibitor, or both should be considered in most. Recalcitrant prostate obstruction post-transplant may require surgical treatment. A delayed surgical approach of 1-2 months post-transplant is recommended in order to decrease infection risks in newly immunosuppressed patients and to ensure the ureterovesical anastomosis has healed.

Microscopic hematuria (MH) is common and should be viewed as a unique entity compared to MH in the general population. New MH immediately following a renal transplant should be expected and is unlikely related to malignancy in those with adequate pre-transplant evaluation. Without supporting evidence, it is reasonable to assume surgical related MH should abate within 6 months post-transplant. Beyond this time, patients who have persistent MH or those who develop de novo MH should undergo standard MH evaluation with a CT urogram or magnetic resonance urography and cystoscopy.

Obstructing urolithiasis in the allograft may not lead to renal colic due to denervation and can result in delayed diagnosis. Percutaneous nephrostomy placement is the initial treatment of choice for any kidney transplant with urosepsis or acute kidney injury due to possible challenges with retrograde access. Conservative management can be undertaken if the stone is small, ≤ 4-5mm in size, and if renal function is near baseline. Flexible ureteroscopy is superior to semi-rigid for accessing the superior transplant ureteral orifice. A stone size reaching 1.5cm is a practical indication for percutaneous nephrolithotomy (PCNL). Extracorporeal shock wave lithotripsy (ESWL) is discouraged as the initial approach because roughly 50% or more of patients require an additional procedure to achieve stone free status.

7.2 Medical Complications

Successful kidney transplantation requires immune suppression thereby predisposing the recipient to infectious complications. Infections immediately after the transplant procedure are most often post-surgical and not unique to immunosuppressed patients. Opportunistic infections commonly associated with transplant immunosuppression tend to occur after the first month and up to 6 months post-transplant. These infections can be secondary to viral (BK, CMV, EBV, HSV, hepatitis B and C virus), bacterial (nocardia, listeria, tuberculosis), fungal (pneumocystis, aspergillus, cryptococcus) and parasitic (strongyloides, toxoplasma, leishmania, trypanosoma) pathogens. Following this time period patients who have had stable allograft function have immunosuppressive medication levels decreased, thus minimizing the potential for infection. Patients with repeated episodes of rejection requiring intensification of immunosuppression remain susceptible to these pathogens. Late viral

reactivation can occur in another subset of patients. [44,45]

SARS-CoV-2, the novel coronavirus that causes COVID-19, first spread to humans in late 2019 and created a worldwide pandemic in 2020. Kidney transplant recipients may be at increased risk for infection and/or severe complications related to COVID-19 given their immunosuppressed state and often frequent encounters with the healthcare system. An early report of hospitalized solid organ transplant recipients in New York City, New York suggested mortality from COVID-19 may be close to 20%. [46] A subsequent multicenter analysis of critically ill COVID-19 patients found similar mortality rates between solid organ transplant recipients and patients who hadn't received a transplant. [47] While to date there have not been any documented cases of donor-derived SARS-CoV-2 infections, the virus has been detected in kidney tissue from autopsy specimens in patients who died of COVID-19. [48] Therefore, viral testing of all deceased and living donors is generally recommended. Pre-operative testing of all potential renal transplant recipients is also advised, especially as extent to which induction immunosuppression may exacerbate an asymptomatic COVID-19 infection is unknown.

Urinary tract infections are a common complication following renal transplantation. They should be diagnosed by culture results and treated with therapy based on antibiotic sensitivity. Recurrent or complicated infections may benefit from an infectious disease consultation.

Immunosuppression increases the incidence of cancer several fold compared to the general population. Transplant recipients have a 5-year cumulative incidence of cancer slightly greater than 4%. Skin cancer is the most frequent malignancy post-transplantation with squamous cell carcinoma and basal cell carcinoma accounting for 95% of skin cancers.

In addition to side effects related to their mechanism of action, renal transplant immunosuppressive medications are also associated with adverse effects that are unrelated to the immune system (**Table 5**). Calcineurin-inhibitor medications (tacrolimus, cyclosporine) cause an acute and chronic nephrotoxicity, hypertension, new onset diabetes and neurotoxicity. Mycophenolic acid, the principal antiproliferative agent, can result in gastrointestinal side effects of diarrhea and vomiting and leukopenia from bone marrow suppression. Side effects from chronic corticosteroid administration include diabetes, increase fragility of skin and soft tissues, osteoporosis and cataract formation.

Table 5. Immunosuppressive Medications in Renal Transplantation

Medication Category	Medications	Main adverse effects/toxicities
Induction Agents		
Lymphocyte depleting Abs	Thymoglobulin Alemtuzumab	Opportunistic infections, malignancy, fever, thrombocytopenia, serum sickness
Maintenance Agents		
Calcineruin inhibitors	Cyclosporine A Tacrolimus	Nephrotoxicity, neurotoxicity, new onset diabetes, hyperkalemia, hypophosphatemia
Antiproliferative agents	Mycophenolic acid Azathioprine	GI-nausea, diarrhea, colitis, leukopenia
Corticosteroids	Prednisone	Diabetes, weight gain, bone loss, cataract formation
MTOR-inhibitors	Sirolimus Everolimus	Hypertension, edema, proteinuria, impaired wound healing, lymphocele, hypertriglyceridemia
Co-stimulation blockade	Abatacept Belatacept	Hypertension, hypotension, infusion reaction
Anti-rejection Agents		
Corticosteroids	Prednisone	Diabetes, weight gain, bone loss, cataract formation

Lymphocyte depleting Abs	Thymoglobulin Rituximab	Opportunistic infections, malignancy, fever, thrombocytopenia, serum sickness
Proteosome inhibitors	Bortezomib	GI-nausea, diarrhea, constipation, hematologic-thrombocytopenia, anemia, peripheral neuropathy
Immunomodulators	Intravenous gamma globulin	Infusion reactions-headache, myalgia, backache, acute renal failure, nephropathy, hypersensitivity
Complement inhibitor	Eculizumab	Headache, back pain Infection (meningococcus)

Since the calcineurin inhibitors are nephrotoxic, prescribing additional medications to renal transplant recipients must avoid additional toxicity. All drugs should be based on the degree of renal function. These medications are metabolized by the liver. If medications are prescribed with effects on metabolism, the blood level of the calcineurin inhibitor needs to be monitored closely (**Table 6**).

Table 6. Drugs which effect levels of calcineurin inhibitors (cyclosporine and tacrolimus)

Decrease	Increase	
Rifampin	Diltiazem	Fluconazole
Rifabutin	Verapamil	Itraconazole
Isoniazid	Nicardipine	Clotrimazole
Phenobarbital	Erythromycin	Bromocriptine
Phenytoin	Clarithromycin	Danazol
Carbamazepine	Ketoconazole	Cimetidine
	Methylprednisolone	Metoclopromide

8. Other Resources

AUA Transplant Podcast

9. Podcasts

AUAUniversity Podcast Series: Episode No. 93

Videos

AUA 2019 Panel Discussion: Urologic Malignancy and Transplant Patients

Renal Transplantation

Presentations

Renal Transplant Presentation 1

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