Kidney Transplantation

I. Kidney Transplantation

Aetna considers kidney transplantation medically necessary when all of the following criteria below are met:

A. Member has completed an evaluation and been accepted by the kidney transplant committee at the kidney transplantation center. Note: Frequently requests for evaluation for transplantation are confused with requests for the transplantation itself. While the transplant evaluation of persons with kidney disease may be indicated, the medical necessity for transplantation itself depends on the results of the evaluation; and

B. Member meets transplanting institution's protocol eligibility criteria regarding age; and

C. Absence of malignancy (except for non-melanomatous skin cancers or low-grade prostate cancer) or the malignancy has had curative therapy (e.g., surgical resection of non-invasive squamous cell or basal cell skin cancer) or the estimated risk of recurrence of the malignancy is less than 10% within the next 2 years. For example, renal cell carcinoma treated by nephrectomy with no evidence of metastatic disease 2 years after the nephrectomy, prostate cancer with negative prostate-specific antigen levels after treatment, surgically treated colon cancer, thyroid cancer...
with normal thyroglobulin levels after therapy, and others. Women should have a negative Pap smear within the past 3 years and mammography, where indicated, within the past 2 years; and

D. Absence of systemic infection; and

E. Absence of symptomatic HIV infection, as defined by all of the following:

1. CD4 count greater than 200 cells/mm³ for more than 6 months; and
2. HIV-1 RNA (viral load) undetectable; and
3. On stable anti-viral therapy for more than 3 months; and
4. No other complications from AIDS, such as opportunistic infection (e.g., aspergillus, coccidiomycosis, resistant fungal infections, tuberculosis), Kaposi’s sarcoma or other neoplasms.

F. Attending physician determines that there is no prohibitive cardiovascular risk; and

G. Attending physician determines that there is no prohibitive pulmonary risk; and

H. Attending physician determines that there is no prohibitive hepatic risk; and

I. Severity of disease

1. Member is already on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD); or
2. Member has chronic renal failure with anticipated deterioration to end stage renal disease, where member is seeking precertification for cadaveric kidney transplantation or
3. Member has end stage renal disease, evidenced by a creatinine clearance below 20 ml/min or development of symptoms of uremia, and member is seeking precertification for a living donor kidney transplantation.

**Note:** Given waiting periods for cadaveric donors averaging 1 to 4 years, kidney transplantation is considered medically necessary for persons with severe chronic renal failure with anticipated progression to end stage renal disease. Severe chronic renal failure is defined as a creatinine clearance of less than 30 ml/min.

J. Kidney transplant is not considered medically necessary for persons who do not meet the transplanting institution's protocol selection criteria, or in the absence of a protocol, for persons who have any of the following (not an all-inclusive list):

- Active vasculitis; or
- Age over 70 years with severe co-morbidities; or
- Life threatening extra-renal congenital abnormalities; or
- Ongoing alcohol or drug abuse; or
- Severe neurological or mental impairment, in persons without adequate social support, such that the person is unable to adhere to the regimen necessary to preserve the transplant; or
- Untreated coagulation disorder

II. Combined Kidney/Pancreas Transplantation

For persons undergoing kidney transplantation due to diabetic nephropathy, a combined kidney/pancreas transplantation may be considered medically necessary under some circumstances (see CPB 0587 - Pancreas Kidney Transplantation (../500_599/0587.html)). Other multi-organ transplants (e.g., kidney/heart, liver/kidney) should be referred to Aetna's National Medical Excellence Program for review.

III. Renal Autotransplantation and Ex-Vivo Bench Surgery

Aetna considers autotransplantation and ex-vivo repair medically necessary where repair of the kidney, ureter, renal artery or its branches are not amenable to in-situ reconstruction.

IV. Gene Microarrays for Diagnosis of Rejection

Aetna considers the use of gene microarrays (e.g., the Kidney Microscope Diagnostic System (MMDx-Kidney)) in diagnosis of rejection of kidney transplantation experimental and investigational because of insufficient evidence of their effectiveness.

V. Evaluation of Urine Immunocytology

Aetna considers evaluation of urine immunocytology for T cells experimental and investigational for the diagnosis of acute kidney rejection because its role has not been established.

VI. Belatacept (Nulojix)

Aetna considers the use of belatacept (Nulojix) medically necessary for the prevention of acute rejection in kidney transplant recipients who are sero-positive for the Epstein Barr virus (EBV).
Aetna considers belatacept experimental and investigational for the prophylaxis of organ rejection in other transplanted organs because its effectiveness for the prevention of acute rejection in organ transplant other than kidney has not been established.

VII. Soluble CD30 Level

Aetna considers measurement of pre-transplantation soluble CD30 level as a predictor of acute rejection in kidney transplantation experimental and investigational because its clinical value has not been established.

VIII. Experimental Markers of Acute Rejection

Aetna considers measurement of cytokines (e.g., cytokine-14, interleukin-1 beta (IL-1β), IL-2, IL-4, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-alpha (TNF-α); not an all-inclusive list) for the diagnosis of acute renal allograft rejection experimental and investigational because the effectiveness of this approach has not been established.

IX. Equine Anti-Thymocyte Immune Globulin

Aetna considers equine anti-thymocyte immune globulin (Atgam) medically necessary for the following indications:

A. prophylaxis or treatment of allograft rejection episodes in renal transplantation in combination with conventional therapy; and
B. moderate to severe aplastic anemia in persons who are not suitable candidates for bone marrow transplantation.

Aetna considers equine antithymocyte immune globulin experimental and investigational for all other indications.

X. Experimental Markers of Rejection Risk

Aetna considers (i) Human leukocyte antigen-G-14-base-pair-insertion/deletion polymorphism, (ii) Interleukin-2-330 T/G promoter and (iii) Interleukin-10-1082 (G/A) promoter polymorphisms testing for evaluating the risk of developing kidney graft rejection experimental and investigational because the effectiveness of this approach has not been established.
XI. Bisphosphonates

Aetna considers bisphosphonates for the treatment of low bone mineral density after kidney transplantation experimental and investigational because their effectiveness of this indication has not been established.

XII. Pre-Conditioning Therapy

Aetna considers pre-conditioning therapy (e.g., immune-adsorption or rituximab) in ABO-incompatible kidney transplantation experimental and investigational because the effectiveness of this approach has not been established.

XIII. Biomarkers of Acute Kidney Injury

Aetna considers urinary neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid-binding protein (L-FABP) as biomarkers of acute kidney injury following kidney transplantation experimental and investigational because the effectiveness of this approach has not been established.

XIV. FASL mRNA

Aetna considers Fas ligand (FASL) mRNA detection as a diagnostic marker for acute renal rejection experimental and investigational because the effectiveness of this approach has not been established.

XV. Urinary Monocyte Chemoattractant Protein-1

Aetna considers urinary monocyte chemoattractant protein-1 (MCP-1/CCL2) for detection and monitoring of renal graft rejection experimental and investigational because the effectiveness of this approach has not been established.

XVI. Donor-Derived Cell-Free DNA Testing

Aetna considers donor-derived cell-free DNA testing (e.g., Allosure) for monitoring acute rejection following renal transplantation experimental and investigational because the effectiveness of this approach has not been established.

XVII. Measurement of Angiotensin II Type 1 (AT1) Receptors or AT1 Antibodies for Evaluation of Renal Transplantation Candidates / Recipients
Aetna considers measurement of angiotensin II type 1 (AT1) receptors or AT1 antibodies for evaluation of renal transplantation candidates / recipients experimental and investigational because the effectiveness of this approach has not been established.

XVIII. Complement Inhibitors (e.g., Eculizumab) for the Treatment of Antibody-Mediated Rejection in Renal Transplantation Recipients

Aetna considers complement inhibitors (e.g., eculizumab) for the treatment of antibody-mediated rejection in renal transplantation recipients experimental and investigational because their effectiveness for this indication has not been established.

XIX. Belimumab for the Treatment of Antibody-Mediated Rejection in Renal Transplantation Recipients

Aetna considers belimumab for the treatment of antibody-mediated rejection in renal transplantation recipients experimental and investigational because its effectiveness for this indication has not been established. See CPB 0818 - Belimumab (Benlysta) (/800_899/0818.html).

XX. Genotyping Donors and Recipients Before Renal Transplantation

Aetna considers genotyping donors and recipients before renal transplantation experimental and investigational because its effectiveness for this indication has not been established.

Background

Chronic renal failure (CRF) occurs in approximately 2 out of 10,000 people. It results in the accumulation of fluid and waste products in the body, causing azotemia and uremia. Azotemia is the build-up of nitrogen waste products in the blood. It may occur without symptoms. Uremia is the state of ill health resulting from renal failure since most body systems are affected by CRF. Treatment of the underlying disorders may help prevent or delay development of CRF.

Chronic renal failure is slowly progressive over a number of years and most often results from any disease that causes gradual destruction of the internal structures of the kidneys. It can range from mild dysfunction to severe kidney failure, termed end stage renal disease (ESRD). In the early stages, there may be no symptoms. In fact, progression may be so gradual that
symptoms do not occur until kidney function is less than 1/10 of normal. Because of the reversible nature of acute renal failure, all patients with this diagnosis should be supported with dialysis, at least for some period of time, to allow return of renal function.

The 3 diseases most commonly leading to CRF and treated by kidney transplantation are (i) type 1 diabetes mellitus, (ii) glomerulonephritis, and (iii) hypertensive nephrosclerosis, accounting for about 75% of the total candidate population. Numerous subsets of patients in several study populations have shown that patients have a better survival if they receive a renal transplant than if they remain on dialysis therapy.

Patients with ESRD have 3 options for renal replacement therapy: (i) hemodialysis; (ii) chronic ambulatory peritoneal dialysis; or (iii) transplantation. The choice should be based on the relative risks and benefits. With the increasing appreciation that transplantation results are superior to those of chronic dialysis, the indications for transplantation have been broadened. Improvements in peri-operative care and immunosuppression have allowed many patients who would previously have been denied transplantation consideration as acceptable candidates. The best recipients for transplantation are young individuals whose renal failure is not due to a systemic disease that will damage the transplanted kidney or cause death from extra-renal causes.

The time a patient has spent on dialysis is an independent predictor of a poorer outcome from renal transplantation. Pre-emptive renal transplantation generally leads to better outcomes than transplantation after dialysis is initiated, and should be pursued in most cases for live donor transplants. The current shortage of cadaveric kidneys makes it unlikely that pre-emptive transplants will be a practical option for recipients of cadaveric kidney transplants.

No specific cause of intrinsic and irreversible renal failure is considered a contraindication to kidney transplantation. Nonetheless, all patients still should have reversible causes of renal dysfunction excluded before considering renal replacement therapy e.g., obstructive nephropathy has to be removed, chronic pyelonephritis secondary to recurrent infection has to be adequately treated, and reflux has to be fixed.

The evaluation of all transplant candidates, in addition to a standard medical work-up, should include cytomegalovirus (CMV) antibody titer; creatinine clearance; serology for syphilis, and hepatitis B (HBV) and C (HCV) viruses; evaluation of parathyroid status; coagulation profile; Pap smear; ABO and histocompatibility typing; urologic evaluation (including a voiding
Patients with renal failure induced by diabetes (Kimmelstiel-Wilson disease) make up the greatest population of patients currently referred for transplantation. Actually, this has become the treatment of choice because persons with diabetes clearly do better with transplantation than with dialysis. In fact, both graft and patient survival for 1 to 2 years are reported to be as good in persons with diabetes as in other patients, whereas on chronic dialysis, less than 20% of persons with diabetes survive 5 years. If diabetic patients can undergo transplantation before extensive damage occurs in other organs, such as the eye and heart, rehabilitation will be more satisfactory. Even patients with diseases in which the transplanted kidney may eventually be damaged by recurrent disease (e.g., lupus erythematosus, cystinosis, and amyloidosis) are often better palliated by transplantation than by dialysis. Indeed, the current results of transplantation mandate serious consideration of this therapy in virtually any patient with terminal renal disease. Not only is the quality of life far better with transplantation than with dialysis, but because the mortality of patients in the first year after transplantation is now less than 5%, survival is also superior.

Careful attention must be given to eradication of all infections including those of the urinary tract, lungs, teeth, and skin. Since cardiovascular complications are as common as infection as a cause of post-transplantation mortality, the patient's cardiovascular status should be carefully evaluated and optimized. In older patients and diabetic patients, this might require stress testing, cardiac catheterization, or even pre-transplant coronary artery bypass. Age is never an absolute contraindication for kidney transplantation. Although infants have had successful transplantations, most centers maintain infants on dialysis until body size is increased to 10 to 20 kg. Older patients are becoming more numerous in transplant clinics. Older age (greater than 65 years) never precludes transplantation, but it increases the risk of complications. Transplant centers usually encourage older patients who have multiple medical problems (rather than isolated kidney failure) to remain on dialysis. On both ends of the age spectrum, however, transplantation is becoming more common. Malignancy is considered a contraindication for kidney transplantation, as is severe atherosclerotic or pulmonary disease. Patients with active liver disease are also usually excluded. Both hepatitis B and C can result in eventual liver failure in some patients after transplantation.

The proper timing of transplantation is a delicate decision because the progression of renal dysfunction is variable and premature imposition of the risks of transplantation is not justified. However, dialysis or transplantation should not be withheld until advanced uremic symptoms,
such as pericarditis, cardiac failure, severe anemia, osteodystrophy and neuropathy, ensure because these complications may become irreversible.

There are 3 sources of donor kidneys for kidney transplantation: (i) living related donors; (ii) cadaver donors; and (iii) living unrelated donors. A donor left kidney is usually transplanted to the right iliac fossa, with the renal artery anastomosed end-to-end to the hypogastric artery, and the renal vein end-to-end to the common iliac vein. The ureter is implanted into the bladder and under special conditions a uretero-ureteral anastomosis or uretero-pyelostomy may be performed. Autotransplantation has developed as an outgrowth of the technique used in renal transplantation. The simultaneous development of an apparatus that could preserve kidneys extracorporeally for long periods of time and of preservation solutions led to extracorporeal renal repair (work-bench surgery) and subsequent autotransplantation for conditions mentioned above.

On rare occasions, kidneys with lesions of the renal artery or its branches are not amenable to in-situ reconstruction. In these circumstances, temporary removal of the kidney, ex-vivo preservation, microvascular repair (work-bench surgery), and autotransplantation may permit salvage.

Some examples of clinical conditions where the renal artery or its branches are not amenable to in-situ reconstruction such that a person might benefit from autotransplantation and/or ex-vivo repair include but are not limited to:

- Abdominal aortic aneurysms that involve the origin of the renal arteries; or
- Disease of the major vessels extends beyond the bifurcation of the main renal artery into the segmental branches; or
- Extensive atheromatous aortic disease when an operation on the aorta itself may prove hazardous; or
- Multiple vessels supplying the affected kidney are involved; or
- Persons who have large aneurysms, arteriovenous fistulas, or malformations of the kidney; or
- Traumatic arterial injuries.

Patients with chronic kidney disease have significant abnormalities of bone remodeling and mineral homeostasis and are at increased risk of fracture. The fracture risk for kidney transplant recipients is 4 times that of the general population and higher than for patients on dialysis. Ebeling (2007) noted that organ transplant candidates should be assessed and pre-transplantation bone disease should be treated. Preventive therapy initiated in the immediate post-transplantation period is indicated in patients with osteopenia or osteoporosis, as further
bone loss will occur in the first several months following transplantation. Long-term organ transplant recipients should also have bone mass measurement and treatment of osteoporosis. Bisphosphonates are the most promising approach for the management of transplantation osteoporosis. Active vitamin D metabolites may have additional benefits in reducing hyperparathyroidism, particularly after kidney transplantation. The author stated that large, multicenter treatment trials with oral or parenteral bisphosphonates and calcitriol are recommended.

In a Cochrane review, Palmer et al (2007) assessed the use of interventions for treating bone disease following kidney transplantation. Randomized controlled trials (RCTs) and quasi-RCTs comparing different treatments for kidney transplant recipients of any age were selected. All other transplant recipients, including kidney-pancreas transplant recipients were excluded. Two authors independently evaluated trial quality and extracted data. Statistical analyses were performed using the random effects model and the results expressed as relative risk (RR) with 95% confidence intervals (CI) for dichotomous variables and mean difference (MD) for continuous outcomes. A total of 24 trials (n = 1,299) were included. No individual intervention (bisphosphonates, vitamin D sterol or calcitonin) was associated with a reduction in fracture risk compared with placebo. Combining results for all active interventions against placebo demonstrated any treatment of bone disease was associated with a reduction in the RR of fracture (RR 0.51, 95% CI: 0.27 to 0.99). Bisphosphonates (any route), vitamin D sterol, and calcitonin all had a beneficial effect on the bone mineral density (BMD) at the lumbar spine. Bisphosphonates and vitamin D sterol also had a beneficial effect on the BMD at the femoral neck. Bisphosphonates were more effective in preventing BMD loss when compared head-to-head with vitamin D sterols. Few or no data were available for combined hormone replacement, testosterone, selective estrogen receptor modulators, fluoride or anabolic steroids. Other outcomes including all-cause mortality and drug-related toxicity were reported infrequently. The authors concluded that treatment with bisphosphonates, vitamin D sterol or calcitonin after kidney transplantation may protect against immunosuppression-induced reductions in BMD and prevent fracture. However, they state that adequately powered clinical studies are needed to ascertain if bisphosphonates are better than vitamin D sterols for fracture prevention in this population. Moreover, the optimal route, timing, and duration of administration of these interventions remains unknown.

Acute rejection is an immune process that begins with the recognition of the allograft as non-self and ends in graft destruction. Histological features of the allograft biopsy are currently used for the differential diagnosis of allograft dysfunction. In view of the safety and the opportunity for repetitive sampling, development of non-invasive biomarkers of allograft status is an important objective in transplantation. Khatri and Sarwal (2009) stated that in the past 10 years, microarray technology has revolutionized biological research by allowing the screening of tens of thousands of genes simultaneously. These investigators reviewed recent studies in organ
transplantation using microarrays and highlighted the issues that should be addressed in order to use microarrays in the diagnosis of rejection. Microarrays have been useful in identifying potential biomarkers for chronic rejection in peripheral blood mononuclear cells, novel pathways for induction of tolerance, and genes involved in protecting the graft from the host immune system. Microarray analysis of peripheral blood mononuclear cells from chronic antibody-mediated rejection has identified potential non-invasive biomarkers. In a recent study, correlation of pathogenesis-based transcripts with histopathological lesions is a promising step towards inclusion of microarrays in clinics for organ transplants. The authors concluded that despite promising results in diagnosis of histopathological lesions using microarrays, the low dynamic range of microarrays and large measured expression changes within the probes for the same gene continue to cast doubts on their readiness for diagnosis of rejection. They stated that more studies are needed to resolve these issues. Dominating expression of globin genes in whole blood poses another challenge for identification of non-invasive biomarkers. In addition, studies are also needed to demonstrate effects of different immunosuppression therapies and their outcomes.

Hartono et al (2010) noted that urinary cell and peripheral blood cell mRNA profiles have been associated with acute rejection of human renal allografts. Emerging data support the idea that development of non-invasive biomarkers predictive of antibody-mediated rejection is feasible. The demonstration that intra-graft microRNA expression predicts renal allograft status suggests that non-invasively ascertained microRNA profiles may be of value. These researchers stated that they are pleased with the progress to date, and anticipate clinical trials investigating the hypotheses that non-invasively ascertained mRNA profiles will minimize the need for invasive biopsy procedures, predict the development of acute rejection and chronic allograft nephropathy, facilitate preemptive therapy capable of preserving graft function, and facilitate personalization of immunosuppressive therapy for the allograft recipient.

Mihovilovic and colleagues (2010) evaluated urine immunocytology for T cells as a method for non-invasive identification of patients with acute renal allograft rejection in comparison to renal biopsy. In this prospective study, a cohort of 56 kidney, or kidney-pancreas transplant recipients was included. Patients either received their transplant at the University Hospital "Merkur", or have been followed at the "Merkur" Hospital. Patients were subject to either protocol or indication kidney biopsy (a total of 70 biopsies), with simultaneous urine immunocytology (determination of CD3-positive cells in the urine sediment). Acute rejection was diagnosed in 24 biopsies; 23 episodes were T-cell mediated (6 grade IA, 5 grade IB, 1 grade IIA, 1 grade III and 10 borderline), while in 1 case acute humoral rejection was diagnosed. A total of 46 biopsies did not demonstrate acute rejection. CD3-positive cells were found in 21 % of cases with acute rejection and in 13 % of cases without rejection (non-significant). A finding of CD3-positive cells in urine had a sensitivity of 21 % and specificity of 87 % for acute rejection (including borderline).
with positive predictive value of 45% and negative predictive value of 68%. The authors concluded that although tubulitis is a hallmark of acute T cell-mediated rejection, detection of T cells in urine sediment was insufficiently sensitive and insufficiently specific for diagnosing acute rejection in this cohort of kidney transplant recipients.

Belatacept, a selective T-cell co-stimulation blocker, is a cytotoxic T-lymphocyte-associated antigen 4-immunoglobulin. It is designed to block CD28, a critical activating receptor on T cells, by binding and saturating its ligands B7-1 and B7-2. In phase II and III clinical trials, belatacept was compared with cyclosporine (in combination with basiliximab, mycophenolate mofetil, and steroids). Advantages observed with belatacept include superior graft function, preservation of renal structure and improved cardiovascular risk profile. Concerns associated with belatacept are a higher frequency of cellular rejection episodes and more post-transplant lymphoproliferative disorder (PTLD) cases especially in Epstein-Barr virus (EBV) sero-negative patients, who should be excluded from belatacept-based regimens (Wekerle and Grinyo, 2012).

On June 15, 2011, the Food and Drug Administration approved belatacept (Nulojix) for the prevention of acute rejection in adult kidney transplant recipient. Nulojix is approved for use with other immunosuppressants, specifically basiliximab, corticosteroids, and mycophenolate mofetil. The approval of Nulojix was based on 2 open-label, randomized, multi-center, controlled phase III clinical trials that enrolled more than 1,200 patients and compared 2 dose regimens of Nulojix with another immunosuppressant, cyclosporine. These trials demonstrated that the recommended Nulojix regimen is safe and effective for the prevention of acute organ rejection.

Nulojix carries a Boxed Warning for an increased risk of developing PTLD. The risk of PTLD is higher for transplant patients who have never been exposed to EBV. Transplant patients who have not been exposed to EBV have more difficulty mounting an effective immune response to the virus if they get infected after transplant; typically they get exposed to the virus at time of transplant, as it is carried in around 80% of donated organs. Patients should be tested for EBV and should only receive Nulojix if the test shows they have already been exposed to EBV. Another Boxed Warning on the Nulojix label, as well as labels of other immunosuppressants, warns of an increased risk of serious infections and other cancers. Common adverse reactions observed in transplant patients in the trials included anemia, constipation, kidney or bladder infection, and swollen legs, ankles, or feet. Any transplant patients, including those receiving Nulojix, should limit the amount of time spent in sunlight because of the risk of skin cancer and should not get live vaccines because of the risk of infection.

Chen and colleagues (2012) stated that the question of whether high pre-transplantation soluble CD30 (sCD30) level can be a predictor of kidney transplant acute rejection (AR) is under debate. These investigators performed a meta-analysis on the predictive efficacy of sCD30 for
AR in renal transplantation. PubMed (1966 to 2012), EMBASE (1988 to 2012), and Web of Science (1986 to 2012) databases were searched for studies concerning the predictive efficacy of sCD30 for AR after kidney transplantation. After a careful review of eligible studies, sensitivity, specificity, and other measures of the accuracy of sCD30 were pooled. A summary receiver operating characteristic curve was used to represent the overall test performance. A total of 12 studies enrolling 2,507 patients met the inclusion criteria. The pooled estimates for pre-transplantation sCD30 in prediction of allograft rejection risk were poor, with a sensitivity of 0.70 (95% CI: 0.66 to 0.74), a specificity of 0.48 (95% CI: 0.46 to 0.50), a positive likelihood ratio of 1.35 (95% CI: 1.20 to 1.53), a negative likelihood ratio of 0.68 (95% CI: 0.55 to 0.84), and a diagnostic odds ratio of 2.07 (95% CI: 1.54 to 2.80). The area under curve of the summary receiver operating characteristic curve was 0.60, indicating poor overall accuracy of the serum sCD30 level in the prediction of patients at risk for AR. The authors concluded that the results of the meta-analysis showed that the accuracy of pre-transplantation sCD30 for predicting post-transplantation AR was poor. They stated that prospective studies are needed to clarify the usefulness of this test for identifying risks of AR in transplant recipients.

Lv and colleagues (2012) noted that results from published studies on the association of donor or recipient interleukin (IL)-6 -174G/C (rs1800795) polymorphism with AR of renal allograft are conflicting. These investigators performed a meta-analysis to estimate the possible association. Studies were identified by searching PUBMED and EMBASE until July 1, 2011. Meta-analysis was performed in a fixed/random effects model using Revman 5.0.25 and STATA10.0. A total of 7 studies addressing the association between donor high producer genotype (G/G and G/C) of IL-6 -174G/C polymorphism and AR of renal allograft were identified. Pooled odds ratio (OR) based on 341 cases (whose recipient developed AR) and 702 controls (whose recipient did not develop AR) was 0.59 (95% CI: 0.26 to 1.33; p = 0.20), with a strong between-study heterogeneity. No association was observed in the subgroup analysis based on ethnicity. A total of 13 studies evaluating the association between recipient IL-6 -174G/C polymorphism and AR were identified. Pooled OR based on 451 cases (patients did not develop AR) and 848 controls was 1.00 (95% CI: 0.72 to 1.37; p = 0.98), with a weak between-study heterogeneity. The authors concluded that donor high producer genotype (G/G and G/C) of IL-6 -174G/C polymorphism had a tendency of decreased risk for AR, although it was not statistically significant. Recipient high producer genotype was not associated with AR of renal allograft. Moreover, they stated that additional well-designed studies with larger sample size are needed to support these findings, especially for the association between donor high producer genotype (G/G and G/C) of IL-6 -174G/C polymorphism and acute renal allograft rejection.

In an observational cross-sectional study, De Serres et al (2012) determined the utility of a non-invasive cytokine assay in screening of AR. A total of 64 patients from 2 centers were recruited upon admission for allograft biopsy to investigate acute graft dysfunction. Blood was collected
before biopsy and assayed for a panel of 21 cytokines secreted by peripheral blood mononucleated cells (PBMCs). Patients were classified as acute rejectors or non-rejectors according to a classification rule derived from an initial set of 32 patients (training cohort) and subsequently validated in the remaining patients (validation cohort). Although 6 cytokines (interleukin-1 beta [IL-1β], IL-6, tumor necrosis factor-alpha [TNF-α], IL-4, granulocyte-macrophage colony-stimulating factor [GM-CSF], and monocyte chemoattractant protein-1 [MCP-1]) distinguished acute rejectors in the training cohort, logistic regression modeling identified a single cytokine, IL-6, as the best predictor. In the validation cohort, IL-6 was consistently the most accurate cytokine (area under the receiver-operating characteristic curve, 0.85; p = 0.006), whereas the application of a pre-specified cut-off level, as determined from the training cohort, resulted in a sensitivity and specificity of 92 % and 63 %, respectively.

Secondary analyses revealed a strong association between IL-6 levels and AR after multivariate adjustment for clinical characteristics (p < 0.001). The authors concluded that in this pilot study, the measurement of a single cytokine can exclude AR with a sensitivity of 92 % in renal transplant recipients presenting with acute graft dysfunction. Moreover, they stated that prospective studies are needed to determine the utility of this simple assay, particularly for low-risk or remote patients.

Wu and associates (2013) stated that cytokines have been implicated in the AR of solid organ transplantation. Many studies have investigated the association between recipient or donor IL-4 polymorphism and AR, with different studies reporting inconclusive results. These investigators searched PUBMED and EMBASE until June 2012 to identify eligible studies investigating the association between IL-4 polymorphism with AR after solid organ transplantation. Statistical analysis was performed using STATA10.0. A total of 12 studies were included. Pooled ORs suggested (i) no significant association was detected between recipient or donor IL-4 -590C/T polymorphism and acute rejection of solid allograft; (ii) no significant association was detected between recipient IL-4 -33C/T polymorphism and AR of solid allograft; (iii) when stratified by transplantation type, IL-4 -590C/T polymorphism was associated with AR of liver transplantation (T/T+C/T versus C/C: OR = 0.36, 95 % CI: 0.14 to 0.90); and (iv) significantly decreased risk of AR was detected in recipient IL-4 -590*T-negative/donor T-positive genotype pairs than all other recipient-donor IL-4 -590T/C pairs (OR = 0.14, 95 % CI: 0.03 to 0.66). The authors concluded that the findings of this meta-analysis suggested that recipient IL-4 -590C/T polymorphism was associated with AR of liver transplantation, but not renal or heart transplantation. It was also suggested that combined recipient IL-4 -590*T-negative/donor T-positive genotype may suffer decreased risk of AR of solid allograft. Moreover, they stated that further well-designed studies with larger sample size were needed to verify these findings, with focus on the association of IL-4 polymorphism with AR in patients with liver transplantation and studies investigating combined recipient-donor genotype.
An UpToDate review on “Clinical manifestations and diagnosis of acute renal allograft rejection” (Chon and Brenna, 2014a) does not mention measurement of cytokines as a management tool.

Furthermore, an UpToDate review on “Investigational methods in the diagnosis of acute renal allograft rejection” (Chon and Brenna, 2014b) states that “The introduction of potent immunosuppressive drugs in the past three decades has led to a dramatic reduction in the incidence of acute rejection in kidney transplant recipients. At the present time, renal allograft biopsy with conventional histologic evaluation remains the gold standard for diagnosing acute rejection among patients with a deterioration in kidney function as detected by measuring serum creatinine levels. However, the lack of additional markers of rejection makes it difficult to optimize anti-rejection therapy for transplant recipients. The evaluation of methods other than conventional renal biopsy and/or measurement of the serum creatinine to help diagnosis acute kidney rejection has been the focus of a large number of investigators. This topic review will discuss some of the methods undergoing investigation for the diagnosis of acute rejection ….

Measuring the levels of urinary or circulating proteins and cytokines, circulating soluble interleukin-2 (IL-2) receptor, the urinary concentration of soluble adhesion molecules, or cellular activation with urinary flow cytometry may be helpful in diagnosing acute allograft rejection …. Interleukin-6 (IL-6) may be a potential biomarker for acute rejection. In an observational study of 32 patients who presented with acute graft dysfunction, of six tested cytokines (including IL-1beta, IL-6, TNF-alpha, IL-4, GM-CSF, and MCP-1), IL-6 best predicted acute rejection. Among a validation cohort of 32 additional patients, using a prespecified IL-6 cutoff level of 85 pg/ml, IL-6 assay had a sensitivity of 92 and specificity of 63 percent for the diagnosis of acute rejection. These results need to be confirmed in a larger prospective trial”.

Kim et al (2014) stated that antibody-mediated rejection (AMR), also known as B-cell-mediated or humoral rejection, is a significant complication after kidney transplantation that carries a poor prognosis. Although fewer than 10 % of kidney transplant patients experience AMR, as many as 30 % of these patients experience graft loss as a consequence. Although AMR is mediated by antibodies against an allograft and results in histologic changes in allograft vasculature that differ from cellular rejection, it has not been recognized as a separate disease process until recently. With an improved understanding about the importance of the development of antibodies against allografts as well as complement activation, significant advances have occurred in the treatment of AMR. The standard of care for AMR includes plasmapheresis and intravenous immunoglobulin that remove and neutralize antibodies, respectively. Agents targeting B cells (rituximab and alemtuzumab), plasma cells (bortezomib), and the complement system (eculizumab) have also been used successfully to treat AMR in kidney transplant recipients. However, the high cost of these medications, their use for unlabeled indications, and a lack of prospective studies evaluating their safety and effectiveness limit the routine use of these agents in the treatment of AMR in kidney transplant recipients.
Gupta et al (2014) stated that although several strategies for treating early AMR in kidney transplants have been investigated, evidence on treatment of late AMR manifesting after 6 months is sparse. In this single-center series, these researchers presented data on 23 consecutive patients treated for late AMR. Late AMR was diagnosed using Banff 2007 criteria along with presence of donor-specific antibodies (DSA) and acute rise in serum creatinine (SCr). Response to therapy was assessed by improvement in SCr, histologic improvement, and decline in DSA strength. Overall, 17 % (4/23) had documented non-adherence while 69 % (16/23) had physician-recommended reduction in immunosuppression before AMR. Eighteen patients (78 %) were treated with plasmapheresis or low-dose IVIG + rituximab; 11 (49 %) with refractory AMR also received 1 to 3 cycles of bortezomib. While there was an improvement (p = 0.02) in mean SCr (2.4 mg/dL) at the end of therapy compared with SCr at the time of diagnosis (2.9 mg/dL), this improvement was not sustained at most recent follow-up. Eleven (48 %) patients had no histologic resolution on follow-up biopsy. Lack of histologic response was associated with older patients (OR = 3.17; p = 0.04), presence of cytotoxic DSA at time of diagnosis (OR = 200; p = 0.04), and severe chronic vasculopathy (cv greater than or equal to 2) on index biopsy (OR = 50; p = 0.06). The authors concluded that a major setting in which late AMR occurred in this cohort was reduction or change in immunosuppression. They stated that these data demonstrated an inadequate response of late AMR to current and novel (bortezomib) therapies. They stated that the benefits of therapy need to be counter-weighted with potential adverse effects especially in older patients, large antibody loads, and chronic allograft vasculopathy.

Eskandary et al (2014) noted that despite major advances in transplant medicine, improvements in long-term kidney allograft survival have not been commensurate with those observed shortly after transplantation. The formation of DSA and ongoing AMR processes may critically contribute to late graft loss. However, appropriate treatment for late AMR has not yet been defined. There is accumulating evidence that bortezomib may substantially affect the function and integrity of alloantibody-secreting plasma cells. The impact of this agent on the course of late AMR has not so far been systematically investigated. The BORTEJECT Study is a RCT designed to clarify the impact of intravenous bortezomib on the course of late AMR. In this single-center study (nephrological outpatient service, Medical University Vienna) these researchers plan an initial cross-sectional DSA screening of 1,000 kidney transplant recipients (functioning graft at greater than or equal to 180 days; estimated glomerular filtration rate (eGFR) greater than 20 ml/min/1.73 m2). DSA-positive recipients will be subjected to kidney allograft biopsy to detect morphological features consistent with AMR. Forty-four patients with biopsy-proven AMR will then be included in a double-blind placebo-controlled intervention trial (1:1 randomization stratified for eGFR and the presence of T-cell-mediated rejection). Patients in the active group will receive 2 cycles of bortezomib (4 × 1.3 mg/m2 over 2 weeks; 3-month interval between cycles). The primary end-point will be the course of eGFR over 24 months (intention-to-treat analysis). The sample size was calculated according to the assumption of a 5 ml/min/1.73
m2 difference in eGFR slope (per year) between the 2 groups (alpha: 0.05; power: 0.8). Secondary end-points will be DSA levels, protein excretion, measured glomerular filtration rate, transplant and patient survival, and the development of acute and chronic morphological lesions in 24-month protocol biopsies. The authors concluded that the impact of anti-humoral treatment on the course of late AMR has not yet been systematically investigated. Based on the hypothesis that proteasome inhibition improves the outcome of DSA-positive late AMR, these investigators suggested that their trial has the potential to provide solid evidence towards the treatment of this type of rejection.

Hou et al (2014) noted that the human leukocyte antigen-G may have a positive role in graft acceptance in human organ transplant. Several studies have reported an association between the human leukocyte antigen-G-14-base-pair-insertion/deletion polymorphism and risk of developing kidney graft rejection, but the results are inconclusive. These researchers performed a meta-analysis to evaluate this association. They included 5 case-control studies that evaluated the association between human leukocyte antigen-G-14-base-pair-insertion/deletion polymorphism and risk of developing kidney transplant rejection, including a total 907 patients (rejection, 271 patients; no rejection, 636 patients). There was no significant association between the human leukocyte antigen-G-14-basepair-insertion/deletion polymorphism and risk of developing kidney transplant rejection in the allele contrast, homozygous, heterozygous, recessive, or dominant genetic models for all rejection or acute rejection. In 2 studies, there was a significant association between human leukocyte antigen-G-14-base-pair-insertion/deletion polymorphism and chronic graft rejection in the allele contrast model (+14 versus -14: OR, 0.68; 95 % CI: 0.48 to 0.96; p = 0.618), heterozygous model (+14/-14 versus -14/-14: OR, 0.44; 95 % CI: 0.23 to 0.83; p = 0.248), and dominant genetic model ([+14/+14 and +14/-14] versus -14/-14: OR, 0.48; 95 % CI: 0.30 to 0.78; p = 0.355). The authors concluded that there may be no association between 14-base-pair polymorphisms and risk of developing kidney allograft rejection. They stated that additional studies with larger sample size and better study design are justified.

Atgam

Atgam (antithymocyte globulin equine) is lymphocyte-selective immunosuppressant. It is prepared from purified concentrated sterile gamma globulin, primarily monomeric IgG, from the serum of hyper-immune horses immunized with human thymus lymphocytes.

Antithymocyte globulin equine acts to reduce the number of circulating, thymus dependent lymphocytes. Subsequently, this is believed to alter the function of Tlymphocytes involved in humoral immunity that are responsible for cell-mediated immunity.
Atgam (antithymocyte immune globulin, equine) has been FDA-approved in adults for moderate to severe aplastic anemia unsuitable for bone marrow transplant, renal allograft transplant rejection, and renal allograft transplant rejection prophylaxis.

Atgam (antithymocyte immune globulin, equine) has shown efficacy in the treatment of aplastic anemia and allograft renal transplant rejection/prophylaxis. These two disease states represent conditions in which a hyperactive immune state is detrimental to patient outcomes. In renal transplant rejection, 3-year overall graft survival rates have been shown to be significantly higher in the antithymocyte immune globulin treated populations when compared to standard therapy. For the prophylaxis of renal transplant rejection, those patients who received antithymocyte immune globulin in addition to standard therapy experienced had longer delays in 14 and 28 day first rejection episodes at rates of 25% vs. 65% and 45% vs. 85%, respectively. In aplastic anemia, a review of several trials found that though patients respond in 54% of the cases, the response is evident in 98% of those patients as early as 6 months with the majority within 3 months. Only 3% of responders experienced a hematologic relapse. Response was defined as a rise in neutrophil and reticulocyte counts.

Each lot of antithymocyte globulin equine is tested by the manufacturer to assure its ability to inhibit rosette formation between human peripheral lymphocytes and sheep red blood cells in vitro before release. Antibody activity is measured against human red blood cells and platelets and determined to be within acceptable limits. Only lots that test negative for antihuman serum protein antibody, antiglomerular basement membrane antibody and pyrogens are released.

A Medicare National Coverage Determination states that the FDA has approved lymphocyte immune globulin, anti-thymocyte globulin (equine), for the management of allograft rejection episodes in renal transplantation. The Centers for Medicare and Medicaid Services has stated that these biologics are viewed as adjunctive to traditional immunosuppressive products such as steroids and anti metabolic drugs. At present, lymphocyte immune globulin preparations are not recommended to replace conventional immunosuppressive drugs, but to supplement them and to be used as alternatives to elevated or accelerated dosing with conventional immunosuppressive agents.

Antithymocyte immune globulin, equine is supplied as Atgam 50 mg/ml 5 ml ampules in packages of five.

The recommended dose for aplastic anemia is 10 to 20 mg/kg once daily for 8-14 days, then every other day up to 21 total doses if needed.
Recommended dosing for treatment of renal transplant rejection is 10 to 15 mg/kg IV once daily for 14 days, then every other day for 14 more days if needed up to 21 total doses.

Recommended dosing for prophylaxis of renal transplant rejection is 15 mg/kg IV once daily for 14 days, then every other day for 14 days for a total of 21 doses in 28 days; begin first dose within 24 hours before or after transplantation.

Atgam (antithymocyte immune globulin, equine) should not be used in persons with aplastic anemia secondary to neoplastic disease, storage disease, myelofibrosis, or Fanconi’s syndrome. Atgam should not be used in persons known to have been exposed to myelotoxic agents or radiation.

Black Box warnings:

- Only physicians experienced in immunosuppressive therapy in the treatment of renal transplant or aplastic anemia patients should use lymphocyte immune globulin, antithymocyte globulin equine.
- Patients receiving lymphocyte immune globulin, antithymocyte globulin equine should be treated in facilities equipped and staffed with adequate laboratory and supportive medical resources.

Discontinue treatment with Atgam (antithymocyte immune globulin, equine) if any of the following occurs:

- Symptoms of anaphylaxis
- Severe and continuous thrombocytopenia in renal transplant members
- Severe and continuous leukopenia in renal transplant members.

To identify those at greatest risk of systemic anaphylaxis, skin testing potential recipients is strongly recommended before commencing treatment. A conservative, conventional approach would first employ epicutaneous (prick) testing with undiluted ATGAM. If the subject does not show a wheal ten minutes after pricking, proceed to intradermal testing with 0.02 mL of a 1:1000 v/v (volume/volume) saline dilution of ATGAM with a separate saline control injection of similar volume. Read the result at 10 minutes: a wheal at the Atgam site 3 or more mm larger in diameter than that at the saline control site (or a positive prick test) suggests clinical sensitivity and an increased possibility of a systemic allergic reaction should the drug be dosed intravenously.

Interleukin-2 / Interleukin-10 Gene Polymorphisms and Graft Rejection Risk
Hu and colleagues (2015) stated that IL-2-330 T/G promoter polymorphism is involved in the AR risk of kidney transplantation. However, results from published studies on the association between recipient IL-2-330 T/G polymorphism and AR risk are conflicting and inconclusive. These investigators searched Medline, Embase, Web of Science, and Cochrane Central Register from their inceptions through January 2015 for relevant studies. Data concerning publication information, population characteristics, and transplant information were extracted. Odds ratios were calculated for the association between IL-2-330 T/G polymorphism and AR risk. This meta-analysis included 8 case-control studies with 1,405 cases of renal transplant recipients. The pooled estimate showed that IL-2-330 T/G polymorphism was not associated with AR risk: TT versus TG+GG: OR (fixed), 0.93; 95 % CI: 0.72 to 1.21; p = 0.60; GG versus TG+TT: OR (fixed), 1.15; 95 % CI: 0.76 to 1.72; p = 0.51; TG versus TT+GG: OR (fixed), 1.01; 95 % CI: 0.78 to 1.31; p = 0.91; T versus G: OR (fixed), 0.93; 95 % CI: 0.77 to 1.13; p = 0.48. None of subgroup analyses yielded significant results in the association between IL-2-330 T/G polymorphism and AR risk. Meta-regression confirmed that there was no significant correlation between the pre-selected trial characteristics and the study results. The authors concluded that the findings of this meta-analysis suggested that IL-2-330 T/G polymorphism may not be associated with AR risk in renal transplant recipients.

Xiong and co-workers (2015) noted that IL-10 is an important immune-modulatory cytokine. Several studies focused the association between IL-10 promoter gene polymorphisms and graft rejection risk in kidney transplantation recipients. However, the results of these studies remain inconclusive. The se researchers performed a meta-analysis to further examine the associations. PubMed, Embase, and Ovid Medline databases were searched. Two independent authors extracted data, and the effects were estimated from an OR with 95 % CIs. Subgroup and sensitivity analyses identified sources of heterogeneity. A total of 16 studies including 595 rejection patients and 1,239 stable graft patients were included in order to study the IL-10 -1082 (rs1800896 G/A), -819 (rs1800871 C/T), -592 (rs1800872 C/A) and IL-10 (-1082,-819,-592) polymorphisms. The -1082 G/A polymorphism was not associated with an increased graft rejection risk (OR = 1.03; 95 % CI: 0.85 to 1.25, p = 0.74 for GA+AA versus GG model). Moreover, all of the -819 C/T (OR = 1.06, 95 % CI: 0.79 to 1.42, p = 0.70 for TA+TT versus CC model), -592 C/A (OR = 1.10, 95 % CI: 0.85 to 1.42, p = 0.47 for AC+AA versus CC model) and IL-10 (-1082,-819,-592) polymorphisms (OR = 1.00, 95 % CI: 0.79 to 1.27, p = 0.98 for I+L versus H model) did not increase the graft rejection risk. In addition, these investigators also performed subgroup analysis by ethnic group (mainly in Europeans or Asians) and rejection type (acute or chronic). There was also lack of evidence of a significant association between the IL-10 gene polymorphism and graft rejection risk. The present meta-analysis indicated that the IL-10 gene polymorphism was not associated with graft rejection risk in kidney transplantation recipients. The authors concluded that this meta-analysis found evidence that the IL-10
polymorphism does not increase the risk of graft rejection in kidney transplantation recipients. They stated that further chronic rejection and other ethnic population studies are needed to confirm these results.

Hu and associates (2016) examined the association between IL-10-1082 (G/A) promoter polymorphism and AR in renal transplant recipients. These investigators searched MEDLINE, EMBASE, Web of Science, and Cochrane Central Register from the inception to March 2015 for relevant studies. Data concerning publication information, population characteristics, and transplant information were extracted. Odds ratios was calculated for the association between IL-10-1082 GG genotype (or IL-10-1082 G allele) and AR risk. This meta-analysis included 22 case-control studies including 2,779 cases of renal transplant recipients. The pooled estimate showed that the IL-10-1082 GG genotype was not significantly associated with AR risk (OR random = 1.07, 95 % CI: 0.80 to 1.43, p = 0.64). Similarly, the pooled estimate showed that the IL-10-1082 G allele was not significantly associated with AR risk (OR fixed = 1.02, 95 % CI: 0.90 to 1.16, p = 0.74). None of subgroup analyses yielded significant results in the association between IL-10-1082 GG genotype (or IL-10-1082 G allele) and AR risk. Meta-regression confirmed that there was no significant correlation between the pre-selected trial characteristics and the study results. The authors concluded that the findings of this meta-analysis suggested that IL-10-1082 G/A polymorphism is not significantly associated with AR risk in renal transplant recipients.

Preconditioning Therapy in ABO-Incompatible Living Kidney Transplantation

Lo and associates (2016) stated that ABO-incompatible (ABOi) kidney transplantation is now an established form of renal replacement therapy, but the safety and effectiveness of the different types of pre-conditioning therapies are unclear. These investigators synthesized the totality of the published evidence about the effects of any form of pre-conditioning therapies in living donor ABOi kidney transplantation on graft and patient outcomes. They searched MEDLINE, Embase, and Clinicaltrial.gov databases (inception through June 2015) to identify all studies that described the outcomes of adult living donor ABOi kidney transplantations using any form of pre-conditioning therapies. Two independent reviewers identified studies, extracted data, and assessed the risk of bias. Data were summarized using the random effects model, and heterogeneity was explored using subgroup analyses. These researchers assessed confidence in the evidence using the Grading of Recommendations Assessment, Development, and Evaluation framework. A total of 83 studies (54 case reports and case series, 25 cohort, 2 case-control, and 2 registry studies) involving 4,810 ABOi transplant recipients were identified.

Overall, confidence in the available evidence was low. During a mean follow-up time of 28 (standard deviation [SD], 26.6) months, the overall graft survival for recipients who received immune-adsorption or apheresis was 94.1 % (95 % CI: 88.2 % to 97.1 %) and 88.0 % (95 % CI:
82.6 % to 91.8 %), respectively. For those who received rituximab or underwent splenectomy, the overall graft survival was 94.5 % (95 % CI: 91.6 % to 96.5 %) and 79.7 % (95 % CI: 72.9 % to 85.1 %), respectively. Data on other longer-term outcomes, including malignancy, were sparse. The authors concluded that rituximab or immune-adsorption appeared to be promising pre-conditioning strategies before ABOi kidney transplantation. However, the overall quality of evidence and the confidence in the observed treatment effects were low. The increased use of ABOi kidney transplantation needs to be matched with randomized trials of different types, dosing, and frequency of pre-conditioning therapies so that this scarce resource can be used most effectively and efficiently.

Treatment of Low Bone Mineral Density after Kidney Transplantation

Kan and colleagues (2016) noted that in patients with low BMD after kidney transplantation, the role of bisphosphonates remains unclear. These researchers performed a systematic review and meta-analysis to examine the safety and effectiveness of bisphosphonates. They retrieved trials from PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception through May 2015. Only RCTs that compared bisphosphonate-treated and control groups of patients with low BMD after kidney transplantation were included. The primary outcomes were the percent change in BMD, the absolute change in BMD, and the BMD at the end of study at the lumbar spine. The results were expressed as the MD or RR with the 95 % CI. These investigators used a random-effects model to pool the outcomes. They included a total of 17 RCTs with 1,067 patients. Only 1 included trial was found to be at low risk of bias. The rest of the included studies were found to have high to uncertain risk of bias. Compared with the control group, those who received bisphosphonates had a significant increase in percent change in BMD (MD = 5.51, 95 % CI: 3.22 to 7.79, p < 0.00001) and absolute change in BMD (MD = 0.05, 95 % CI: 0.04 to 0.05, p < 0.00001), but a non-significant increase in BMD at the end of the study (MD = 0.02, 95 % CI: -0.01 to 0.05, p = 0.25) at the lumbar spine. Bisphosphonates resulted in a significant improvement in percent change in BMD (MD = 4.95, 95 % CI: 2.57 to 7.33, p < 0.0001), but a non-significant improvement in absolute change in BMD (MD = 0.03, 95 % CI: -0.00 to 0.06, p = 0.07) and BMD at the end of the study (MD = -0.01, 95 % CI: -0.04 to 0.02, p = 0.40) at the femoral neck. No significant differences were found in vertebral fractures, non-vertebral fractures, adverse events, and gastro-intestinal adverse events. The authors concluded that bisphosphonates appeared to have a beneficial effect on BMD at the lumbar spine; and did not significantly decrease fracture events in recipients. Moreover, they stated that the results should be interpreted cautiously due to the lack of robustness and the heterogeneity among studies.

Furthermore, an UpToDate review on “Bone disease after renal transplantation” (Yarlagadda et al, 2016) states that “Bisphosphonates -- We do not give bisphosphonates to prevent bone loss among renal transplant recipients, because there is a risk that they may worsen low-turnover
(i.e., adynamic) bone disease. However, some studies have suggested that bisphosphonates may provide a benefit. However, despite these reports that suggest a benefit, we do not use bisphosphonates to prevent bone loss. This is because many transplant recipients have low-turnover bone disease, which could be made worse by bisphosphonates. Low-turnover bone disease is a mineral and bone disease of chronic kidney disease (CKD-MBD) that is associated with over-suppression of PTH. An adverse effect of bisphosphonates on low-turnover bone disease was suggested by a study of 72 new renal transplant recipients who were randomly assigned to either pamidronate with calcitriol plus calcium or only calcitriol plus calcium. At 6 months, adynamic bone disease was observed in all patients receiving pamidronate compared with 50% in the control group. If antiresorptive therapies worsen low-turnover bone disease, they could increase the risk of atypical fractures related to low-turnover bone disease. Thus, the overall risk of fracture could increase even if BMD is improved by bisphosphate therapy. The prevalence of bisphosphonate-associated atypical fractures is not known, but a potential case report has been documented. Among transplant recipients, it is not clear whether antiresorptive therapy has an effect on the overall number of fractures, although trials that have evaluated bisphosphonates were not powered for fracture outcomes.

Urinary Biomarkers

**Urinary Neutrophil Gelatinase-Associated Lipocalin for Renal Rejection**

Iguchi and associates (2015) stated that neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid-binding protein (L-FABP) are promising early biomarkers for acute kidney injury (AKI). In organ transplant recipients, AKI predictability based on NGAL and L-FABP remains to be elucidated. Furthermore, the association between serial NGAL and L-FABP measurements and AKI outcome is unknown. These researchers evaluated the ability of NGAL and L-FABP to predict AKI after organ transplantation and examined the association between NGAL, L-FABP and AKI outcome. A total of 25 organ transplant recipients admitted to the intensive care unit (ICU) immediately after transplant surgery were studied prospectively. Plasma NGAL (P-NGAL), urinary NGAL (U-NGAL) and L-FABP were measured from ICU admission to ICU discharge; U-NGAL and L-FABP were corrected for dilution/concentration by calculating U-NGAL/urine creatinine ratios (U-NGAL/Cr) and L-FABP/urine creatinine ratios (L-FABP/Cr). Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes criteria. Acute kidney injury occurred in 11 patients; P-NGAL, U-NGAL/Cr and L-FABP/Cr upon ICU admission were unrelated to AKI development (p = 0.24, 0.22, and 0.53, respectively). There were no differences in P-NGAL, U-NGAL/Cr, and L-FABP/Cr levels from day 1 to day 6 between patients who did not recover from AKI and patients who recovered from AKI (p = 0.82, 0.26, and 0.61, respectively). The authors concluded that the findings of this
study suggested that NGAL and L-FABP upon ICU admission were not predictive of AKI and serial NGAL and L-FABP measurements may be ineffective for monitoring the status and treatment of post-transplantation AKI.

In a prospective, single-center study, Seeman and co-workers (2017) examined the ability of urinary NGAL to distinguish AR from other causes of AKI in children after renal transplantation. A total of 15 children fulfilled the inclusion criteria (AKI with allograft biopsy, at least 21 days after renal transplantation, no sepsis) during 2013 to 2014 in the authors’ pediatric transplantation center. The mean age was 14.8 +/- 2.8 years, median time after renal transplantation was 0.4 years (range of 0.1 to 3.8). Urinary NGAL was measured in spot urine by chemiluminescent microparticle immunoassay technology. A total of 4 patients had biopsy proven AR (rejection group), 11 children had AKI of other cause (non-rejection group). The median urinary NGAL concentration in the rejection group was not significantly different from NGAL in the non-rejection group (7.3 ng/ml, range of 3.0 to 42.3 versus 8.6 ng/ml, range of 3.4 to 54.7, p = 0.48). There was a significant negative correlation between eGFR and urinary NGAL concentrations (r = -0.77, p < 0.001). The authors concluded that the findings of this small study suggested that in children after renal transplantation, urinary NGAL cannot be used as a specific marker for distinguishing AR from other non-rejection causes of AKI; urinary NGAL was mainly associated with graft function but not with the etiology of AKI.

Urinary Monocyte Chemoattractant Protein-1 (MCP-1/CCL2) for Renal Rejection

Wang and colleagues (2016) stated that there is a high risk for the survival of patients with an end-stage renal disease for kidney transplantation. To avoid rejection by strict medication adherence is of utmost importance to avoid the failure of a kidney transplant. It is imperative to develop non-invasive biomarkers to assess immunity risk, and to ultimately provide guidance for therapeutic decision-making following kidney transplantation. Urine biomarkers may represent the promising non-invasive tools that will help in predicting risk or success rates of kidney transplantations. Furthermore, composite urinary biomarkers or urinary biomarker panel array might be critical in improving the sensitivity and specificity in reflecting various risks of kidney failure during transplantation. These investigators focused on the role of such biomarkers in predicting chronic kidney disease (CKD) progression and/or cardiovascular disease (CVD) risk in renal allograft. Chemokine ligand 2 (CCL2) is a small cytokine that belongs to the CC chemokine family; CCL2 recruits monocytes, memory T cells, and dendritic cells to the sites of inflammation produced by either tissue injury or infection. The advancing age of renal transplant recipients (RTRs) correlates with the increasing CCL2 concentrations, which is reflected in the smoldering inflammation and alterations in matrix metallo-proteinases (MMPs)/tissue inhibitor metallo-proteinases (TIMPs) profiles, especially with increased plasma MMP-2 and urine TIMP-1 concentrations. The advanced age of RTRs has a negative impact on kidney allograft survival
through impaired extracellular matrix degradation by the MMPs/TIMPs system. The authors concluded that “The development of novel biomarkers and detection technologies may lead to the creation of multiplex assays, which allows for the measurement of multiple specific biomarkers simultaneously in the same analyte. Such assays may prove useful for determining the nature of renal injury or the stage of disease in patients. Novel multiplex technologies such as Biomarker Panel Array (BPA) may provide a new perspective for diagnosis and prognosis of renal rejection after kidney transplantation; more importantly, these technologies could significantly improve the sensitivity and specificity in reflecting the clinical manifestations. It is important to note that the advancement of proteomics technologies may become a critical drive for the discovery of novel urinary biomarkers which could specifically and accurately reflect underlying molecular events of allograft rejection. The validation and assessment of the performance of urinary biomarkers for allograft rejection remains a significant, costly, and high-risk undertaking process”.

Raza and associates (2017) noted that CCL2 is a chemoattractant for monocytes/macrophages, T cells, and natural killer cells. It is shown to be involved in the immunological responses against renal allograft. These researchers evaluated the role of urinary CCL2 expression in predicting the rejection episodes in renal transplant patients. A total of 409 urine samples were included in this study. The samples consisted of (a) biopsy-proven graft rejection (n = 165); (b) non-rejection (n = 93); (c) non-biopsy stable-graft (n = 42), and (d) healthy renal donors (n = 109). Samples were quantified for the CCL2 using the MCP-1/CCL2 ELISA kit. Data were analyzed using the Statistical Package for Social Sciences (SPSS) and MedCalc statistical software. Results showed that the CCL2 levels were significantly increased in rejection group when compared with the non-rejection, stable-graft, and control (p < 0.05). The receiver operating curve’s characteristics illustrated that the urinary CCL2 level is a good predictor for graft rejection, with an area under the curve of 0.81 ± 0.03 with optimum sensitivity and specificity of 87 % and 62 %, respectively, at a cut-off value of 198 pg/ml. Kaplan-Meier curve also showed better cumulative rejection-free graft survival time in group with less than 198 pg/ml of CCL2 as compared to those with expression levels of more than 198 pg/ml (30 weeks versus 3 weeks; log-rank test, p < 0.001). The authors concluded that non-invasive measurement of CCL2 levels in urine has showed potential to predict rejection episodes. It is suggested that the CCL2, with others markers, may help in early detection and monitoring of graft rejection episodes.

Fas Ligand (FASL) mRNA Detection for Acute Renal Rejection

Heng and colleagues (2016) stated that the value of Fas ligand (FASL) as a diagnostic immune marker for acute renal rejection is controversial; this meta-analysis aimed to clarify the role of FASL in acute renal rejection. The relevant literature was included by systematic searching the Medline, Embase, and Cochrane Library databases. Accuracy data for AR and potential
confounding variables (the year of publication, area, sample source, quantitative techniques, housekeeping genes, fluorescence staining, sample collection time post-renal transplantation, and clinical classification of AR) were extracted after carefully reviewing the studies. Data were analyzed by Meta-DiSc 1.4, RevMan 5.0, and the Midas module in Stata 11.0 software. A total of 12 relevant studies involving 496 subjects were included. The overall pooled sensitivity, specificity, positive likelihood ratio (LR), negative LR, and diagnostic OR, together with the 95 % CI were 0.64 (0.57 to 0.70), 0.90 (0.85 to 0.93), 5.66 (3.51 to 9.11), 0.30 (0.16 to 0.54), and 30.63 (14.67 to 63.92), respectively. The area under the summary receiver operating characteristic curve (AUC) was 0.9389. Fagan’s nomogram showed that the probability of AR episodes in the kidney transplant recipient increased from 15 % to 69 % when FASL was positive, and was reduced to 4 % when FASL was negative. No threshold effect, sensitivity analyses, meta-regression, and subgroup analyses based on the potential variables had a significant statistical change for heterogeneity. The authors concluded that current evidence suggested the diagnostic potential for FASL mRNA detection as a reliable immune marker for AR in renal allograft recipients. Moreover, they stated that further large, multi-center, prospective studies are needed to validate the power of this test marker in the non-invasive diagnosis of AR after renal transplantation.

Donor-Derived Cell-Free DNA Testing

Bloom and colleagues (2017) stated that histologic analysis of the allograft biopsy specimen is the standard method used to differentiate rejection from other injury in kidney transplants. Donor-derived cell-free DNA (dd-cfDNA) is a non-invasive test of allograft injury that may enable more frequent, quantitative, and safer assessment of allograft rejection and injury status. These investigators examined this possibility by prospectively collected blood specimens at scheduled intervals and at the time of clinically indicated biopsies. In 102 kidney recipients, these researchers measured plasma levels of dd-cfDNA and correlated the levels with allograft rejection status ascertained by histology in 107 biopsy specimens. The dd-cfDNA level discriminated between biopsy specimens showing any rejection (T cell-mediated rejection or antibody-mediated rejection [ABMR]) and controls (no rejection histologically), p < 0.001 (receiver operating characteristic area under the curve [AUC], 0.74; 95 % confidence interval [95% CI]: 0.61 to 0.86). Positive and negative predictive values (PPV and NPV) for active rejection at a cut-off of 1.0 % dd-cfDNA were 61 % and 84 %, respectively. The AUC for discriminating ABMR from samples without ABMR was 0.87 (95 % CI: 0.75 to 0.97). PPV and NPV for ABMR at a cut-off of 1.0 % dd-cfDNA were 44 % and 96 %, respectively. Median dd-cfDNA was 2.9 % (ABMR), 1.2 % (T cell-mediated types ≥ IB), 0.2 % (T cell-mediated type IA), and 0.3 % in controls (p = 0.05 for T cell-mediated rejection types ≥ IB versus controls). The authors concluded that dd-cfDNA may be used to assess allograft rejection and injury; dd-cfDNA levels of less than 1 % reflected the absence of active rejection (T cell-mediated type ≥ IB or
ABMR) and levels greater than 1 % indicated a probability of active rejection. They stated that the next steps of development include studies to validate these findings and to demonstrate the clinical utility of this new type of immune monitoring of the graft.

This study had several drawbacks. First, these researchers were unable to estimate the performance of dd-cfDNA to discriminate active rejection or ABMR in patients who may have had sub-clinical rejection because there were only 34 surveillance biopsies and only 1 finding of active rejection. However, this low rejection frequency was consistent with reports by others in an era of tacrolimus-mycophenolic acid-prednisone-based maintenance immunosuppression that question the utility of protocol biopsy for this purpose. Second, the number of active rejections (n = 27) and sub-classes of rejection observed among these biopsy specimens was limited. However, these met the target total number of rejections prospectively stated in the statistical analysis, and indeed, the results proved this number to be sufficient to demonstrate statistically significant performance characteristics. Third, biopsy-matched blood samples were not collected for all biopsy specimens, and some of the matched blood samples were excluded due to issues such as inadequate amount of total DNA or timing of the blood draw relative to the biopsy. Of all collected blood samples, 4.5 % did not render results due to some aspect of sample collection or testing. Most patients completed surveillance visits in compliance (77 %) with the center schedule.

Lee and associates (2017) noted that early detection and proper management of kidney rejection are crucial for the long-term health of a transplant recipient. Recipients are normally monitored by serum creatinine measurement and sometimes with graft biopsies. Donor-derived cell-free deoxyribonucleic acid (cfDNA) in the recipient's plasma and/or urine may be a better indicator of acute rejection. These investigators evaluated digital PCR (dPCR) as a system for monitoring graft status using single nucleotide polymorphism (SNP)-based detection of donor DNA in plasma or urine. They compared the detection abilities of the QX200, RainDrop, and QuantStudio 3D dPCR systems. The QX200 was the most accurate and sensitive. Plasma and/or urine samples were isolated from 34 kidney recipients at multiple time-points after transplantation, and analyzed by dPCR using the QX200. They found that donor DNA was almost undetectable in plasma DNA samples, whereas a high percentage of donor DNA was measured in urine DNA samples, indicating that urine is a good source of cfDNA for patient monitoring. These researchers found that at least 24 % of the highly polymorphic SNPs used to identify individuals could also identify donor cfDNA in transplant patient samples. The authors concluded that these findings showed that autosomal, sex-specific, and mitochondrial SNPs were suitable markers for identifying donor cfDNA. They found that donor-derived cfDNA measurement by dPCR was not sufficient to predict a patient's clinical condition; these results indicated that donor-derived cfDNA is not an accurate predictor of kidney status in kidney transplant patients.
Furthermore, an UpToDate review on “Investigational methods in the diagnosis of acute renal allograft rejection” (Anglicheau et al, 2018) lists donor-derived cell-free DNA as an investigational method. It states that “During allograft rejection, large amounts of dd-cfDNA are released from the injured allograft into the bloodstream. Quantification of plasma levels of dd-cfDNA has been proposed as a noninvasive test for the early diagnosis of acute renal allograft rejection. Methods for measuring dd-cfDNA include quantitative reverse transcription PCR (RT-PCR), droplet digital PCR (ddPCR), and targeted next-generation sequencing. In one multicenter study, plasma levels of dd-cfDNA were measured by targeted next-generation sequencing in 102 renal transplant recipients and correlated with allograft rejection status as determined by renal allograft biopsy. The dd-cfDNA level was able to differentiate between biopsy specimens showing any form of rejection (TCMR or ABMR) and those without rejection. Using a cutoff of 1.0 %, dd-cfDNA had a PPV and NPV for active rejection of 61 and 84 %, respectively. Studies in heart, lung, and liver transplant recipients have also shown an association between increased plasma dd-cfDNA levels and acute rejection”.

Measurement of Angiotensin II Type 1 (AT1) Receptors or AT1 Antibodies for Evaluation of Renal Transplantation Candidates / Recipients

Michielsen and associates (2016) stated that HLA antibodies play a major role in the recipient's immune response against the renal allograft and are an established risk factor for antibody-mediated rejection (AMR) and subsequent impaired graft survival. Evidence originating from HLA-identical donor-recipient pairs indicated that non-HLA antibodies may play a role as well. Numerous non-HLA antibodies have been identified in renal organ transplantation, directed against a heterogeneous subset of both allo- and auto-antigens including MHC Class-I-related chain A (MICA) and Angiotensin II type 1 receptor (AT1R). These researchers discussed the mechanisms predisposing to non-HLA antibody formation, the possible synergy with HLA-antibodies in their pathologic potential and the mechanisms involved in allograft damage. Furthermore, an overview of the identified non-HLA antibodies and antigens and their relation with rejection and graft survival was provided. The authors stated that “… these studies all indicate that AT1R-antibodies are associated with an increased incidence of graft failure. Remarkably, despite the fact that all studies used the same ELISA-based assay, the prevalence of AT1R-antibodies pre-transplantation ranged from 17 % to 47 %”. Moreover, they noted that the determination of the exact clinical relevance of non-HLA antibodies in renal transplantation is impaired by highly heterogenic study designs including differences in testing methods, immunosuppressive regimens and outcome measures. Considering the technical difficulties of current non-HLA antibodies assays and the large variation in reported incidences of antibodies even with the same assays, continuous efforts to develop reliable and sensitive diagnostic tests are essential.
Pinelli and colleagues (2017) noted that endothelial cell antigens have been reported as potential targets for antibodies in the context of organ transplantation, leading to increased risk for graft failure. Serum samples from 142 consecutive living donor kidney recipients were tested for the presence of antibodies to AT1R, donor endothelial cells, and donor HLA. Graft survival was monitored for 5 years post-transplant, and secondary outcomes, including biopsy-proven rejection, proteinuria, biopsy-proven vasculopathy, and renal function based on serum creatinine were also assessed for the first 2 to 3 years. AT1R antibody levels were positive (greater than 17U/ml) in 11.3 %, 18.8 % and 8.1 % of patients pre-transplant, post-transplant and at time of indication biopsy, respectively. XM-ONE assay was positive in 17.6 % of patients pre-transplant (7 IgG+; 15 IgM+; 3 IgG+/IgM+). Overall, 4 patients experienced AMR, 31 borderline cellular rejection (BCR), 19 cellular rejection (CR) and 3 mixed AMR and CR within the first 24 months. The authors concluded that while pre-existing and de-novo donor-specific HLA antibodies were associated with graft failure and many secondary outcomes, no statistical association was found for either anti-endothelial or anti-AT1R antibodies, indicating that these tests may not be the best predictors of graft outcome in living donor renal transplantation.

Furthermore, UpToDate reviews on “Evaluation of the potential renal transplant recipient” (Rossi and Klein, 2018), and “Overview of care of the adult kidney transplant recipient” (Chandraker and Yeung, 2018) do not mention measurement of AT1 receptors or AT1 antibodies as a management tool.

Complement Inhibitors (e.g., Eculizumab) for the Treatment of Antibody-Mediated Rejection

Wan and colleagues (2018) stated that current treatments for AMR in kidney transplantation are based on low-quality data from a small number of controlled trials. Novel agents targeting B cells, plasma cells, and the complement system have featured in recent studies of AMR. These investigators conducted a systematic review and meta-analysis of controlled trials in kidney transplant recipients using Medline, Embase, and CENTRAL from inception to February 2017. Of 14,380 citations, these researchers identified 21 studies, including 10 RCTs, involving 751 participants. Since the last systematic review conducted in 2011, these researchers found 9 additional studies evaluating plasmapheresis + intravenous immunoglobulin (IVIG) (n = 2), rituximab (n = 2), bortezomib (n = 2), C1 inhibitor (n = 2), and eculizumab (n = 1). Risk of bias was serious or unclear overall and evidence quality was low for the majority of treatment strategies. Sufficient RCTs for pooled analysis were available only for antibody removal, and here there was no significant difference between groups for graft survival (hazard ratio [HR] 0.76; 95 % CI: 0.35 to 1.63; p = 0.475). Studies showed important heterogeneity in treatments, definition of AMR, quality, and follow-up. Plasmapheresis and IVIG were used as standard-of-care in recent studies, and to this combination, rituximab appeared to add little or no benefit.
Insufficient data were available to assess the efficacy of bortezomib and complement inhibitors. The authors concluded that newer studies evaluating rituximab showed little or no difference to early graft survival, and the efficacy of bortezomib and complement inhibitors for the treatment of AMR remains unclear. Despite the evidence uncertainty, plasmapheresis and IVIG have become standard-of-care for the treatment of acute AMR.

Belimumab for the Treatment of Antibody-Mediated Rejection

Banham and colleagues (2018) stated that B cells produce allo-antibodies and activate allo-reactive T cells, negatively affecting kidney transplant survival. By contrast, regulatory B cells are associated with transplant tolerance. Immunotherapies are needed that inhibit B-cell effector function, including antibody secretion, while sparing regulators and minimizing infection risk. B lymphocyte stimulator (BLyS) is a cytokine that promotes B-cell activation and has not previously been targeted in kidney transplant recipients. These researchers examined the safety and activity of an anti-BLyS antibody, belimumab, in addition to standard-of-care immunosuppression in adult kidney transplant recipients. They used an experimental medicine study design with multiple secondary and exploratory end-points to gain further insight into the effect of belimumab on the generation of de-novo IgG and on the regulatory B-cell compartment. In a randomized, double-blind, placebo-controlled, phase-II clinical trial, these researchers employed belimumab, in addition to standard-of-care immunosuppression (basiliximab, mycophenolate mofetil, tacrolimus, and prednisolone) at 2 centers. Subjects were eligible if they were aged 18 to 75 years and receiving a kidney transplant and were planned to receive standard-of-care immunosuppression. They were randomly assigned (1:1) to receive either intravenous belimumab 10 mg/kg body weight or placebo, given at day 0, 14, and 28, and then every 4 weeks for a total of 7 infusions. The co-primary end-points were safety and change in the concentration of naive B cells from baseline to week 24, both of which were analyzed in all patients who received a transplant and at least 1 dose of drug or placebo (the modified intention-to-treat [mITT] population). Between September 13, 2013, and February 8, 2015, of 303 patients assessed for eligibility, 28 kidney transplant recipients were randomly assigned to receive belimumab (n = 14) or placebo (n = 14); 25 patients (12 [86 %] patients assigned to the belimumab group and 13 [93 %] patients assigned to the placebo group) received a transplant and were included in the mITT population. These investigators observed similar proportions of adverse events (AEs) in the belimumab and placebo groups, including serious infections (1 [8 %] of 12 in the belimumab group and 5 [38 %] of 13 in the placebo group during the 6-month on-treatment phase; and none in the belimumab group and 2 [15 %] in the placebo group during the 6-month follow-up). In the on-treatment phase, 1 patient in the placebo group died because of fatal myocardial infarction (MI) and acute cardiac failure. The co-primary end-point of a reduction in naive B cells from baseline to week 24 was not met. Treatment with belimumab did not significantly reduce the number of naive B cells from baseline to week 24 (adjusted MD between
the belimumab and placebo treatment groups -34.4 cells/μL, 95% CI: -109.5 to 40.7). The authors concluded that belimumab might be a useful adjunct to standard-of-care immunosuppression in renal transplantation, with no major increased risk of infection and potential beneficial effects on humoral allo-immunity. These preliminary findings need to be validated by well-designed studies.

Genotyping Donors and Recipients Before Renal Transplantation

Huart and colleagues (2018) noted that delayed graft function (DGF) is defined as the need for dialysis within 7 days following kidney transplantation (KTx). DGF is associated with increased costs, higher risk for acute rejection and decreased long-term graft function. Renal ischemia/reperfusion (I/R) injury plays a major role in DGF occurrence; SNPs in certain genes may aggravate kidney susceptibility to I/R injury, thereby worsening post-transplant outcomes. These investigators presented an extensive review of the literature regarding the putative impact of donor or recipient SNPs on DGF occurrence in kidney transplant recipients (KTRs). Among 30 relevant PubMed reports, 16 articles identified an association between 18 SNPs and DGF. These polymorphisms concerned 14 different well-known genes and 1 not-yet-identified gene located on chromosome 18. They have been categorized into 5 groups according to the role of the corresponding proteins in I/R cascade: oxidative stress, telomere shortening, chemokines, T-cell homeostasis, and metabolism of anti-inflammatory molecules. The remaining 14 studies failed to demonstrate any association between the studied SNPs and the occurrence of DGF. The authors concluded that several polymorphisms in either the donor or the recipient or both have been associated with DGF in KTRs. These polymorphisms are involved in oxidative stress, telomere length, cytokine secretion and modulation, immunity and inflammation. These processes are involved in I/R injury, which is regarded as one of the most important causes of DGF. These researchers stated that identifying the polymorphisms linked to renal I/R may lead to better understand pathophysiology of DGF in KTRs and find new therapeutic targets.

The authors stated that the present review highlighted the state of knowledge in the field of genetic susceptibility to renal I/R. Although SNPs may only have minor impacts per se on gene expression and protein function, interactions among multiple SNPs may have a major impact on molecular cascades. Furthermore, some SNPs showed very low frequency. Validation studies are lacking or inadequately powered for most SNPs studied thus far, which may explain the controversial observations. These researchers stated that replication studies will need to include multi-variate analyses to isolate the putative effects of SNPs among other well-established risk factors of DGF. They stated that most importantly, one must clearly distinguish the impact of SNPs in donors versus in recipients versus in both. Polymorphisms involved in I/R severity may be especially relevant in donors, whereas polymorphisms implicated in AR and inflammation
may rather concern recipients. These investigators stated that prospective, multi-center studies including patients of various genetic backgrounds are needed to clinically determine the benefits (and harms) of genotyping donors and recipients before KTx.

Routine Stenting of Extravesical Ureteroneocystostomy in Renal Transplantation

Abrol and colleagues (2018) stated that although rare, major urologic complications (MUC) in kidney transplantation can cause significant morbidity, increased cost, and may even lead to graft loss. Ureteric stents are routinely used to prevent MUC, although complications related to their use have been reported. These investigators reviewed the role of routine stenting in preventing MUC in kidney transplantation with extravesical ureteric implantation and performed a meta-analysis of 6 RCTs. A PubMed search was performed for studies on MUC and stents in kidney transplant recipients; RCTs were short-listed for the review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. RevMan 5 was used for statistical analysis, and outcome analysis was done with Cochran-Mantel-Haenszel test using random effect model. A total of 6 trials meeting the criteria were identified. Although stent use did not decrease the incidence of urinary leak (OR 0.39; 95 % CI: 0.14 to 1.11; p = 0.08) or obstruction (OR, 0.41; 95 % CI: 0.13 to 1.24; p = 0.11), it was associated with a higher incidence of urinary tract infection (UTI; OR, 3.59; 95 % CI: 1.33 to 9.75; p = 0.01). The authors concluded that in the present era of extravesical ureterovesical anastomosis, routine stenting has a limited role in decreasing MUC and may be associated with higher incidence of UTIs.

Furthermore, an UpToDate review on "Overview of care of the adult kidney transplant recipient" (Chandraker and Yeung, 2019) does not mention routine stenting of extravesical ureteroneocystostomy as a management option of urologic complications in kidney transplantation.

Kidney Molecular Microscope Diagnostic System (MMDx-Kidney)

The Kidney Molecular Microscope Diagnostic System (MMDx-Kidney) refers to mRNA gene expression analysis of 1,494 genes utilizing microarray; it measures mRNA transcript levels in transplant kidney biopsy tissue, with allograft rejection and injury algorithm reported as a probability score.

In a prospective study, Halloran and colleagues (2017) examined the feasibility of real time central molecular evaluation of kidney transplant biopsy samples from 10 North American or European centers. Biopsy samples taken 1 day to 34 years post-transplantation were stabilized in RNAlater, sent via courier over-night at ambient temperature to the central laboratory, and processed (29-hour work-flow) using microarrays to assess T cell- and antibody-mediated
rejection (TCMR and ABMR, respectively). Of 538 biopsy samples submitted, 519 (96%) were sufficient for microarray analysis (average length, 3 mm). Automated reports were generated without knowledge of histology and HLA antibody, with diagnoses assigned based on Molecular Microscope Diagnostic System (MMDx) classifier algorithms and signed out by 1 observer. Agreement between MMDx and histology (balanced accuracy) was 77% for TCMR, 77% for ABMR, and 76% for no rejection. A classification tree derived to provide automated sign-outs predicted the observer sign-outs with greater than 90% accuracy. In 451 biopsy samples where feedback was obtained, clinicians indicated that MMDx more frequently agreed with clinical judgment (87%) than did histology (80%) (p = 0.0042). In 81% of feedback forms, clinicians reported that MMDx increased confidence in management compared with conventional assessment alone. The authors concluded that real time central molecular assessment was feasible and offered a useful new dimension in biopsy interpretation. These researchers stated that the fact that the clinicians indicated that MMDx would add valuable support for clinical decisions beyond their current standard-of-care is encouraging for further development of MMDx testing. The findings of this feasibility study need to be validated by further investigation.

Reeve and associates (2019) previously reported a system for evaluating rejection in kidney transplant biopsies using microarray-based gene expression data, the MMDx. The present study was designed to optimize the accuracy and stability of MMDx diagnoses by replacing single machine learning classifiers with ensembles of diverse classifier methods. These researchers also examined the use of automated report sign-outs and the agreement between multiple human interpreters of the molecular results. Ensembles generated diagnoses that were both more accurate than the best individual classifiers, and nearly as stable as the best, consistent with expectations from the machine learning literature. Human experts had approximately 93% agreement (balanced accuracy) signing out the reports, and random forest-based automated sign-outs showed similar levels of agreement with the human experts (92% and 94% for predicting the expert MMDx sign-outs for TCMR and ABMR, respectively). In most cases disagreements, whether between experts or between experts and automated sign-outs, were in biopsies near diagnostic thresholds. Considerable disagreement with histology persisted. The balanced accuracies of MMDx sign-outs for histology diagnoses of TCMR and ABMR were 73% and 78%, respectively. Disagreement with histology was largely due to the known noise in histology assessments.

Furthermore, an UpToDate review on “Clinical features and diagnosis of acute renal allograft rejection” (Brennan et al, 2019) states that “The 2017 Banff Kidney Meeting Report modified the diagnostic criteria for ABMR by stating that both C4d staining and validated molecular assays could serve as potential alternatives to DSAs in the diagnosis of ABMR”.

www.aetna.com/cpb/medical/data/400_499/0493.html
CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+".

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>50300</td>
<td>Donor nephrectomy, (including cold preservation); from cadaver donor, unilateral</td>
</tr>
<tr>
<td></td>
<td>or bilateral</td>
</tr>
<tr>
<td>50320</td>
<td>Donor nephrectomy, (including cold preservation); open from living donor</td>
</tr>
<tr>
<td>50323</td>
<td>Backbench standard preparation of cadaver donor renal allograft prior to</td>
</tr>
<tr>
<td></td>
<td>transplantation, including dissection of allograft and removal or perinephric fat,</td>
</tr>
<tr>
<td></td>
<td>diaphragmatic and retroperitoneal attachments, excision of adrenal gland, and</td>
</tr>
<tr>
<td></td>
<td>preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as</td>
</tr>
<tr>
<td></td>
<td>necessary</td>
</tr>
<tr>
<td>50325</td>
<td>Backbench standard preparation of living donor renal allograft (open or laparoscopic) prior to transplantation, including dissection and removal of perinephric fat and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary</td>
</tr>
<tr>
<td>50327</td>
<td>Backbench reconstruction of cadaver or living donor renal allograft prior to</td>
</tr>
<tr>
<td></td>
<td>transplantation; venous anastomosis, each</td>
</tr>
<tr>
<td>50328</td>
<td>arterial anastomosis, each</td>
</tr>
<tr>
<td>50329</td>
<td>ureteral anastomosis, each</td>
</tr>
<tr>
<td>50340</td>
<td>Recipient nephrectomy (separate procedure)</td>
</tr>
<tr>
<td>50360</td>
<td>Renal allotransplantation, implantation of graft; without recipient nephrectomy</td>
</tr>
<tr>
<td>50365</td>
<td>Renal allotransplantation, implantation of graft; with recipient nephrectomy</td>
</tr>
<tr>
<td>50370</td>
<td>Removal of transplanted renal allograft</td>
</tr>
<tr>
<td>50380</td>
<td>Renal autotransplantation, reimplantation of kidney</td>
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<tr>
<td>50547</td>
<td>Laparoscopy, surgical; donor nephrectomy (including cold preservation); from living</td>
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<td>donor</td>
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Other CPT codes related to the CPB:

<table>
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<tr>
<th>Code Range</th>
<th>Description</th>
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<tbody>
<tr>
<td>77051 - 77057</td>
<td>Breast Mammography[female candidates should have a negative result within the past two years]</td>
</tr>
<tr>
<td>88141 - 88175</td>
<td>Cytopathology [female candidates should have a negative result within the past three years]</td>
</tr>
<tr>
<td>90918 - 90940</td>
<td>End stage renal disease services and hemodialysis</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td>96366</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96367</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion of a new drug/substance, up to 1 hour (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>96368</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (List separately in addition to code for primary procedure)</td>
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<td>99512</td>
<td>Home visit for hemodialysis</td>
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</table>

Other HCPCS codes related to the CPB:

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<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0101</td>
<td>Cervical or vaginal cancer screening; pelvic and clinical breast examination[female candidates should have a negative result within the past three years]</td>
</tr>
<tr>
<td>G0123</td>
<td>Screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; screening by cytotechnologist under physician supervision[female candidates should have a negative result within the past three years]</td>
</tr>
<tr>
<td>G0124</td>
<td>requiring interpretation by physician [female candidates should have a negative result within the past three years]</td>
</tr>
<tr>
<td>G0141 - G0148</td>
<td>Screening, cytopathology, other</td>
</tr>
<tr>
<td>G0202 - G0206</td>
<td>Mammography</td>
</tr>
<tr>
<td>G0308 - G0327</td>
<td>End stage renal disease services</td>
</tr>
<tr>
<td>S9335</td>
<td>Home therapy, hemodialysis; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing services coded separately), per diem</td>
</tr>
<tr>
<td>S9339</td>
<td>Home therapy; peritoneal dialysis, administrative services, professional pharmacy services, care coordination and all necessary supplies and equipment (drugs and nursing visits coded separately)</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>N18.5</td>
<td>Chronic kidney disease, Stage V</td>
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<tr>
<td>N18.6</td>
<td>End stage renal disease</td>
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</tbody>
</table>

ICD-10 codes contraindicated for this CPB:
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<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>D65 - D68.9</td>
<td>Coagulation defects [untreated]</td>
</tr>
<tr>
<td>C00.0 - C96.9, D00.00 - D09.9</td>
<td>Malignant neoplasms and carcinoma in situ [other than low grade prostate cancer and non-melatomatous skin cancers]</td>
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<td>E75.00 - E75.19, E75.23, E75.25 - E75.29, E75.4</td>
<td>Disorders of sphingolipid metabolism and other lipid storage disorders [severe neurological or mental impairment]</td>
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<tr>
<td>F10.10 - F19.99</td>
<td>Mental and behavioral disorders due to psychoactive substance [ongoing alcohol or drug abuse]</td>
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<tr>
<td>F84.2</td>
<td>Rett's syndrome [severe neurological or mental impairment]</td>
</tr>
<tr>
<td>G11.0 - G12.9, G13.8, G20 - G26, G30.0 - G32.8, G80.3, G90.01 - G91.9, G93.7, G93.89 - G93.9, G94, G95.0 - G95.9, G99.0, G99.2</td>
<td>Hereditary and degenerative diseases of the central nervous system [severe neurological or mental impairment]</td>
</tr>
<tr>
<td>I77.6</td>
<td>Arteritis, unspecified [active vasculitis]</td>
</tr>
<tr>
<td>Q00.0 - Q56.4, Q65.00 - Q99.9</td>
<td>Congenital anomalies [extrarenal congenital abnormalities]</td>
</tr>
</tbody>
</table>

**Kidney Microscope Diagnostic System (MMDx-Kidney):**

CPT codes not covered for indications listed in the CPB:

| 0088U | Transplantation medicine (kidney allograft rejection), microarray gene expression profiling of 1494 genes, utilizing transplant biopsy tissue, algorithm reported as a probability score for rejection |

**Belatacept (Nulojix):**

HCPCS codes covered if selection criteria are met:

| J0485 | Injection, belatacept, 1 mg |

ICD-10 codes covered if selection criteria are met:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>T86.10 - T86.19</td>
<td>Complications of kidney transplant [for the prevention of acute rejection in kidney transplant recipients who are sero-positive for the Epstein Barr virus (EBV)] [not covered for the prophylaxis of organ rejection in other transplanted organs]</td>
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<tr>
<td>Z94.0</td>
<td>Kidney transplant status [for the prevention of acute rejection in kidney transplant recipients who are sero-positive for the Epstein Barr virus (EBV)] [not covered for the prophylaxis of organ rejection in other transplanted organs]</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>T86.00 - T86.09, T86.20 - T86.99</td>
<td>Complications of transplanted organs and tissue [excludes kidney]</td>
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<tr>
<td></td>
<td><em>Soluble CD30:</em></td>
</tr>
<tr>
<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [not covered for measurement of pre-transplantation soluble CD30 level as a predictor of acute rejection in kidney transplantation]</td>
</tr>
<tr>
<td></td>
<td><em>Anti-thymocyte globulin:</em></td>
</tr>
<tr>
<td></td>
<td>HCPCS code covered if selection criteria are met:</td>
</tr>
<tr>
<td>J7504</td>
<td>Lymphocyte immune globulin, antithymocyte globulin, equine, parenteral, 250 mg</td>
</tr>
<tr>
<td>J7511</td>
<td>Lymphocyte immune globulin, antithymocyte globulin, rabbit, parenteral, 25mg</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes covered if selection criteria are met::</td>
</tr>
<tr>
<td>D61.0 - D61.9</td>
<td>Other aplastic anemias and other bone marrow failure syndromes [moderate to severe]</td>
</tr>
<tr>
<td>T86.10 - T86.19</td>
<td>Complications of kidney transplant [prophylaxis of allograft rejection episodes]</td>
</tr>
<tr>
<td>Z94.0</td>
<td>Kidney transplant status</td>
</tr>
<tr>
<td></td>
<td><em>Measurement of cytokines:</em></td>
</tr>
<tr>
<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [(e.g., cytokine-14, interleukin-1 beta [IL-1β], IL-2, IL-4, IL-6, granulocyte-macrophage colony-stimulating factor [GM-CSF], monocyte chemoattractant protein-1 [MCP-1], and tumor necrosis factor-alpha [TNF-α]; not an all-inclusive list) for the diagnosis of acute renal allograft rejection]</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>T86.10 - T86.19</td>
<td>Complications of transplanted kidney [not covered for the diagnosis of acute renal allograft rejection]</td>
</tr>
<tr>
<td>Z13.89</td>
<td>Encounter for screening for other disorder [Not covered for evaluating the risk of developing kidney graft rejection]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>------</td>
<td>------------------</td>
</tr>
<tr>
<td>Z94.0</td>
<td>Kidney transplant status [not covered for the diagnosis of acute renal allograft rejection]</td>
</tr>
</tbody>
</table>

**Bisphosphonate:**

HCPCS code covered if selection criteria are met:

- **J1436** Injection, Etidronate disodium, per 300 Mg
- **J1740** Injection, Ibandronate sodium, 1 mg
- **J2340** Injection, Pamidronate disodium, per 30 mg
- **J3489** Injection, Zoledronic acid, 1 mg

ICD-10 codes not covered for indications listed in the CPB:

- **Z94.0** Kidney transplant status [low bone mineral density]

**Interleukin-2-330 T/G and interleukin-10-1082 (G/A) promoter polymorphisms testing:**

There is no specific code for interleukin-2-330 T/G and interleukin-10-1082 (G/A) promoter polymorphisms testing:

**Pre-conditioning Therapy**

HCPCS code covered if selection criteria are met:

- **J9312** Injection, rituximab, 10 mg

ICD-10 codes not covered for indications listed in the CPB:

- **T86.10 - T86.19** Complications of transplanted kidney [ABO-incompatible kidney transplantation]

**Urinary neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid-binding protein (L-FABP):**

No specific code

ICD-10 codes not covered for indications listed in the CPB:

- **T86.19** Other complication of kidney transplant [acute kidney injury following kidney transplantation]

**Fas ligand (FASL) mRNA detection:**

CPT codes not covered for indications listed in the CPB:

- **83520** Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [fas-ligand (FASL) mRNA detection as a diagnostic marker for acute renal rejection]

ICD-10 codes not covered for indications listed in the CPB:

- **T86.10 - T86.19** Complications of kidney transplant [not covered as a diagnostic marker for acute renal rejection]
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z94.0</td>
<td>Kidney transplant status [not covered as a diagnostic marker for acute renal rejection]</td>
</tr>
</tbody>
</table>

**Urinary monocyte chemoattractant protein-1 (MCP-1/CCL2):**

CPT codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [urinary monocyte chemoattractant protein-1 (MCP-1/CCL2) for the detection and monitoring of renal graft rejection]</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T86.10 - T86.19</td>
<td>Complications of kidney transplant [not covered for the detection and monitoring of renal graft rejection]</td>
</tr>
<tr>
<td>Z94.0</td>
<td>Kidney transplant status [not covered for the detection and monitoring of renal graft rejection]</td>
</tr>
</tbody>
</table>

**Donor-Derived Cell-Free DNA Testing (e.g., Allosure):** no specific code:

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T86.10 - T86.19</td>
<td>Complications of kidney transplant</td>
</tr>
<tr>
<td>Z94.0</td>
<td>Kidney transplant status</td>
</tr>
</tbody>
</table>

**Measurement of angiotensin II type 1 (AT1) receptors or AT1 antibodies:** no specific code:

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z94.0</td>
<td>Kidney transplant status</td>
</tr>
</tbody>
</table>

**Complement inhibitors:**

HCPCS codes not covered for indications listed in the CPB:

- **Pexelizumab:** no specific code:
  
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0596</td>
<td>Injection, c1 esterase inhibitor (recombinant), ruconest, 10 units</td>
</tr>
<tr>
<td>J0597</td>
<td>Injection, c-1 esterase inhibitor (human), berinert, 10 units</td>
</tr>
<tr>
<td>J0598</td>
<td>Injection, c-1 esterase inhibitor (human), cinryze, 10 units</td>
</tr>
<tr>
<td>J0599</td>
<td>Injection, c-1 esterase inhibitor (human), (haegarda), 10 units</td>
</tr>
<tr>
<td>J1300</td>
<td>Injection, eculizumab, 10 mg</td>
</tr>
</tbody>
</table>

**Belimumab:**

HCPCS codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0490</td>
<td>Injection, belimumab, 10 mg</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T86.10 - T86.19</td>
<td>Complications of kidney transplant</td>
</tr>
<tr>
<td>Z94.0</td>
<td>Kidney transplant status</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


77. Yarlagadda SG, Nicholas T, Quarles LD. Bone disease after renal transplantation. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed March 2016.


86. Anglicheau D, Malone A, Chon WJ. Investigational methods in the diagnosis of acute renal allograft rejection. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed April 2018.

87. Rossi AP, Klein CL. Evaluation of the potential renal transplant recipient. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2018.


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AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0493
Kidney Transplantation

The Pennsylvania Medical Assistance Program considers symptomatic HIV infection to be absent when all of the following criteria are met:

1. CD4 count greater than 200 cells/mm³ for more than 6 months; and

2. HIV-1 RNA (viral load) undetectable or sustained virologic suppression below 200 copies/ml; and

3. On stable anti-viral therapy for more than 3 months; and

4. No other ongoing or untreated complications from AIDS, such as opportunistic infection (e.g., aspergillus, coccidiomycosis, resistant fungal infections, tuberculosis), Kaposi’s sarcoma or other neoplasms.