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Kidney transplantation is the optimal treatment for kidney failure, associated with a lower risk of mortality compared with dialysis (1) and improved quality of life (2). The number of kidney transplants in the United States continues to increase on an annual basis; 23,401 kidney transplants were performed in 2019, an 11% increase over the year prior (3). Advances in immunosuppression management have led to a marked decrease in early acute rejection episodes (4) as well as excellent 1-year allograft survival (>95%) (5); however, this success has been slow to translate into improved long-term graft longevity. Although there has been an incremental decline in late graft-loss rates over time, the median kidney transplant survival in the United States is only 11.2 years, compared with >14 years in the United Kingdom, Australia, and New Zealand (6).

Several factors contribute to the observed outcomes. Recipients of kidney transplants have aged over time and have more comorbidities; the number of recipients over age 65 has doubled since 2001, and the percentage of recipients with a body mass index >30 kg/m² or long dialysis vintage has also risen (7). Increased medical complexity has translated into diminished long-term patient and graft survival. Despite rigorous pretransplant screening, cardiovascular disease is the primary cause of mortality among recipients of kidney transplants; infection and malignancy represent the other main contributors. Simultaneously, due to a mismatch in organ supply and growing transplant demand, there has been greater use of more “marginal” kidneys for transplantation; although these organs are associated with reduced patient mortality compared with dialysis (8,9), they contribute negatively to national allograft survival rates. Late graft loss is frequently multifactorial (10), due to both immunologic and nonimmune-mediated mechanisms. It presents as slowly progressive kidney dysfunction, with generic histopathologic findings, historically called “chronic allograft nephropathy” (11), and now, more commonly, “interstitial fibrosis and tubular atrophy,” for lack of a better term. This and other progressive conditions, such as recurrent glomerular disease, eventually lead to graft failure. Recipients of transplants transitioning back to dialysis or being evaluated for retransplantation merit additional consideration in how their immunosuppression withdrawal is handled to maximize their KRT options. Unique populations, such as pediatric recipients of transplants, require special attention from clinicians, especially when they transition to care by adult nephrologists. Likewise, for female recipients of childbearing potential, transplantation offers an opportunity to become pregnant; their care also requires dedicated expertise and immunosuppression modifications to optimize outcomes for both mother and child.

Historically, due to the regulations of Centers for Medicare & Medicaid Services (12), 1- and 3-year patient and allograft survival had been the predominant focus, often to the detriment of longer-term outcomes, but this approach is changing (13). Given the large and growing number of recipients of transplants with a functioning allograft, long-term management of recipients of kidney transplants often falls to general nephrologists—frequently, but not always, in consultation with the transplant center. Thus, we believe this series of reviews will serve as an important resource for the larger nephrology community when caring for transplant patients in their practice and highlight the clinical issues that general nephrologists are most likely to encounter. With that in mind, we have created a series of 13 reviews authored by basic scientists and clinical experts in the field that will focus on two main areas of practice: (1) contemporary immunosuppression regimens and innovative immune-monitoring strategies to optimize outcomes for both mother and child.
strategies, and (2) post-transplant complications (Table 1). Reviews will cover state-of-the-art immunosuppression regimens and novel immune-monitoring strategies that provide additional insights beyond the kidney biopsy; sequelae of immune dysfunction, such as chronic allograft rejection and injury, will be reviewed. The long-term management concerns discussed will include common complications seen beyond the first post-transplant year, such as cardiovascular disease, infections, post-transplant malignancy, recurrent and de novo glomerular disease, and bone and mineral disease. The care of special populations, including recipients with a failing allograft, pediatric recipients transitioning to adult care, and pregnant recipients of kidney transplants, will also be reviewed in this series.

Successful kidney transplantation requires a team-based approach. In the early post-transplant period, this is centered around transplant nephrologists and surgeons, but partnership between general and transplant nephrologists is crucial in the long-term care of their mutual patients. We hope this series will foster a deeper understanding of the major clinical issues faced by recipients of transplants and prompt consideration of how we can optimize our joint care of this patient population.

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13. Centers for Medicare & Medicaid Services, Department of Health and Human Services: Medicare and Medicaid programs; organ procurement organizations conditions for coverage: Revisions to the outcome measure requirements for organ procurement organization. Fed Regist 84: 70628–70710, 2019

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Abstract
The long-term management of maintenance immunosuppression in kidney transplant recipients remains complex. The vast majority of patients are treated with the calcineurin inhibitor tacrolimus as the primary agent in combination with mycophenolate, with or without corticosteroids. A tacrolimus trough target 5–8 ng/ml seems to be optimal for rejection prophylaxis, but long-term tacrolimus-related side effects and nephrotoxicity support the ongoing evaluation of noncalcineurin inhibitor–based regimens. Current alternatives include belatacept or mammalian target of rapamycin inhibitors. For the former, superior kidney function at 7 years post-transplant compared with cyclosporin generated initial enthusiasm, but utilization has been hampered by high initial rejection rates. Mammalian target of rapamycin inhibitors have yielded mixed results as well, with improved kidney function tempered by higher risk of rejection, proteinuria, and adverse effects leading to higher discontinuation rates. Mammalian target of rapamycin inhibitors may play a role in the secondary prevention of squamous cell skin cancer as conversion from a calcineurin inhibitor to an mammalian target of rapamycin inhibitor resulted in a reduction of new lesion development. Early withdrawal of corticosteroids remains an attractive strategy but also is associated with a higher risk of rejection despite no difference in 5-year patient or graft survival. A major barrier to long-term graft survival is chronic alloimmunity, and regardless of agent used, managing the toxicities of immunosuppression against the risk of chronic antibody-mediated rejection remains a fragile balance.

Introduction
The long-term management of immunosuppression remains a tale of immediate gratification followed by frustrations and occasional disappointment. The introduction of calcineurin inhibitors and mycophenolate as immunosuppressive therapies began an era of improved maintenance immunosuppression efficacy. Short-term acute rejection rates decreased, and 1-year outcomes improved. Despite this short-term success, long-term kidney allograft survival has frustratingly not enjoyed a similar rate of improvement (1). In evaluating this discrepancy of short- versus long-term outcomes, it is apparent that the same maintenance immunosuppression that provides excellent short-term results may contribute to graft attrition with long-term exposure. In this review, we evaluate the current state of maintenance immunosuppression in kidney transplant recipients and discuss areas of opportunity and uncertainty in their long-term use.

Ideal Calcineurin Inhibitor Targets
The current standard of care in kidney transplant immunosuppression in the United States has evolved to be a calcineurin inhibitor–based immunosuppression regimen with tacrolimus and mycophenolate. Over 90% of patients in the United States are maintained on these two agents, with or without steroids (2). This is largely attributed to the landmark Symphony trial, which demonstrated superior outcomes in terms of both acute rejection rates and GFR at 1 in 3 years using a tacrolimus-based regimen when compared with cyclosporin- or sirolimus-based regimens (3), and historical studies that support mycophenolate over azathio-
No study to date has demonstrated superior outcomes with low-dose tacrolimus exposure <$5 mg/ml (7,8). A number of recent studies lend support to maintenance of tacrolimus \( C_{0} > 5 \) mg/ml in the prevention of \( \text{de novo} \) DSA formation, a marker currently used as a surrogate for future alloimmune injury, chronic antibody needed rejection, and alloimmune graft loss (9). In a single-center study of 538 patients followed from 2007 to 2013 who were maintained on tacrolimus and mycophenolate, a mean tacrolimus \( C_{0} < 8 \) ng/ml was associated with \( \text{de novo} \) DSAs by 12 months (odds ratio, 2.32; 95% confidence interval [95% CI], 1.30 to 4.15; \( P = 0.004 \)), whereas tacrolimus time in the therapeutic range 5–10 ng/ml of <60% during the first year was associated with \( \text{de novo} \) DSA (odds ratio, 2.05; 95% CI, 1.28 to 3.30; \( P = 0.003 \)), acute rejection (hazard ratio [HR], 4.18; 95% CI, 2.31 to 7.58; \( P < 0.001 \)) by 12 months, and death-censored graft loss by 5 years (HR, 3.12; 95% CI, 1.53 to 6.37; \( P = 0.002 \)) (10). Another single-center analysis of 596 kidney transplant recipients found an independent relationship of mean tacrolimus \( C_{0} < 5 \) and HLA-DR/DQ eplet mismatch with \( \text{de novo} \) DSA development (11). After \( \text{de novo} \) DSA develops, a higher mean tacrolimus \( C_{0} \) may protect against future graft loss (HR, 0.52; 95% CI, 0.30 to 0.89), with a threshold mean tacrolimus \( C_{0} < 5.3 \) ng/ml predictive of graft loss (12). Taken together, these data support recommendations to maintain tacrolimus \( C_{0} > 5 \) ng/ml for adequate immunosuppression. Appropriate tacrolimus trough goals must be adjusted downward when using tacrolimus in combination with mammalian target of rapamycin (mTOR) inhibitors, such as everolimus or sirolimus, due to a synergistic nephrotoxic effect noted with this combination. In the TRANSFORM trial, 2037 subjects were randomized to reduced-dose tacrolimus (tacrolimus \( C_{0} 2–4 \) ng/ml in combination with everolimus or standard tacrolimus/mycophenolate–based immunosuppression (tacrolimus \( C_{0} 6–10 \) ng/ml) (13). At 12 months post-transplant, no differences were noted between treatment arms for the combined end point of treated biopsy-proven acute rejection or eGFR <$50 ml/min per 1.73 m\(^2\) (48.2% in the everolimus arm versus 45.1% in the mycophenolate arm), graft loss, or death. There were fewer reported CMV and BKV events in the EVR arm, with higher discontinuation rates in the everolimus arm (23.0% versus 11.9%). Although this study suggests that one can achieve similar graft outcomes with a calcineurin inhibitor/mycophenolate–based regimen compared with a low-dose calcineurin inhibitor/everolimus regimen, longer-term kidney outcomes and \( \text{de novo} \) DSA formation were not evaluated, and different side effect profiles may make one strategy better suited for an individual patient.

**Noncalcineurin Inhibitor–Based Regimens**

Despite the predominant use of calcineurin inhibitors in the United States as the primary immunosuppressant agent (2), they are accompanied by multiple off-target side effects. Calcineurin inhibitors are associated with a higher risk of post-transplant diabetes, elevated BP, worsening hyperlipidemia, neurotoxicity, and acute and chronic nephrotoxicity (14–22). Currently, only one calcineurin inhibitor–free regimen, belatacept in combination with mycophenolate and corticosteroids, is US Food and Drug Administration (FDA) approved for use in adult kidney transplant recipients seropositive for Epstein–Barr virus. Belatacept is a soluble fusion protein that binds to CD80 and CD86 on the surfaces of antigen-presenting cells, thereby inhibiting CD28-mediated T cell costimulation (23). The regulatory approval of belatacept was, in part, on the basis of the results from two randomized phase 3 trials: BENEFIT and BENEFIT-EXT (24–27). In these studies, two dosing regimens of belatacept (“more intense” and “less intense”) were compared with a cyclosporin-based immunosuppression regimen. Under the FDA-approved “less intense” regimen, belatacept 10 mg/kg is administered intravenously on days 1 and 5 and weeks 2, 4, 8, and 12 post-transplantation, and 5 mg/kg belatacept is given every 4 weeks thereafter; outcomes with this dosing regimen are summarized below.

**BENEFIT and BENEFIT-EXT** differed primarily in the donor population that was utilized for transplantation. In BENEFIT, patients were transplanted with a living or standard criteria deceased donor kidney (26). At 12 months post-transplantation, the acute rejection rates for belatacept and cyclosporin were 17% and 7%, respectively; however, GFR was higher in the belatacept arm, even in those with rejection (mean measured GFR at month 12 in belatacept-treated patients with acute rejection was 61 versus 51 ml/min per 1.73 m\(^2\) in cyclosporin-treated patients without acute rejection). Patients enrolled to BENEFIT-EXT were recipients of extended criteria donor kidneys, kidneys with an anticipated cold ischemia time ≥24 hours, or kidneys donated after cardiac death (24). At 12 months post-transplantation, 18% of patients randomized to belatacept and 14% of those randomized to cyclosporin experienced acute rejection.

Acute rejection episodes under belatacept-based treatment tend to occur early in the post-transplantation period, with a low incidence of late rejections (24,26), and few events are reported after month 12 (25,27). The acute rejection rates at 3 years post-transplantation among belatacept-treated and cyclosporin-treated patients in BENEFIT were 17% and 10%, respectively (27); the corresponding values in BENEFIT-EXT were 19% and 16%, respectively (25).

In analyses of BENEFIT performed at 7 years post-transplantation, belatacept-based immunosuppression was associated with a reduction in the risk of death or graft loss compared with cyclosporin-based immunosuppression (HR, 0.57; 95% CI, 0.35 to 0.94; \( P = 0.02 \)) (28), whereas in BENEFIT-EXT, the risk of death or graft loss at 7 years post-transplantation was similar between the groups (HR, 0.93; 95% CI, 0.63 to 1.36; \( P = 0.70 \)) (29). Despite the difference in acute rejection between belatacept and cyclosporin at 7 years, belatacept-based immunosuppression was associated with superior kidney function in both studies as eGFR maintained a positive slope and increased by +1.39 ml/min per 1.73 m\(^2\) per year in BENEFIT and +1.51 ml/min per 1.73 m\(^2\) per year in BENEFIT-EXT, with mean 7-year eGFRs of 63.3 and 54.2 ml/min per 1.73 m\(^2\) in BENEFIT and BENEFIT-EXT, respectively. In contrast, eGFR decreased over time in the cyclosporin group by −1.04 ml/min per 1.73 m\(^2\) per year in BENEFIT and −0.01 ml/min per 1.73 m\(^2\) per year in BENEFIT-EXT (both \( P < 0.001 \)), with mean 7-year eGFRs of 56.6 and 35.3 ml/min per 1.73 m\(^2\) for BENEFIT and BENEFIT-EXT, respectively (29,30). Additionally, patients treated with belatacept were noted to have lower
The remaining 300 patients were randomly assigned to and/or elevated values of serum creatinine or proteinuria. From the study at 4.5 months because of adverse events. Sodium, and corticosteroids, 203 patients were dropped induction and maintenance cyclosporin, mycophenolate mus. In the ZEUS trial, 503 patients were enrolled. After initial treatment with basiliximab, 443 patients with kidney transplants were randomized to continue their calcineurin inhibitor or conversion from calcineurin inhibitor to SRL (40). At 2 years, the rates of biopsy-proven rejection were 7.9% and 6.9% for patients on sirolimus and patients on calcineurin inhibitor, respectively. There was no difference in 2-year patient or graft survival. In patients converted to sirolimus, malignancy rates were significantly lower, but the cumulative number of side effects was significantly higher. Median proteinuria increased significantly after conversion to sirolimus. In patients with eGFR < 40 ml/min at the time of randomization, kidney function tended to deteriorate earlier in the sirolimus group (40). Overall, the role of mTOR inhibitors to replace calcineurin inhibitors as part of a conversion strategy has not been met with mixed results. Current data suggest that patients with an already reduced eGFR and/or proteinuria will receive no benefit (40) from calcineurin inhibitor elimination with mTOR inhibitor conversion, and early use of mTOR inhibitors without a calcineurin inhibitor may be mired by high rejection rates and a high side effect profile, thus potentially limiting their use.

There is some evidence supporting a role for mTOR inhibitors in reducing the risk of cancer, particularly skin cancer. The most common cancer in kidney transplant recipients is squamous cell carcinoma (SCC), with a 65- to 250-fold higher risk compared with the general population (41). The immunosuppression risk in SCC results from both a decrease in immune surveillance and drug-specific effects. Calcineurin inhibitors may enhance SCC development through mechanisms independent of host immunity (42,43). In contrast, some studies have noted a lower rate of SCC in transplant recipients treated with an mTOR inhibitor compared with those on a calcineurin inhibitor (44-46). In one multicenter randomized trial of kidney transplant recipients, the effect of conversion from a calcineurin inhibitor to the mTOR inhibitor sirolimus for secondary prevention of SCC versus staying on a calcineurin inhibitor was evaluated (47). New SCC developed in 22% and 39% of the sirolimus conversion group and the calcineurin inhibitor group, respectively (P = 0.02), with a relative risk in the sirolimus group of 0.56 (95% CI, 0.32 to 0.98) despite a higher discontinuation rate. Graft function remained stable in the two groups. It should be noted that this benefit primarily extended to patients who experienced a single SCC event prior to conversion. The potential protective effects of mTOR inhibitors for malignancy must be balanced against the inferior graft outcomes noted with this agent, as evidenced by a large meta-analysis describing a 40% reduced risk of malignancy but a 43% higher risk of mortality with SRL use or conversion (48).
Steroid Withdrawal

Early corticosteroid withdrawal (within the first week post-transplant) is a common immunosuppression strategy, as approximately 30% of all kidney transplant recipients are maintained on tacrolimus/mycophenolate steroid-free immunosuppression at 1 year following transplant in the United States (2). However, the long-term benefits (and risks) of steroid-free regimens are unclear. A well-performed randomized controlled trial with 5-year follow-up demonstrated no differences in graft or patient survival, cardiovascular risk factors, weight gain, or incidence of post-transplant diabetes, with more acute rejection in the early corticosteroid withdrawal arm and fewer bone complications in the steroid-containing arm (49). The increase in acute rejection rates in early corticosteroid withdrawal can be mitigated, but not entirely eliminated, by the use of depleting antibody induction (50). A number of registry analyses have corroborated the findings of a lower acute rejection risk when using depleting antibody therapy and a steroid-free regimen with acceptable short-term graft and patient survival (51–53); however, a recent registry analysis reported higher graft loss and mortality in deceased donor recipients with delayed graft function who underwent early corticosteroid withdrawal (54).

In a large meta-analysis of studies comparing steroid withdrawal versus steroid maintenance, the cumulative data reiterated this increase in acute rejection risk (seven studies, 835 participants: RR, 1.58; 95% CI, 1.08 to 2.30) but found no significant difference in 1-year patient mortality (ten studies, 1913 participants: RR, 0.68; 95% CI, 0.36 to 1.30), graft loss (eight studies, 1817 participants), or graft loss excluding death with functioning graft (RR, 1.17; 95% CI, 0.72 to 1.92) (55). There was no evidence to suggest a difference in harmful events, such as infection and malignancy. Beyond these hard end points and examining other corticosteroid-associated complications, a single-center experience reported 15-year outcomes in 1553 patients transplanted from 1999 to 2015 utilizing an early corticosteroid withdrawal protocol (56). Compared with a historical cohort, nongraft-related complications (avascular necrosis, cytomegalovirus infection, cataract formation, new-onset diabetes after transplant, and cardiac complications) were significantly lower in the early corticosteroid withdrawal cohort. A single well-performed, prospective, randomized controlled trial of 615 patients with stringent diagnoses of post-transplant diabetes using current American Diabetes Association guidelines demonstrated equivalent acute rejection rates using depleting or nondepleting antibody induction therapy and significantly lower rates of post-transplant diabetes in early corticosteroid withdrawal (24%) versus continued corticosteroid therapy (39%) at 12 months (57). One potential explanation for the differences found in this trial compared with previous reports includes utilization of low-immunologic risk patients, primarily first transplant recipients with no sensitization (0% calculated panel-reactive antibodies) (57). Overall, the overwhelming evidence suggests that steroid withdrawal after kidney transplantation significantly increases the risk of acute rejection yet provides comparable short- and medium-term graft survival, but withdrawal has limited effect on traditionally considered steroid-related side effects. In the absence of more robust findings, early corticosteroid withdrawal will likely continue at the approximately 30% rate that it has maintained for the past decade (2).

Balancing Risk of Chronic Alloimmunity with Chronic Nephrotoxicity

The problem of chronic alloimmunity (chronic antibody-mediated rejection) versus chronic nephrotoxicity has become the yin and yang of tacrolimus-based immunosuppression. The untoward effects of tacrolimus-based immunosuppression are perhaps best exemplified by a recent comprehensive surveillance biopsy study that described histologic injury 10 years after transplant in functioning grafts. In 145 surveillance biopsies performed 10 years following transplant, arteriolar hyalinosis, mesangial sclerosis, and global glomerulosclerosis were the most common lesions identified in 50%–70% of biopsies (58). These lesions generally are considered nonimmunologic in nature and often are associated with the systemic and vascular effects of calcineurin inhibitors. These findings are in contrast to prior studies of kidneys biopsied in a state of impending failure (mean 4.2 years following transplant) or “for cause” (with failure at a median 2.7 years following biopsy), in which glomerular lesions and antibody-mediated injury were the most common findings (59,60). In the short term, control of alloimmunity is critical, but the price to be paid for this control is later nephrotoxicity. Long-term transplant outcomes are clearly limited, at least in part, by adverse effects of calcineurin inhibitor–based immunosuppression, which has led to the search for minimization or withdrawal strategies as described above. Many have been reported, and although some result in improved kidney function, this is often at higher risk of rejection, best summarized by a comprehensive meta-analysis by Sawinski et al. (61). Perhaps a combination of low-dose tacrolimus in combination with angiotensin-converting enzyme inhibitor/angiotensin II receptor 1 blocker therapy may permit both adequate immunosuppression and protection from chronic scarring related to tacrolimus use. A recent randomized controlled trial supports this hypothesis, demonstrating that early low-dose tacrolimus exposure during the first 6 months post-transplant (tacrolimus C0 target of 5 ± 1 versus 8–12 ± 2 ng/ml) together with angiotensin-converting enzyme inhibitor/angiotensin II receptor 1 blocker use demonstrated equivalent GFR, acute rejection rates, and de novo DSA rates compared with “standard” tacrolimus exposure, with reductions in interstitial fibrosis and tubular atrophy on surveillance biopsy at 24 months following transplant (62).

Are There New Immunosuppression Agents on the Horizon?

At present, there is a paucity of novel maintenance immunosuppressive agents in the pipeline. Iscalimab, an anti-CD40 mAb, has been studied in a phase 2 trial, and other agents targeting costimulation blockade are in preclinical development (63). Clinicians are thus left to determine how best to optimize the agents currently available, including use of once-daily formulations of tacrolimus (64), alternative dosing strategies for belatacept (65), and risk assessment of patients (using both clinical and emerging immune
<table>
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<tr>
<th>Trial Name</th>
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<th>Future Strategies (Applicable to All Studies)</th>
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<tr>
<td>Symphony</td>
<td>Tacrolimus superior to cyclosporin or sirolimus for the end points of 1-yr acute rejection, GFR</td>
<td>Optimal MMF dose unknown</td>
<td>Risk stratify patients for enrollment into minimization/withdrawal studies not only on the basis of traditional clinical and immunologic risk factors but also on novel immunologic assessments (e.g., baseline T cell reactivity, epitope matching)</td>
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<td>TRANSFORM</td>
<td>Everolimus/low calcineurin inhibitor/ prednisone is noninferior to standard calcineurin inhibitor/ mycophenolate/prednisone</td>
<td>No long-term outcomes of DSA, proteinuria, GFR</td>
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<tr>
<td>BENEFIT</td>
<td>Belatacept with superior GFR despite higher AR rates than cyclosporin</td>
<td>Control arm not standard of care</td>
<td>Investigate end points beyond 1 year graft survival, patient survival, rejection (e.g., iBox, GFR, histological end points)</td>
</tr>
<tr>
<td>Astellas corticosteroid withdrawal</td>
<td>Tacrolimus/mycophenolate with comparable graft survival and GFR despite higher AR than tacrolimus/mycophenolate/prednisone</td>
<td>Details regarding rejection and effect on outcomes not described</td>
<td>Utilize emerging biomarker assessments to risk stratify patients for enrollment and randomization to determine timing of protocol-specified immunosuppression change/increase/decrease, and as surrogate end points (e.g., blood genomic profiling, molecular assessment of kidney transplant biopsy tissue, urinary chemokines and mRNA, blood donor-derived cellfree DNA)</td>
</tr>
<tr>
<td>CONVERT</td>
<td>Calcineurin inhibitor to sirolimus conversion at 6-120 mo was associated with inferior outcomes in those with GFR&lt;40 and proteinuria in those above GFR 40</td>
<td>Randomized by GFR and not by histologic features (e.g., IFTA with lack of glomerulosclerosis)</td>
<td></td>
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<tr>
<td>ZEUS</td>
<td>Cyclosporin to everolimus conversion at 4.5 mo was associated with higher GFR but more rejection and higher discontinuation rate</td>
<td>No DSA data or formal histologic assessments</td>
<td></td>
</tr>
<tr>
<td>BEST</td>
<td>Belatacept/early steroid withdrawal with depleting antibody induction was not superior to TAC/early steroid withdrawal</td>
<td>No long-term GFR follow-up or formal histologic assessments</td>
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MMF, mycophenolate; DSA, donor-specific antibody; AR, acute rejection; IFTA, interstitial fibrosis and tubular atrophy; TAC, tacrolimus.
monitoring tools) in whom deviation from standard immunosuppression is desired. Future studies will need to examine clinically important end points beyond 1-year graft and patient survival and 1-year rejection rates in order for new immunosuppression and immunosuppressive strategies to gain traction. For example, a comprehensive predictor of long-term survival has recently been proposed, the “Box score,” that includes histology, GFR, DSA, and other clinical characteristics that have been validated as tools to predict long-term graft survival (66). General considerations to advance our current knowledge and clinical practice are provided in Table 1.

Long-term immunosuppression management remains a balancing act, with efforts being made to maximize outcome (patient and graft survival) and minimize toxicity. Thus far, no immunosuppression regimen has proven to be without a potential pitfall. Efforts, however, are underway in the transplant community to take a more balanced approach to immunosuppression by utilizing tools, such as donor-derived cellfree DNA, gene expression profiling, and HLA matching/DSA monitoring, to achieve a personalized approach to long-term immunosuppression management. Randomized clinical trials utilizing these tools are needed to better elucidate their role in long-term patient care and outcomes.

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Beyond the Biopsy: Monitoring Immune Status in Kidney Recipients

Roy D. Bloom1 and Joshua J. Augustine2

Abstract
Improved long-term kidney allograft survival is largely related to better outcomes at 12 months, in association with declining acute rejection rates and more efficacious immunosuppression. Finding the right balance between under- and overimmunosuppression or rejection versus immunosuppression toxicity remains one of transplant’s holy grails. In the absence of precise measures of immunosuppression burden, transplant clinicians rely on nonspecific, noninvasive tests and kidney allograft biopsy generally performed for cause. This review appraises recent advances of conventional monitoring strategies and critically examines the plethora of emerging tests utilizing tissue, urine, and blood samples to improve upon the diagnostic precision of allograft surveillance.

Introduction
Long-term improvement in kidney transplant outcomes is mostly related to better 1-year allograft survival (1–3), concomitant with declining acute rejection under contemporary immunosuppression largely comprising T cell–depleting induction and tacrolimus/mycophenolic acid-corticosteroid maintenance therapy (2). Between years 2 and 10 post-transplant, allograft attrition rates approximate 5%–7% per year (1). Allograft failure occurs from immunologic or nonimmunologic causes, whereas immunosuppression toxicity affects patient morbidity and mortality. Optimizing transplant outcomes is a central recipient care tenet, commencing with pretransplant immunologic assessment. Without a post-transplant measure of immunosuppression burden or risk of rejection versus overimmunosuppression, clinicians rely on nonspecific markers and indication biopsies for guidance, with allograft histology or transplant failure the gold standard against which nonspecific tests are measured. Noninvasive monitoring tools are being developed for use in several contexts, including as diagnostic, prognostic, and/or predictive markers (Table 1). We herein review conventional tools used for these assessments and highlight emerging tissue, urine, and blood biomarkers aimed at improving precision.

Pretransplant Immunologic Risk Assessment
Preexisting Donor-Specific Antibody and Histocompatibility Leukocyte Antigen Epitope Mismatch
Detectable preexisting donor-specific antibody (DSA), ascertained at transplant, is associated with chronic allograft failure (4). Patients with pretransplant DSA and positive crossmatches have high rates of persistent or recurrent DSA post-transplant. Despite desensitization protocols, antibody-mediated rejection occurs in approximately 50% of patients with persistent DSA post-transplant (5,6).

Allotantibodies to HLA engage the HLA molecule’s epitope. Epitope binding affinity is determined by an eplet, a single or small number of polymorphic amino acids near the HLA surface that influence antibody specificity and immunologic risk (7). A seminal 286-patient study demonstrated that locus-specific epitope mismatch correlated more robustly with de novo DSA formation than traditional DR/DQ mismatch (8). Epitope mismatch has since been correlated with rejection and allograft loss when combined with nonadherence (9) and with immunosuppression minimization (10). More recent application of HLA-DR/DQ single-molecular eplet mismatch further improved correlation with de novo DSA and facilitated stratification of recipients into low–, intermediate–, and high–alloimmune risk categories (11). Molecular mismatch risk category was associated with de novo DSA, antibody- and T cell–mediated rejection, and graft loss, findings since validated elsewhere (12,13). Molecular mismatch risk stratification should be easily implementable in HLA laboratories, with potential to positively affect post-transplant outcomes.

Nonhistocompatibility Leukocyte Antigen Mismatching and Nonhistocompatibility Leukocyte Antigen Antibodies
Recently, donor/recipient non-HLA allelic mismatches associating with antibody-mediated rejection were identified through exome sequencing of mononuclear cell DNA (14). Genes for kidney and blood vessel cell surface proteins incurred risk independent of HLA mismatch. In an unrelated study, the presence pretransplant of non-HLA antibodies targeting glomerular endothelium (MHCl class 1–related chain A, endothelin 1 type A, and angiotensin type 1 receptor) has been...
associated with early post-transplant microvascular injury resembling antibody-mediated rejection (15). These preliminary observations indicate that non-HLA-related biomarkers are promising tools to assess post-transplant immunologic risk of potential candidates.

**Enzyme-Linked Immune Absorbent Spot**

Enzyme-linked immune absorbent spot (ELISPOT) quantitatively measures the cytokine secreting cell frequency. ELISPOT assays for IFN-γ identify effector memory T cells pretransplant when mixed with T cell-depleted donor cells. Pretransplant ELISPOT positivity correlated with rejection in higher-risk populations (16) and during tacrolimus withdrawal in lower-risk patients (17). The association of pretransplant ELISPOT with rejection is tempered by antithymocyte globulin therapy. A recent analysis found a rejection rate of 15% in ELISPOT-positive patients versus 3% in negative patients (18). Among ELISPOT-positive patients who received antithymocyte globulin induction, there was no rejection. In Clinical Trials in Organ Transplantation 01 (CTOT-01), pretransplant ELISPOT similarly predicted allograft function only in the nondepleting induction subgroup (17).

**Peripheral Blood Gene Signature**

Investigators from the Study of the Genomics of Chronic Allograft Rejection (GoCAR) recently performed whole-blood RNA sequencing in patients pretransplant, developing a 23-gene set that predicted early T cell rejection and associated with late graft loss (19). Further validation of this signature is underway.

**Conventional Post-Transplant Monitoring Allograft Function**

Studies demonstrate that 1-year kidney transplant function predicts longer-term failure (20,21), a risk that is greater with worsening albuminuria (22–24). Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend ongoing serum creatinine and urine protein monitoring, with dysfunction episodes evaluated by allograft ultrasound (25). Allograft biopsy is indicated when diagnosis is uncertain, for evaluating proteinuria, or where histologic findings will affect treatment.

**Drug-Level Monitoring**

Although drug monitoring for tacrolimus, cyclosporin, sirolimus, and everolimus is routine, the utility of mycophenolic acid levels is not established (26). Trough calcineurin inhibitor levels correlate fairly well with total drug exposure. Out of range levels may signify nonadherence; underdosing; formulation change; or unrecognized drug-drug, food-drug, or gut-drug interactions, providing opportunity for patient counseling or regimen adjustment before rejection or toxicity ensues.

Tacrolimus-level variability over time predicts underdosing/nonadherence and rejection (27–30). High intrapatient tacrolimus-level variability is associated with interstitial fibrosis/tubular atrophy (IFTA) (27), rejection, and allograft failure (28). In one study, recipients with de novo DSA had higher proportions of tacrolimus levels <5 ng/ml; moreover, levels were significantly lower in the 6 months preceding de novo DSA detection than at earlier time points (29).

Time in therapeutic range, typically used in anticoagulation management, is a newer concept in transplantation. Time in therapeutic range—a calculation of the percentage of time a level is within the predefined target range in individual patients—has been applied to tacrolimus therapy (30). On the basis of target levels 5–10 ng/ml within the first post-transplant year, time in therapeutic range <60% associates with de novo DSA and rejection risk by 12 months
and allograft loss by 5 years post-transplant. Analysis incorporating both time in therapeutic range and coefficient of variation suggests the immunologic risk associated with high intrapatient tacrolimus-level variation is due to low time in therapeutic range rather than variability in and of itself (31). Use of these simple tracking tools is an actionable strategy to monitor medication nonadherence, optimize dosing, and improve outcomes.

**Donor-Specific Antibody**

*De novo* DSA develops in 15%–20% of patients within the first few post-transplant years (7,13). One study monitored *de novo* DSA over a mean of 6.2 years in 315 nonsensitized patients, demonstrating that its presence associated with HLA-DR mismatch and patient nonadherence and adversely affected 10-year allograft survival (7). Other DSA risk factors include immunosuppression minimization, DQ mismatching, and early T cell–mediated rejection (32), with mostly class 2 DSA identified in this latter setting (33,34).

In patients with antibody-mediated rejection, *de novo* DSA appears to have greater negative effect than preexisting DSA. In a 205-patient antibody-mediated rejection cohort evenly divided between recipients with pretransplant DSA and *de novo* DSA, antibody-mediated rejection occurred earlier in the latter group (median 85 versus 1437 days). Patients with *de novo* DSA demonstrated more proteinuria, greater class 2 antibody, higher antibody titers, more frequent transplant glomerulopathy, and worse allograft survival at 8 years (35).

Transplantation Society guidelines recommend DSA monitoring in the setting of recipients with pretransplant DSA (36), immunosuppression reduction, patient nonadherence, or a rejection episode occurrence, with close allograft function surveillance when detected (37). Transplant biopsy, similarly recommended upon DSA detection, notably has no evidence grade. In this setting, we believe biopsy may have diagnostic utility, although acknowledge absence of data demonstrating the procedure results in improved outcomes.

**Viral Screening**

Through the interplay between antiviral and alloimmune responses, viruses result from immunosuppression but may also trigger rejection. Virus-specific T cells crossreactive to alloantigen have been demonstrated in the circulation of Epstein–Barr virus (EBV)– and/or cytomegalovirus-infected patients (38). BK virus (BKV) impairs allograft function through cytopathic injury yet is associated with *de novo* DSA and rejection (39,40). Mechanisms linking BKV to alloimmunity are unclear but include immunosuppression reduction or heterologous immunity. Supporting the latter, BKV nephropathy allograft biopsies have been shown to simultaneously contain both BKV-reactive and alloreactive T cell clones (41).

These viral infections typically occur within 6 months post-transplant. Except for pre-emptive treatment strategies or guiding therapy in infected individuals, no cytomegalovirus screening recommendations exist (23). KDIGO guidelines suggest EBV nucleic acid testing in EBV-seronegative recipients of EBV-seropositive kidneys once in week 1, monthly for 3–6 months, then quarterly until 12 months post-transplant, and when treating rejection (23). Although American Society of Transplantation (AST) Infectious Diseases Community of Practice (IDCOP) guidelines suggest more frequent testing (42), both guidelines advocate immunosuppression reduction for worsening EBV viremia.

BK viremia and BKV nephropathy prevalence rates are 10%–30% and 2%, respectively (43). Routine screening enables BKV detection before nephropathy affects kidney function (44). KDIGO suggests monthly testing until 9 months and then quarterly until 24 months because 30% of BKV infections occur beyond 6 months post-transplant (46). Because intragraft BKV replication may be focal, up to one third of BKV-infected biopsy samples may test negative; this false-negative rate declines as viral loads exceed six log10 copies per milliliter (46). We recommend allograft biopsy in recipients with both BK viremia and either new allograft dysfunction or another abnormal diagnostic biomarker.

**Torque Teno Virus—An Emerging Immunosurrogate**

Torque teno virus (TTV) is an apathogenic virus with no known therapies (47). In the transplant context, a recent study reported that around 43 days prebiopsy, patients with rejection had lower blood TTV levels than nonrejecting patients (48). A subsequent prospective, observational study incorporated TTV viral load measurements weekly initially and then quarterly until 12 months post-transplant (49). Torque Teno viral load peaked 3 months post-transplant; thereafter, each TTV viral load log increase associated with a 22% lower rejection odds and an 11% greater odds for another infection. Viral loads between $1 \times 10^{6}$–$10^{9}$ copies per milliliter were identified as the “sweet spot” for optimally minimized risk for rejection and infection. Although further validation is required, TTV represents another potential immune status monitoring tool.

**Surveillance Biopsies**

Historically performed in “high-risk” patients, the rationale for surveillance kidney transplant biopsy is determination of “subclinical rejection” described in cyclosporin-treated patients, where 30% of recipients biopsied by protocol early post-transplant displayed histologic tubulitis despite stable laboratory values (50,51). A similar study subsequently conducted in tacrolimus-MMF-prednisone–treated patients observed subclinical rejection rates <5%, with no differences in patient/allograft survival or IFTA at 2 years post-transplant (52,53). The investigators concluded there was no benefit to surveillance biopsies in patients receiving this immunosuppression regimen.

Recent surveillance biopsy studies have focused on subclinical borderline T cell–mediated rejection, detected in approximately 25%–40% of participants (54–56). Follow-up biopsies have demonstrated histologic progression despite treatment (54,55). Although these data may support surveillance biopsy (and potentially, rebiopsy when
subclinical injury is detected), it should be borne in mind that consensus around the histologic definition of borderline T cell rejection (57) and effectiveness of treatment in this setting is not established.

Surveillance biopsies may have value in patients undergoing major immunosuppression modification. Heilman et al. (58) correlated 1- or 4-month post-transplant biopsy findings with a 12-month biopsy in 256 recipients who underwent rapid corticosteroid withdrawal. Although 6% developed overt rejection by 12 months, early surveillance biopsy revealed subclinical rejection or inflammation in 27%. Both subclinical rejection and inflammation predicted greater IFTA at 12 months. Another study randomized low-immunologic risk recipients to continued tacrolimus versus conversion to sirolimus at 3 months post-transplant (59). Despite similar kidney function, 24-month surveillance biopsies showed more subclinical inflammation and IFTA in the sirolimus arm.

A recent US transplant center survey found that surveillance biopsies were performed by 38 of 83 (46%) responding centers; 20 centers biopsied all patients, whereas 18 were more selective (60). This increased biopsy rate compared with a prior survey (61) may reflect currently perceived need for histology in lieu of reliable immune monitoring tools. An analysis that examined complications after 2514 kidney allograft biopsies observed fewer major complications in surveillance than for-cause procedures (0.3% versus 3%), with surgical intervention undertaken in 0.6% and no attributable graft losses or death (62). These findings support that surveillance kidney transplant biopsies are safe.

Limitations of Conventional Monitoring and Biopsy

Serum creatinine, widely available, inexpensive, and with rapid turnaround, is neither specific nor sensitive, and often, it is a late injury indicator. Kidney biopsy is costly, sampling error prone, limited by subjective interpretation, and inconvenient, and it carries some risk. Surveillance biopsies are lower yield than indication biopsies because many patients with unremarkable history will be biopsied. Moreover, optimal timing and surveillance biopsy frequency are unknown. Finally, although identifying morphologic changes that predict outcomes, surveillance biopsies have yet to result in interventions established to improve outcomes.

These collective limitations, coupled with technological advancement, have spawned interest in finding more specific, noninvasive tissue, urine, and blood biomarkers. An important premise for seeking status quo alternatives is that allograft injury and damage are driven by subclinical, often repetitive events (63), underscoring the need for scalable monitoring strategies.

Novel Tissue Diagnostics

Halloran et al. (64) analyzed molecular allograft rejection phenotypes by measuring mRNA transcripts in biopsy tissue. Comparing T cell–mediated and antibody-mediated rejection biopsies with normal histology revealed that prominent transcripts for both rejection types were induced by IFN-γ. Effector T cell and myeloid cell expressions were T cell–mediated rejection specific, whereas transcripts for natural killer cell localization and endothelial injury were unique to antibody-mediated rejection. There was some transcript overlap between rejecting and nonrejecting allografts (65), but generally strong associations of transcripts with rejection and rejection subtypes were preserved in validation testing.

Application of this “microarray-based molecular diagnostic system” (MMDX) was demonstrated in a multicenter study (66). MMDX defined antibody-mediated rejection in 41% of biopsies where it was not reported originally and revealed antibody-mediated rejection transcript signaling in C4d-positive and -negative biopsies. The MMDX system has been used to analyze biopsies with inflammation in areas of IFTA, revealing predominant antibody-mediated rather than T cell–mediated rejection (67). Recently, the Banff Working Group described a 770 biopsy tissue–derived gene panel using a Nano-String platform. Genes were categorized by host organ transplant responses, including rejection, tolerance, drug toxicity, and viral infection, with plans for future multicenter validation using a commercially available assay (68).

The GoCAR study utilized mRNA microarray analysis to predict fibrosis progression at 1 year from biopsy tissue collected at 3 months post-transplant (69). Using the Chronic Allograft Damage Index score, 12-month biopsies with scores of >2 were analyzed, identifying a gene set that correlated with fibrosis. After application to 3-month biopsies in cases where fibrosis worsened by month 12, a 13–gene set panel was derived that predicted subsequent fibrosis, independent of clinicopathologic variables.

Novel Noninvasive Biomarkers

Ideal diagnostic biomarkers should identify patients with high disease probability (high positive predictive value). Prognostic and predictive biomarkers can then be applied to determine both patients at high risk for a bad prognosis and predicted treatment benefit. Assays should provide greater lead time for detecting and monitoring allograft injury, be reproducible, have a low coefficient of variation, have rapid turnaround, and permit cost-effective surveillance. Moreover, they could provide dynamic analyses of allograft and immune status, enabling precise risk stratification, with potential to guide need for biopsy or immunosuppression modification.

Urinary Biomarkers

Chemokines CXCL9 and CXCL10 recruit effector T cells in response to IFN-γ and have been identified as urinary markers of acute rejection in separate clinical trials. In CTOT-04, Suthanthiran et al. (70) analyzed urinary mRNA collected serially from 485 kidney recipients within the first post-transplant year. A three-gene signature was derived using CD3ε, CXCL10, and 18S ribosomal RNA that discriminated T cell–mediated rejection from no rejection. Analysis of urine samples from reiectors showed increased chemokine gene expression as early as 120 days before biopsy.
Table 2. Conventional and emerging biomarkers used in kidney transplant

<table>
<thead>
<tr>
<th>Test</th>
<th>Suggested Testing Frequency</th>
<th>Potential Benefit</th>
<th>Limitation(s)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UP/Cr</td>
<td>1, 3 mo, then quarterly</td>
<td>Low cost, actionable surveillance test</td>
<td>• Lacks sensitivity to detect some rejection, inflammation</td>
<td>Opportunity for antiproteinuric therapy/targeted therapy</td>
</tr>
<tr>
<td>Tacrolimus TTR/CV</td>
<td>Ongoing</td>
<td>Actionable, low cost, monitor nonadherence</td>
<td>• Targeted levels not specific for immune response of individual patients</td>
<td>Can incorporate into electronic medical record</td>
</tr>
<tr>
<td>EBV NAT</td>
<td>Monthly for 6–12 mo</td>
<td>IS management guide in EBV + /− recipients</td>
<td>• Not standardized</td>
<td>Reduce IS for rising viral load</td>
</tr>
<tr>
<td>BKV NAT</td>
<td>1, 3, 6, 12 mo</td>
<td>Guide IS management</td>
<td>• Not standardized</td>
<td>Reduce IS for rising viral load</td>
</tr>
<tr>
<td>DSA</td>
<td>1, 3, 6, 12 mo</td>
<td>Risk stratification/guide IS management</td>
<td>• Not standardized</td>
<td>Opportunity to enroll in contemporary clinical trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No proven surveillance benefit</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• $$</td>
<td></td>
</tr>
<tr>
<td><strong>Emerging</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surveillance biopsy</td>
<td>Once in first 3 mo?</td>
<td>Risk stratification, relatively safe</td>
<td>• Risk of complications</td>
<td>Possible use in conversion/minimization regimens, patients with DSA, clinical trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Sampling error</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• No proven outcome benefit</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• $$</td>
<td></td>
</tr>
<tr>
<td>MMDX</td>
<td>TBD</td>
<td>Discriminates rejection types, with improved consistency</td>
<td>• Some diagnostic overlap</td>
<td>Consider for patients being biopsied where histology findings are unclear to guide therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No prospective intervention or outcome data</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• $$</td>
<td></td>
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<tr>
<td>Urine chemokines</td>
<td>TBD</td>
<td>Predicts rejection, reproducible</td>
<td>• Not specific, standardized</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Not commercially available</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• No proven outcome benefit</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• $$</td>
<td></td>
</tr>
<tr>
<td>ELISPOT</td>
<td>Prior to transplant</td>
<td>Risk stratification</td>
<td>• Limited utility in depleting induction setting</td>
<td>May be more practical in live donor recipients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• $$</td>
<td></td>
</tr>
<tr>
<td>Blood gene profiling</td>
<td>TBD</td>
<td>High NPV for subclinical rejection</td>
<td>• No proven outcome benefit</td>
<td>Consider where 2- to 3-d result delay will not affect management plan</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Multiday turnaround</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• $$</td>
<td></td>
</tr>
<tr>
<td>kSORT</td>
<td>TBD</td>
<td>May risk stratify rejection</td>
<td>• No proven outcome benefit</td>
<td>Lack of benefit in recent large, multicenter, retrospective study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Multiday turnaround</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• $$</td>
<td></td>
</tr>
<tr>
<td>dd-cfDNA</td>
<td>TBD</td>
<td>High NPV for rejection</td>
<td>• No proven outcome benefit</td>
<td>Consider for ruling out AMR, where 2- to 3-d result delay will not affect management plan</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Multiday turnaround</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Not proven for surveillance</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• $$</td>
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</table>

UP/Cr, urine protein-urine creatinine ratio; TTR/CV, time in therapeutic ratio/coefficient of variation; EBV, Epstein–Barr virus; NAT, nucleic acid testing; IS, immunosuppression; BKV, BK virus; DSA, donor-specific antibody; MMDX, microarray-based molecular diagnostic system; TBD, to be determined; ELISPOT, enzyme-linked immune absorbent spot; NPV, negative predictive value; kSORT, kidney Solid Organ Response Test; dd-cfDNA, donor-derived cellfree DNA; AMR, antibody-mediated rejection.
In CTOT-01, Hricik et al. (71) analyzed protocol and for-cause biopsies in 255 first kidney recipients. Rejection was present in 33% of indication biopsies, and urinary CXCL9 protein could detect rejection. CXCL9 also correlated with inflammation and was elevated up to 30 days before rejection. For the entire cohort, CXCL9 at 6 months correlated with rejection and functional deterioration by 24 months post-transplant.

In CTOT-09, tacrolimus withdrawal resulted in urinary CXCL9 elevation in six of 14 patients; four had rejection, five had de novo DSA, and two had BKV (25). Urinary CXCL9 alone could not differentiate BKV from rejection. Prospective trials investigating urinary chemokine monitoring and outcomes are planned (72).

### Blood Biomarkers

To date, three blood biomarker assays have been evaluated in the post-transplant setting: kidney Solid Organ Response Test (kSORT), whole-genome peripheral blood gene expression profiling, and donor-derived cellfree DNA (cfDNA). One caveat with these assays in their quest to supplant allograft biopsy is that histology continues to serve as their rejection “gold standard.”

#### Kidney Solid Organ Response Test.

This whole blood–derived molecular assay uses quantitative PCR to detect a 17-gene panel. The Assessment of Acute Rejection Trial study, involving 436 patients, collected aggregated blood samples in a cross-sectional manner and matched them with contemporaneous kidney allograft biopsy. The kSORT analysis suite, an algorithm that used varying numbers of smaller subsets of the gene panel, differentiated rejection from no rejection on the basis of patterns consistent with increased inflammation or immune quiescence (73). Study limitations included lack of serial blood samples, cohort

#### Table 3. Information gaps with novel tests to monitor kidney transplant health

<table>
<thead>
<tr>
<th>Current Knowledge Gaps</th>
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<tbody>
<tr>
<td>Utility for diagnosis versus surveillance</td>
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<tr>
<td>Optimal use of each test</td>
</tr>
<tr>
<td>Timing and frequency of testing</td>
</tr>
<tr>
<td>Diagnostic thresholds</td>
</tr>
<tr>
<td>Measure of immunosuppression</td>
</tr>
<tr>
<td>Rejection subtype/severity</td>
</tr>
<tr>
<td>Discriminating allograft injury not due to rejection</td>
</tr>
<tr>
<td>Recurrent disease</td>
</tr>
<tr>
<td>BK nephropathy</td>
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<tr>
<td>Other infection (CMV, adenovirus, bacterial, etc.)</td>
</tr>
<tr>
<td>Drug toxicity</td>
</tr>
<tr>
<td>De novo disease</td>
</tr>
<tr>
<td>Donor quality parameters</td>
</tr>
</tbody>
</table>

| Comparative performance of each test |
| Combined use of tests |
| Which |
| When |
| How |

| Logistic and technologic considerations |
| Timely turnaround |
| Scalability |
| Access to all patients |
| Changes in the Banff classification |

| Cost-benefit versus conventional testing |
| CMV, cytomegalovirus. |

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**Figure 1.** Schematic depicting potential time frames for using conventional and emerging transplant biomarkers. Conventional testing is shown below the timeline with pretransplant (grey) and post-transplant (tan) testing. Novel and experimental tests are shown above the timeline with pretransplant (blue) and post-transplant (light red) testing. DSA, donor-specific antibody; ELISPOT, enzyme-linked immune absorbent spot; MMDX, microarray-based molecular diagnostic system.
heterogeneity, and inability to distinguish T cell–mediated rejection. A real-world, retrospective, multicenter study comprising 1763 samples from 1134 patients could not validate kSORT for detecting rejection in the first post-transplant year (74). Observational and interventional studies are ongoing.

**Peripheral Blood Gene Expression Profiling.** Most established is a DNA microarray-based gene expression test that identifies 57 classifier genes that distinguish subclinical acute rejection (with stable allograft function) from histologic quiescence. In the pivotal study, where subclinical acute rejection was the primary end point, patients were followed for 24 months with gene profiling paired with surveillance biopsies between 2 and 6 months, at 12 and 24 months, and with for-cause biopsies (54). The subclinical acute rejection incidence was 42%, although it was mostly “borderline” T cell rejection. At the optimal diagnostic threshold, the sensitivity, specificity, positive predictive value, and negative predictive value of the biomarker for subclinical acute rejection were 64%, 87%, 61%, and 88%, respectively. Secondarily, investigators observed that the biomarker profile that correlated with subclinical acute rejection also associated with worse transplant outcomes after 24 months. Real-world experience in centers not using surveillance biopsies reflects similar performance characteristics in confirming immune quiescence (75).

A peripheral blood 17-gene signature using targeted RNA expression has been reported from GoCAR that associates with rejection on 3-month surveillance biopsy, although it requires further validation (76).

**Donor-Derived Cell-free DNA.** Cell-free DNA (cfDNA) is nonencapsulated circulating DNA. Degradation into approximately 166-base nucleosomal units, cfDNA has a half-life around 30 minutes. Donor-derived cfDNA are DNA fragments in recipient circulation originating from donor tissue injury. The most common detection approach is on the basis of detecting differences in highly homozygous single-nucleotide polymorphisms with high allelic frequency between donor and recipient. Normally a miniscule fraction of total cfDNA, donor-derived cfDNA increases with increasing allograft injury. Levels are elevated very early post-transplant after ischemia-reperfusion injury, declining to baseline steady state more rapidly in living than deceased donor recipients (77).

The prospective, observational Diagnosing Active Rejection in Kidney Transplant Recipients (DART) trial investigated donor-derived cfDNA as a rejection marker (78). At a 1% diagnostic cutoff, donor-derived cfDNA levels measured concomitantly with for-cause biopsy differentiated active rejection from no rejection, outperforming serum creatinine. Donor-derived cfDNA performed most robustly for discriminating antibody-mediated rejection from no antibody-mediated rejection, with sensitivity, specificity, positive predictive, and negative predictive values of 81%, 83%, 44%, and 96%, respectively. Data, frequently single center, with different donor-derived cfDNA assays from the United States, Europe, and Australia have since been reported. Most (77,79–81), although not all (82), studies have confirmed DART’s observation. Some assays have additionally shown promise for T cell–mediated rejection (79,83) and ATN (77). Reported differences in performance characteristic between assays, and between studies with the same assay, are likely related to differences in diagnostic thresholds used or different histologic classifications (Banff 2013 versus 2017). Although attention has focused on donor-derived cfDNA’s ability to discriminate rejection from nonrejection, it most plausibly reflects overall injury burden regardless of triggering cause. Better-quality data are required to evaluate donor-derived cfDNA’s potential for diagnosing and predicting rejection and other allograft injury, as well as postintervention surveillance.

**Where to from Here?**

At present, the published quality of evidence regarding emerging biomarkers is variable, the clinical framework for their use is not clearly established (Table 2), and they have not been independently validated. Despite these limitations, costly commercially available biomarkers are now widely used in various unproven contexts. All demonstrate a strong negative predictive value, indicating potential to avoid unnecessary biopsies; however, they perform less well in identifying patients at risk for a poor outcome (lower positive predictive value). Furthermore, studies have not compared these biomarkers against most conventional approaches or against one another. Table 3 highlights knowledge gaps related to optimal use of novel biomarkers, including testing frequency and timely resulting as well as other logistic and technical considerations. Finally, it is necessary to determine whether they are cost effective in low– and high–immunologic risk recipients alike. Figure 1 depicts hypothetical time frames for using these biomarkers in practice assuming their clinical utility was established.

Kidney transplantation’s successful evolution has created a high bar for biomarkers to overcome. Outcomes have improved with conventional monitoring, and death accounts for most allograft loss. Moreover, acute rejection rates are <10% (2), while subclinical acute rejection is relatively infrequent and its treatment benefit unproven (43,44). Moving beyond measuring serum creatinine, immunosuppression drug levels and indication biopsy will require large, prospective, observational and interventional randomized controlled studies to demonstrate that these promising biomarkers result in improved outcomes in order to justify their incorporation into routine post-transplant care.

**Disclosures**

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Urinary Cell mRNA Profiles Predictive of Human Kidney Allograft Status

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Abstract
Immune monitoring of kidney allograft recipients and personalized therapeutics may help reach the aspirational goal of “one transplant for life.” The invasive kidney biopsy procedure, the diagnostic tool of choice, has become safer and the biopsy classification more refined. Nevertheless, biopsy-associated complications, interobserver variability in biopsy specimen scoring, and costs continue to be significant concerns. The dynamics of the immune repertoire make frequent assessments of allograft status necessary, but repeat biopsies of the kidney are neither practical nor safe. To address the existing challenges, we developed urinary cell mRNA profiling and investigated the diagnostic, prognostic, and predictive accuracy of absolute levels of a hypothesis-based panel of mRNAs encoding immunoregulatory proteins. Enabled by our refinements of the PCR assay and by investigating mechanistic hypotheses, our single-center studies identified urinary cell mRNAs associated with T cell–mediated rejection, antibody-mediated rejection, interstitial fibrosis and tubular atrophy, and BK virus nephropathy. In the multicenter National Institutes of Health Clinical Trials in Organ Transplantation-04, we discovered and validated a urinary cell three-gene signature of T-cell CD3 ε chain mRNA, interferon gamma inducible protein 10 (IP-10) mRNA, and 18s ribosomal RNA that is diagnostic of subclinical acute cellular rejection and acute cellular rejection and prognostic of acute cellular rejection and graft function. The trajectory of the signature score remained flat and below the diagnostic threshold for acute cellular rejection in the patients with no rejection biopsy specimens, whereas a sharp rise was observed during the weeks before the biopsy specimen that showed acute cellular rejection. Our RNA sequencing and bioinformatics identified kidney allograft biopsy specimen gene signatures of acute rejection to be enriched in urinary cells matched to acute rejection biopsy specimens. The urinary cellular landscape was more diverse and more enriched for immune cell types compared with kidney allograft biopsy specimens. Urinary cell mRNA profile–guided clinical trials are needed to evaluate their value compared with current standard of care.

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Introduction
Although kidney transplantation is the treatment of choice for patients with irreversible kidney failure, the long-term outcome of transplanted kidneys has not improved substantially over the years (1,2). Allograft rejection, nephrotoxic drugs, nonadherence, metabolic factors, and kidney disease recurrence have undermined the aspirational goal of “one transplant for life,” so much so that 12% of the patients waitlisted for a kidney transplant are repeat transplants (1,3).

The kidney allograft biopsy remains an essential diagnostic component. This invasive procedure, however, is not without risks such as bleeding, arteriovenous fistula formation, and even death, albeit in rare cases. Biopsy-associated costs and interobserver variability in biopsy specimen scoring are additional concerns (4,5). Serum creatinine, used to monitor kidney allograft status, is nonspecific and has a low sensitivity to detect acute rejection, as reflected by acute rejection being detected on surveillance biopsy specimens without a concurrent increase in creatinine level (6–9). A compelling need exists for more sensitive and more specific tools, preferably noninvasive, to assess kidney allograft status. The immune response is dynamic, and a noninvasive tool would have the advantage of monitoring its kinetics. We postulate that the much-needed transition toward precision medicine would be accelerated by the development of noninvasive biomarkers of kidney allograft status.

Kidney Allograft: An In Vivo Flow Cytometer?
Acute T cell–mediated rejection is characterized by the infiltration of the kidney allograft by T cells, macrophages, and an assortment of other cell types. The concurrent presence of graft-infiltrating cells in the interstitial space and the presence of cells within the tubules (tubulitis) are the histologic hallmarks of T cell–mediated rejection (10). We hypothesized that the kidney allograft undergoing immune rejection functions as an “in vivo flow cytometer,” sorting graft-infiltrating cells and targeted kidney parenchymal cells into urine, and that mRNA phenotyping of urinary cells offers a noninvasive means of diagnosing immune rejection (Figure 1) (11).

Table 1 lists our urinary cell mRNA studies. Representative biomarker studies from other investigators are...
Acute rejection

Cell sorting by kidney tubules

Urine with graft-infiltrating cells and kidney parenchymal cells

Figure 1. | Formulation that a kidney allograft functions as an in vivo flow cytometer. Acute T cell–mediated rejection is characterized by the infiltration of the kidney allograft by T cells, macrophages, and other cell types. The concurrent presence of graft-infiltrating cells in the interstitial space and the presence of cells within the tubules (tubulitis) are the histologic hallmarks of T cell–mediated rejection. In our conceptualization, a kidney allograft undergoing acute T cell–mediated rejection functions as an in vivo flow cytometer and sorts graft-infiltrating cells and targeted graft parenchymal cells into the urinary space; therefore, profiling of urinary cells for their gene expression pattern offers a noninvasive means of diagnosing acute T cell–mediated rejection. Adapted from ref. 11, with permission.

Development of Our Urinary Cell mRNA Profiling Protocol

Isolation of RNA from urinary cells and absolute quantification of mRNAs using the PCR assay are logistically and technically challenging. Urine should be processed within a few hours of collection because of the high abundance of RNA-hydrolyzing enzymes in urine (12). RNA is also inherently unstable. We have largely overcome this challenge by adding an RNA-stabilizing reagent to the urinary cell pellet (13). Our RNA isolation method involves a centrifugation step to sediment urinary cells. A filtration method for capturing urinary cells represents a viable alternative to centrifugation to sediment the urinary cells (14,15). We have processed urine using a filter-based method and have trained kidney allograft recipients to use a commercially available filter (16). We have isolated RNA from the samples prepared using the filtration method and shown that absolute levels of mRNAs are similar to that using the centrifugation protocol (16).

The PCR assay, invented by Mullis et al. (17), has had a transformative effect on biomedicine. We incorporated a pre-amplification step and a customized amplicon, thereby improving the performance of the PCR assay. This preamplification procedure compensates for the low RNA yield from a urine sample, and the amplicon—by serving as the universal reference standard—obviates the need for gene-specific standard curves and enables absolute quantification of any mRNA.

Noninvasive Diagnosis of T Cell–Mediated Rejection

T cell–mediated rejection involves the infiltration of cytotoxic T cells into the allograft. Perforin mRNA encodes a pore-forming protein, and granzyme-B mRNA encodes a serine peptidase, and these proteins are integral components of the lytic machinery of cytotoxic cells (18–20). We designed and developed gene-specific DNA competitor constructs for the absolute quantification of mRNAs in competitive quantitative PCR assays (21), and identified that absolute levels of mRNA for granzyme B and perforin in urine from kidney allograft recipients are diagnostic of acute rejection; the area under the receiver operating characteristic curve (AUROC) was 0.86 for perforin mRNA and 0.86 for granzyme B mRNA (22). A perfect predictor has an AUROC of 1.0, whereas a measure that has no association yields an AUROC of ≤0.5. Levels of mRNA for perforin and granzyme B in sequential urine samples foretold the development of acute rejection (22). These findings have been confirmed and extended by others (23,24).

Serine proteinase inhibitor-9 (PI-9) is a natural antagonist of granzyme B and is expressed in cytotoxic T cells (25,26). Using real-time quantitative PCR assays, we found that the PI-9 mRNA level is significantly higher in urine matched to acute rejection biopsy specimens than in urine matched to chronic allograft nephropathy biopsy specimens, urine matched to other biopsy specimens, or urine from patients with stable graft function (27). PI-9 levels were significantly higher in patients with Banff acute rejection grade II or higher compared with those with less than grade II, and PI-9 levels predicted future graft function after an episode of acute rejection (27).

CD103 is expressed on CD8 T cells involved in kidney allograft rejection (28), and is essential for the intraepithelial homing of T cells (29). Because tubulitis is an essential
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Biomarker</th>
<th>Analyte</th>
<th>Subjects/Samples</th>
<th>Diagnostic Use</th>
<th>AUROC</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Li et al. (22)</td>
<td>Granzyme B, perforin</td>
<td>Urinary cell mRNA</td>
<td>85/151</td>
<td>Acute rejection</td>
<td>0.86</td>
<td>Prospective, single center</td>
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<tr>
<td>2003</td>
<td>Muthukumar et al. (27)</td>
<td>PI-9, granzyme B, perforin</td>
<td>Urinary cell mRNA</td>
<td>87/95</td>
<td>Acute rejection</td>
<td>0.88</td>
<td>Cross-sectional, single center</td>
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<tr>
<td>2003</td>
<td>Dadhania et al. (56)</td>
<td>Granzyme B</td>
<td>Urinary cell mRNA</td>
<td>99/99</td>
<td>UTI</td>
<td>Not reported</td>
<td>Cross-sectional, single center</td>
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<td>2003</td>
<td>Ding et al. (30)</td>
<td>CD103</td>
<td>Urinary cell mRNA</td>
<td>79/89</td>
<td>Acute rejection</td>
<td>0.73</td>
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<td>2004</td>
<td>Tatapudi et al. (31)</td>
<td>IP-10, CXCR3</td>
<td>Urinary cell mRNA</td>
<td>82/90</td>
<td>Acute rejection</td>
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<td>Cross-sectional, single center</td>
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<td>2005</td>
<td>Muthukumar et al. (45)</td>
<td>FOXP3</td>
<td>Urinary cell mRNA</td>
<td>83/83</td>
<td>Acute rejection</td>
<td>0.74</td>
<td>Cross-sectional, single center</td>
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<td>2006</td>
<td>Yannaraki et al. (23)</td>
<td>Perforin, granzyme B, Fas ligand</td>
<td>Urinary cell mRNA</td>
<td>37/162</td>
<td>Acute rejection</td>
<td>0.85</td>
<td>Prospective, single center</td>
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<tr>
<td>2008</td>
<td>Aquino-Dias et al. (24)</td>
<td>Perforin, granzyme B, Fas ligand, PI-9, FOXP3</td>
<td>Peripheral blood monocytes and urinary cell mRNA</td>
<td>65/65</td>
<td>Acute rejection</td>
<td>0.85</td>
<td>Cross-sectional, single center</td>
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<td>2010</td>
<td>Afaneh et al. (47)</td>
<td>Signature of OX40, OX40L, PD-1, and FOXP3</td>
<td>Urinary cell mRNA</td>
<td>46/46</td>
<td>Acute rejection</td>
<td>0.98</td>
<td>Cross-sectional, single center</td>
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<td>2011</td>
<td>Lorenzen et al. (61)</td>
<td>miR-210</td>
<td>Urinary mRNA</td>
<td>81/88</td>
<td>Acute rejection</td>
<td>0.7±0.07</td>
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<td>2012</td>
<td>Hirt-Minkowski et al. (32)</td>
<td>CXCL10</td>
<td>Urinary protein in urine cellfree supernatant</td>
<td>213/442</td>
<td>Acute rejection and subclinical inflammation</td>
<td>0.74</td>
<td>Cross-sectional, single center</td>
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<td>2013</td>
<td>Suthanthiran et al. (37)</td>
<td>Signature of CD3ε mRNA, IP-10 mRNA, and 18S rRNA</td>
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<td>485/4300</td>
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<td>Hricik et al. (39)</td>
<td>CXCL9</td>
<td>Urinary cell mRNA and urinary protein</td>
<td>280/2770</td>
<td>Acute rejection</td>
<td>0.89</td>
<td>Prospective, multicenter</td>
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<td>2016</td>
<td>Suhre et al. (63)</td>
<td>Signature of CD3ε mRNA, IP-10 mRNA, 18S rRNA, 3-sialyllactose/saxithosine, quinoline/X-16397</td>
<td>Urinary cell mRNA and metabolites in urine cellfree supernatant</td>
<td>241/1516</td>
<td>Acute rejection</td>
<td>0.93</td>
<td>Prospective, multicenter</td>
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<td>2017</td>
<td>Raza et al. (55)</td>
<td>MCP-1/CCL2</td>
<td>Urinary protein in urine cellfree supernatant</td>
<td>409/409</td>
<td>Acute rejection</td>
<td>0.81±0.03</td>
<td>Cross-sectional, single center</td>
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<td>2020</td>
<td>Sigdel et al. (64)</td>
<td>11-Metabolite panel: glycine, glutaric acid, adipic acid, iminobiose, threose, sulfuric acid, taurine, N-methylalanine, asparagine, 5-</td>
<td>Urinary metabolite in urine cellfree supernatant</td>
<td>310/326</td>
<td>Acute rejection: 11-metabolite panel BKVN versus acute rejection:</td>
<td>0.985</td>
<td>Cross-sectional, single center</td>
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<td>Year</td>
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<td>Diagnostic Usea</td>
<td>AUROCb</td>
<td>Study Design</td>
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<td>2020</td>
<td>Yang et al. (65)</td>
<td>Urinary Q score of cfDNA, m-cfDNA, clusterin, CXCL10, creatinine, and total protein</td>
<td>Urinary cellfree supernatant: urinary cfDNA, m-cfDNA, CXCL10, clusterin, total protein, and creatinine</td>
<td>601/601</td>
<td>Acute rejection</td>
<td>0.99</td>
<td>Prospective, multicenter</td>
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<td>2020</td>
<td>Nolan et al. (66)</td>
<td>Urinary Q score of cfDNA, m-cfDNA, clusterin, CXCL10, creatinine, and total protein</td>
<td>Urinary cellfree supernatant: urinary cfDNA, m-cfDNA, CXCL10, clusterin, total protein, and creatinine</td>
<td>215/223</td>
<td>Acute rejection</td>
<td>0.983</td>
<td>Prospective, multicenter</td>
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<td></td>
<td><strong>Subclinical inflammation</strong></td>
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<td>2011</td>
<td>Ho et al. (33)</td>
<td>Ratio of urinary CXCL10 to creatinine</td>
<td>Urinary protein</td>
<td>91/102</td>
<td>Borderline, subclinical, and clinical tubulitis</td>
<td>0.835</td>
<td>Cross-sectional, single center</td>
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<td>2015</td>
<td>Rabant et al. (36)</td>
<td>CXCL9 and CXCL10</td>
<td>Urinary cellfree supernatant</td>
<td>300/1722</td>
<td>Low levels predictive of immunologic quiescence</td>
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<td>Prospective, single center</td>
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<td></td>
<td><strong>Interstitial fibrosis and tubular atrophy</strong></td>
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<tr>
<td>2010</td>
<td>Ho et al. (54)</td>
<td>CCL2</td>
<td>Urinary protein at 6 mo</td>
<td>111/111</td>
<td>Allograft fibrosis (urinary protein level at 6 mo predictive of IFTA and graft dysfunction at 24 mo)</td>
<td>Not reported</td>
<td>Prospective, multicenter</td>
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<td>2012</td>
<td>Anglicheau et al. (53)</td>
<td>Four-gene signature of vimentin mRNA, NKCC2 mRNA, E-cadherin mRNA, and 18S rRNA</td>
<td>Urinary cell mRNA and 18S rRNA</td>
<td>114/114</td>
<td>Allograft fibrosis</td>
<td>0.95</td>
<td>Cross-sectional, single center</td>
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Table 1. (Continued)

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<th>Analyte</th>
<th>Subjects / Samples</th>
<th>Diagnostic Usea</th>
<th>AUROCb</th>
<th>Study Design</th>
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<tr>
<td>2002</td>
<td>Ding et al. (57)</td>
<td>BKV VP1 mRNA</td>
<td>Urinary cell mRNA</td>
<td>180/120</td>
<td>BKVN</td>
<td>0.949</td>
<td>Cross-sectional, single center</td>
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<td>2010</td>
<td>Dadhania et al. (58)</td>
<td>BKV VP1 mRNA, granzyme B, PI-9</td>
<td>Urinary cell mRNA</td>
<td>89/89</td>
<td>Validation of noninvasive diagnosis of BKVN, and prognostication of kidney allograft function after BKVN diagnosis by measurement of transcripts for BKV VP1, granzyme B, and PI-9</td>
<td>BKV VP1 mRNA: 0.99</td>
<td>Cross-sectional, single center</td>
</tr>
<tr>
<td>2018</td>
<td>Burnham et al. (68)</td>
<td>Urine cellfree supernatant cfDNA</td>
<td>Escherichia coli: 0.966 Enterococcus Faecalis: 0.968 Klebsiella pneumonia: 1.000 Pseudomonas aeruginosa: 1.000</td>
<td>82/141</td>
<td>UTI, BKV</td>
<td>1.000 0.64</td>
<td>Cross-sectional, single center</td>
</tr>
<tr>
<td>2019</td>
<td>Cheng et al. (69)</td>
<td>Urine cellfree supernatant cfDNA</td>
<td>51/51 UTI, BKV</td>
<td>51/51</td>
<td>UTI, BKV</td>
<td>1.000 0.64</td>
<td>Cross-sectional, single center</td>
</tr>
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<td>2019</td>
<td>Khalid et al. (62)</td>
<td>MicroRNA panel: miR-9, -10a, -21, -29a, -221, and -429</td>
<td>165/33 Delayed graft function</td>
<td>165/33</td>
<td>Delayed graft function</td>
<td>0.94</td>
<td>Prospective, single center</td>
</tr>
</tbody>
</table>

AUROC, area under the receiver operating characteristic curve; PI-9, proteinase inhibitor-9; UTI, urinary tract infection; CXCR3, C-X-C Motif Chemokine Receptor 3; FOXP3, forkhead box P3; OX40, tumor necrosis factor receptor superfamily, member 4; OX40L, OX40 ligand; PD-1, programmed cell death protein-1; m-cfDNA, microbial cellfree DNA; NKCC2, sodium-potassium-chloride-cotransporter; miRNA, microRNA; CD3ε, CD3 ε chain; rRNA, ribosomal RNA; MCP-1, monocyte chemoattractant protein 1; BKVN, BK virus nephropathy; cfDNA, cellfree DNA; AR, acute rejection; IFTA, interstitial fibrosis and tubular atrophy; BKV VP1, BK virus virion protein 1.

aLi et al. (22), Suthanthiran et al. (37), and Suhre et al. (63) report on both diagnostic and anticipatory ability of the measured biomarkers. Suthanthiran et al. (37), Afaneh et al. (47), Anglicheau et al. (53), Dadhania et al. (59), and Suhre et al. (63) report on the diagnostic accuracy of a single biomarker and the parsimonious signatures developed by combining measured biomarkers. Muthukumar et al. (27), Muthukumar et al. (45), Afaneh et al. (47), and Dadhania et al. (59) report both the diagnostic and prognostic utility of measured biomarkers.

bA perfect predictor has an AUROC of 1.0, whereas a measure that has no association yields an AUROC of 0.5.

aAcute rejection and acute T cell–mediated rejection are used interchangeably in this review, reflecting—in part—the evolution of Banff diagnostic categories over time.
feature of T cell–mediated rejection (10), we investigated whether the CD103 mRNA level in urinary cells is associated with acute rejection (30). Our study showed the CD103 mRNA level is significantly higher in urine matched to acute rejection biopsy specimens than in urine matched to biopsy specimens classified as chronic allograft nephropathy or other findings, and in urine from patients with stable graft function (30).

Soluble mediators and their receptors govern cellular traffic into an allograft. mRNA levels of chemokine IP-10, and its receptor C-X-C Motif Chemokine Receptor 3 (CXCR3), were significantly higher in urine matched to acute rejection biopsy specimens compared with urine from patients with biopsy specimens classified as chronic allograft nephropathy or other findings and urine from patients with stable graft function (31). Immunoperoxidase staining of biopsy samples showed prominent staining for IP-10 protein and CXCR3 protein in kidney tubules and graft-infiltrating cells in biopsy specimens classified as acute rejection but not in those from patients with stable graft function. Furthermore, IP-10+ cells and CXCR3+ cells were observed crossing kidney tubular cells. The level of IP-10/C-X-C Motif Chemokinin Ligand 10 (CXCL10) in urine, at the mRNA level and at the protein level, has been associated with acute rejection, and levels of C-X-C Motif Chemokinin Ligand 9 (CXCL9) and CXCL10 have been associated with subclinical acute rejection and kidney allograft function (32–36).

Clinical Trials in Organ Transplantation

The Clinical Trials in Organ Transplantation-01 (CTOT-01) study evaluated the diagnostic utility of urinary cell mRNAs and proteins in 280 kidney transplant recipients and identified that CXCL9 mRNA level and CXCL9 protein level are significantly higher in urine matched to acute rejection biopsy specimens than in biopsy specimens showing no rejection, and the CXCL9 level at 6 months is lower in those less likely to develop acute rejection (35). The CTOT-04 study investigated the following hypotheses: (1) urinary cell mRNA profiles are diagnostic of acute cellular rejection; and (2) urinary cell mRNA profiles, ascertained in sequentially collected urine specimens, predict future development of acute cellular rejection (37). A total of 4300 urine samples were collected at designated time points in the post-transplantation period and at the time of biopsies from 485 kidney allograft recipients. Absolute levels of mRNA for perforin, granzyme B, PI-9, CD103, CD3 ε chain (CD3e), IP-10, and CXCR3 were measured using preamplification-enhanced, real-time, quantitative PCR assays developed in our laboratory. Levels of mRNA for TGF-β1 and 18S ribosomal RNA (18S rRNA) served as measures of RNA integrity. Data analyses showed that 18S-normalized levels of mRNA for CD3ε, perforin, granzyme B, and IP-10 were higher in urine matched to acute cellular rejection biopsy specimens compared with urine matched to biopsy specimens without rejection, and in urine from patients with stable graft function (P<0.001 using separate Kruskal–Wallis tests comparing the three groups for each of the four mRNAs).

The CTOT-04 study developed and validated a urinary cell three-gene signature of 18S-normalized CD3ε mRNA, 18S-normalized IP-10 mRNA, and 18S rRNA. This signature distinguished patients with acute cellular rejection biopsy specimens from patients with no rejection biopsy specimens with an AUROC of 0.85 (P<0.001). Bootstrap resampling yielded a crossvalidated AUROC of 0.83. The three-gene signature yielded an AUROC of 0.75 in an external validation set, a value not significantly lower than the AUROC of 0.85. The level of the three-gene signature differed between patients who received anti-IL-2 receptor antibodies and those who received T cell–depleting antibodies, but was diagnostic of acute cellular rejection in both groups.

The three-gene diagnostic signature predicted future episodes of acute cellular rejection. Figure 2 shows the LOESS curves with 95% confidence interval bands for the group of patients who developed acute cellular rejection and the group of patients with no rejection biopsy specimens. The signature score trajectory remained flat in the group without rejection biopsy samples, whereas the score progressively increased in the group who developed acute cellular rejection.

Acute Rejection and Urinary Cell Transcriptomics

RNA sequencing is a powerful molecular tool for the unbiased characterization of genome-wide transcriptional changes at an unprecedented level of precision, and for deciphering mechanisms and prioritization of biomarkers. Our RNA sequencing of urinary cells and bioinformatics identified, at a false discovery rate <0.01 and log2 fold change ≥2, 180 genes that were differentially expressed in urine matched to T cell–mediated rejection biopsy specimens versus urine matched to specimens showing no rejection, and 544 genes that were differentially expressed in urine matched to antibody-mediated rejection biopsy specimens versus urine matched to biopsy specimens showing no rejection (38). RNA sequencing—in addition to validating the diagnostic accuracy of urinary cell levels of mRNA for CD3ε, IP-10, granzyme B, perforin, CXCR3, CD103, and PI-9—identified several novel biomarkers of T cell–mediated rejection, including CD2, CD8A, CCL5, GZMA, NKG7, CTLA4, ITM2A, SLAM F6, and IKZF3 (38,39).

A large number of genes were shared between T cell–mediated rejection and antibody-mediated rejection. Supervised gene name–based pathway analysis, using the ENRICHR database (40) and the KEGG 2016 human molecular pathways database (https://www.genome.jp/kegg/) (41), showed T cell–receptor signaling pathways, chemokine-signaling pathways, T helper 1 and 2 cell differentiation, necroptosis, natural killer cell–mediated cytotoxicity, cell adhesion molecules, cytokine-to-cytokine receptor interaction, phagosome, and antigen processing and presentation were shared between T cell–mediated rejection and antibody-mediated rejection.

Gene-set enrichment analysis (42) identified that the gene signatures of T cell–mediated rejection and of antibody-mediated rejection are enriched in urine matched to these biopsy specimens (Figure 3). Cell-type enrichment analysis (43) revealed a diverse immune cellular landscape in urine compared with biopsy specimens. Together, RNA sequencing and bioinformatics supported the idea that the
kidney allograft may function as an in vivo flow cytometer and sort graft-infiltrating cells into urine.

**Urinary Cell mRNA Levels Predictive of Reversal of Acute Rejection**

Forkhead box P3 (FOXP3) is a specification factor for regulatory T cells (44). Our single-center study found the FOXP3 mRNA level is significantly higher in urine from kidney allograft recipients who responded to antirejection therapy for acute rejection than in urine from those who did not, and the AUROC for predicting reversal was 0.85 (45). We replicated the predictive utility of urinary cell FOXP3 mRNA levels using an external cohort (46). In this validation study, reversal was associated with a reduction in the urinary cell three-gene signature from above the acute rejection diagnostic threshold to a level below the threshold after antirejection treatment, whereas the signature remained above the threshold in those without reversal during the 4 weeks after antirejection therapy. Measurement of urinary cell FOXP3 mRNA levels and the urinary cell three-gene signature at the time of diagnostic biopsy (and weekly thereafter over a 4-week period) and kidney allograft biopsies after antirejection therapy may help discern the relationship among clinical, histologic, and molecular responses to antirejection treatment and decipher the basis for the differential responsiveness of T cell-mediated rejection to antirejection therapy.

OX40 and OX40L are T-cell costimulatory proteins, whereas PD-1 and its ligands PD-L1 and PD-L2 are negative...
regulators that promote T-cell apoptosis. We found the OX40 mRNA level in urine predicted reversal of acute rejection, with an AUROC of 0.84, and the best linear combination of OX40 mRNA and FOXP3 mRNA predicts reversal with an AUROC of 0.90 (47).

Urinary Cell mRNA Levels Diagnostic of Interstitial Fibrosis and Tubular Atrophy

Development of interstitial fibrosis and tubular atrophy (IFTA) involves both inflammatory and noninflammatory mechanisms (48–52). We discovered and validated a four-gene model of vimentin, NKCC2, E-cadherin, and 18S that is diagnostic of IFTA (53).

CCL2 is a chemoattractant for monocytes, macrophages, T cells, and natural killer cells. In a study of 122 kidney allograft recipients, urinary CCL2 levels were predictive of IFTA after controlling for donor age, delayed graft function, deceased kidney donation, and use of angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker (54). CCL2 levels have also been associated with kidney allograft rejection (55).
Urinary Cell mRNA Profile and Urinary Tract Infection

Bacterial urinary tract infections (UTIs) are common after kidney transplantation. We measured the granzyme-B mRNA level in urine from kidney allograft recipients with UTIs, acute rejection but without UTIs, and patients with neither rejection nor UTIs. We also measured transcript levels in urine from those with or without UTIs who were not transplant recipients. This study revealed bacterial UTI increases the urinary cell granzyme-B mRNA level (56). The finding that bacterial UTI does not confound the diagnosis of acute cellular rejection using urinary cell mRNAs was validated in the CTOT-04 study (37).

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**Figure 4.** Preliminary consort diagrams for two potential randomized clinical trials (RCTs) to evaluate the utility of the Clinical Trials in Organ Transplantation-04 three-gene (18S-normalized CD3ε mRNA, 18S-normalized IP-10 mRNA, and 18S rRNA) signature diagnostic of acute cellular rejection. (A) Single-center RCT to evaluate the efficacy of preemptive antirejection therapy to prevent acute cellular rejection. Starting 30 days post-transplant, eligible patients with kidney allografts would be screened biweekly for elevated levels of the three-gene signature. Inclusion criteria: single kidney transplant, adult recipients (>18 years of age), single kidney graft, and stable graft function. Exclusion criteria: multiorgan recipient, rejection in the preceding 30 days, recipient or donor positive for hepatitis C virus recipient or donor, HIV+ recipient or donor, three-gene signature score greater than 1.213. Upon detection of an elevated signature score postenrollment, the patient would be randomized to 7 days of preemptive treatment with either low-dose steroids (e.g., 60 mg, oral, per day, active arm) or placebo. The primary outcomes would be (1) incident biopsy specimen–confirmed acute rejection during the 3 months post-randomization; and (2) a composite end point of incident biopsy specimen–confirmed acute rejection, the presence of subclinical acute rejection, Banff grade II or more interstitial fibrosis/tubular atrophy (IF/TA), arteriolar hyalinosis, donor-specific anti-HLA antibodies, C4d deposition in the 12-month surveillance biopsy specimen, graft loss, or death. Secondary end points: kidney allograft functional status (eGFR, incidence and degree of albuminuria [measured by albumin-creatinine ratio]), incidence of BK virus nephropathy, and incidence of cytomegalovirus disease. (B) Single-center RCT to evaluate the efficacy of urinary cell three-gene signature to facilitate a 50% reduction in tacrolimus dosage. At 12 months post-transplant, eligible, consented patients would undergo a stepwise reduction in tacrolimus dosage to 50% of pre-enrollment dosage. The patients will be randomized to either a biweekly monitoring of three-gene signature arm or no three-gene signature monitoring arm. In those assigned to the urinary cell mRNA monitoring arm, stepwise reduction will stop if the score is greater than 1.213. Both groups would receive standard-of-care monitoring for graft dysfunction, with for-cause biopsies and treatment as indicated for the next 12 months. At 12 months post-randomization, all patients would be evaluated for overt graft dysfunction and have a protocol biopsy for the detection of subclinical rejection and/or graft dysfunction. The primary outcomes would be (1) a composite end point of incident biopsy specimen–confirmed acute rejection, the presence of subclinical acute rejection, Banff grade II or more IF/TA, arteriolar hyalinosis, donor-specific anti-HLA antibodies, C4d deposition in the 12-month surveillance biopsy specimen, graft loss, or death; and (2) cumulative tacrolimus dosage. Secondary end points: kidney allograft functional status (eGFR, incidence and degree of albuminuria [measured by albumin-creatinine ratio]), incidence of BK virus replication, incidence of BK virus nephropathy, and incidence of cytomegalovirus disease. An independent data safety monitoring board will monitor these institutional review board–approved trials. Tx, treatment.
Polyomavirus BK has emerged as a significant post-transplant complication. We determined and validated that BK virus VP1 (the polyoma capsid protein of the polyoma-virus) mRNA levels in urinary cells are diagnostic of BK virus nephropathy (57). Urinary cell levels of granzyme B and PI-9 were higher in those who developed subsequent graft dysfunction, compared with those who did not, after BK virus nephropathy (58). A two-biomarker model of levels of serum creatinine and plasminogen activator inhibitor-1 mRNA predicted graft failure within 36 months, with an AUROC of 0.92 (59); this finding was recently validated in an independent cohort (60).

Additional Profiling Strategies

MicroRNA (miRNA) profiling, metabolomics, proteomics, and cellfree DNA each hold considerable promise as biomarkers of kidney allograft status. miRNAs are endogenous, small (about 22 nt long), non-coding RNAs that target a vast array of mRNAs, reducing their abundance and/or impairing their translation, and are considered master regulators of immune cell development and function. In the transplantation arena, miRNA-10b and -210 were regulators of immune cell development and function. In getting a vast array of mRNAs, reducing their abundance and/or impairing their translation, and are considered master regulators of immune cell development and function. In the transplantation arena, miRNA-10b and -210 were reported to be downregulated and miRNA-10a upregulated in urine from kidney graft recipients with acute rejection compared with patients without rejection; the miRNA-210 level was also associated with long-term graft function (61). A panel of six miRNAs—miRNA-9, -10a, -21, -29a, -221, and -429—has been reported to be predictive of delayed graft function in kidney allograft recipients (62).

Metabolomics provides biologic readouts for perturbations of biochemical processes. In our study, a composite signature of the ratios of urinary 3-sialyllactose to xanthosine and quinolinate to X-16397 along with the urinary cell three-gene signature outperformed either signature alone in diagnosing acute rejection in kidney allografts (63). Recently, an 11-metabolite panel diagnostic of acute rejection and a four-metabolite panel discriminating acute rejection from BK virus nephropathy have been identified (64).

Multimodal profiling may offer advantages over measurement of a single analyte. A combination of six urinary biomarkers consisting of cellfree DNA, methylated cellfree DNA, clusterin, CXCL10, creatinine, and total protein (measured in urine supernatant using an ELISA-based approach) was reported to discriminate acute rejection from no rejection in kidney allografts, with an AUROC of 0.99 and an accuracy of 96% (65). In a follow-up study, a composite Q score >32 was diagnostic of acute rejection, with an overall sensitivity of 96% and specificity of 99% (66).

Translation to the Clinic

On the basis of data showing that the urinary cell three-gene signature diagnostic of acute cellular rejection tends to cross the diagnostic threshold almost a month before biopsy specimen-confirmed rejection (Figure 2), an interventional trial of preemptive antirejection therapy could test the hypotheses that (1) this signature predicts the development of acute rejection, and (2) preemptive therapy prevents the development of acute rejection. In this trial, urinary cell three-gene signature of CD3ε mRNA, IP-10 mRNA, and 18s rRNA would be measured in serial urine specimens collected from kidney allograft recipients, and study participants would be randomized to a preemptive antirejection-therapy arm or a standard-of-care arm. Figure 4A outlines the envisioned trial.

On the basis of data showing that this three-gene signature reflects the potency of immunosuppressive therapy (37), a randomized controlled interventional trial of stepwise reduction in immunosuppressive therapy could test whether urinary cell mRNA profile–guided immunosuppression minimization is safe. In this trial, illustrated in Figure 4B, kidney allograft recipients with stable graft function, normal protocol biopsy specimens, and no donor-specific antibodies would undergo a stepwise reduction in tacrolimus dosage to 50% of the pre-enrollment dosage. The patients randomized to the three-gene signature–guided arm will not undergo the scheduled reduction in dosage if the signature crosses the acute rejection diagnostic threshold, and they will be reverted to their prior dosage. This study design would test the hypothesis that a 50% reduction in tacrolimus dosage is safe in patients monitored using the three-gene signature. Multimodal profiling of study participants using urinary cell BK-VPI mRNA levels, plasma donor-derived cellfree DNA (57,67,68), urinary cell DNA metagenomic sequencing (69), and antibodies to donor HLA would be performed as safety measures.

These two single-center trials could serve as precursors to a multicenter randomized controlled trial of biomarker-guided management (70). Additional clinical trials incorporating decision analysis may help reduce the need for clinically indicated or surveillance biopsies of the kidney allograft.

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References


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Chronic Allograft Injury

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Abstract
With the incremental improvements in long-term kidney transplant survival, there is renewed focus on what causes failure of the transplanted allograft. Over the past decade, our understanding of the injuries that lead to loss of graft function over time has evolved. Chronic allograft injury includes both immune-mediated and nonimmune-mediated injuries, which may involve the organ donor, the recipient, or both. The targets of injury include the kidney tubular epithelium, the endothelium, and the glomerulus. As a response to injury, there are the expected tissue remodeling and repair processes. However, if inflammation persists, which is not uncommon in the transplant setting, the resulting maladaptive response is matrix deposition and/or fibrosis. This ultimately leads to declining graft function and, finally, failure. With our advancing knowledge of the multiple etiologies and mechanisms, enhanced by more recent cohort studies in humans, there is an opportunity to identify those at greater risk to initiate new strategies to ameliorate the process. Although the most recent studies focus on immune-mediated injuries, there is a critical need to identify both markers of injury and mechanisms of injury. In this review, we highlight the findings of recent studies, highlight the potential therapeutic targets, and identify the continued unmet need for understanding the mechanisms of late graft failure.

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Introduction
In the last 30 years, kidney transplantation has achieved incredible success, with well over 90% patient and graft survival in the first year after transplant, accompanied by infrequent rejection (1). This success is primarily due to the potency of immune-suppressive therapy and improved recognition of recipient immune risk. However, at 10 years, only about half of deceased donor and 70% of living donor kidney grafts remain functional (1), due to a combination of death with a functioning allograft and death-censored graft loss. In the latter, graft failure results in significant morbidity and a financial cost of returning to dialysis, with an associated higher risk of death. This adds to the ever-increasing demand on transplantable organs, with repeat transplants accounting for approximately 15% of all kidney transplants (2). Thus, understanding the etiology of chronic allograft injury and identifying therapeutic targets are important research priorities in kidney transplantation.

The classic understanding of late allograft failure has evolved from “chronic rejection” to the recognition of specific entities that require proactive clinical monitoring and biopsy diagnosis (3,4). Such studies identify a broad, complex end result that encompasses both immune-mediated and nonimmune-mediated injuries. In this review, we provide an overview of these entities, with emphasis on mechanism.

A Historical Perspective
Prior to the 1990s, kidney graft failure was attributed to the oft-used but misleading term “chronic rejection.” However, this diagnosis did not adequately encompass all causes of chronic graft injury. Moreover, it assumed that there was “rejection,” with the common clinical practice not to perform late biopsies. In 1991, the first Banff Conference on Allograft Pathology defined chronic allograft nephropathy as kidney transplants with significant interstitial fibrosis and tubular atrophy (IF/TA) (5), but this histologic description was non-descriptive of specifying the etiology. By 2005, at the eighth Banff Conference, the term chronic allograft nephropathy was replaced by “interstitial fibrosis and tubular atrophy (IF/TA) without evidence of specific etiology,” a diagnosis to be used when the underlying process could not be identified (6). This descriptive categorization also advocated for specific annotation of morphology that could distinguish entities, such as rejection, hypertension, calcineurin inhibitor toxicity, chronic obstruction, recurrent bacterial infection, and viral nephropathy. The recognition that IF/TA is a final common pathway for many injuries led to a call for improved allograft surveillance, including biomarkers, obtaining a biopsy before chronic injury caused irreversible fibrosis, and improved recognition of changes in the slope of GFR, which may be a late finding in chronic allograft injury (7). Thus, the context (clinical features and timing) of histology became an important advancement in our understanding of late graft failure and would facilitate better insights into disease pathogenesis, biomarkers, and proper trial design.

Mechanistic Insights into Graft Failure
Classically, the causes of chronic allograft injury are divided into immune mediated and nonimmune mediated, with divergent diagnostic and therapeutic
implications. The former reflects alloimmune responses to donor tissue, including cellular and antibody-mediated rejection, and infections, such as BK nephropathy and recurrent urinary tract infections, that may begin with innate immune responses with subsequent adaptive alloimmune injury. The nonimmune-mediated, antigen-independent etiologies include calcineurin inhibitor nephrotoxicity, obstruction or reflux disease, recurrence of native kidney disease, and secondary causes, such as diabetic nephropathy. Rather than providing detail on each entity, the reader is encouraged to consult these recent publications (8–10).

We suggest an alternative paradigm, where injuries are oriented around the kidney compartment directly affected (Figure 1). This approach demonstrates the interactive nature of injury among the compartments. For example, endothelial injury in the peritubular capillaries leads to tubular interstitial injury and fibrosis and demonstrates the multiple clinical entities that may present with injury in that compartment. Likewise, both immune and nonimmune injuries may affect each compartment.

Underscoring the potential contributions of these insults to the allograft is the recognition that there may be fixed “deficits,” at the start of transplantation, on the basis of reduced nephron mass. Such suboptimal donor tissue derives in part from older donors, with reduced baseline function and kidney reserve. In such allografts, there is reduced capacity to respond to injury, with accumulation of senescent cells with associated inflammatory response leading to impaired organ function (11). This is reflected by a higher Kidney Donor Risk Index. This index was developed by assessing post-transplant outcomes data from the Scientific Registry of Transplant Recipients, taking into account 14 variables in the deceased donor at transplantation (12), expressed as the relative rate of graft failure of the donor kidney. Although higher–Kidney Donor Risk Index kidneys still are associated with better survival of the recipient than remaining on the waiting list (13), older age or size mismatch between donor and recipient may lead to hyperfiltration and progressive loss of kidney function (14), even in the absence of other intervening injuries over time. This is further aggravated by brain death and ischemia-reperfusion injury, resulting in a proinflammatory environment in the allograft that may worsen rejection risk as well (reviewed in ref. 15).

**Targets of Injury: The Interstitium**

Studies on late allograft failure have focused on profibrogenic pathways in the kidney as potential therapeutic targets. Such investigations are derived in part from studies of acute injury models where maladaptive repair of tubular epithelium following injury is associated with persistent structural and metabolic abnormalities (16). Recognizing the regenerative capacity of the kidney epithelium, reports indicate that within the environment of repeated stress, injury, or under duress of calcineurin inhibitors (17), tubular epithelial cells, as well as T cells and macrophages, express profibrotic growth factors (18). This results in downstream activation of mesenchymal cells, including pericytes, fibroblasts, and fibrocytes, which themselves may now produce matrix. Key in this pathway were reports of TGF-β as well as enhanced expression of microRNA21, a profibrogenic signal seen in other organs, resulting in loss of epithelial phenotype (19). Although it has...
been debated whether epithelial (or endothelial) cells may undergo myofibroblast transformation, more recent studies using fate tracing of cells in mice determined that epithelial mesenchymal transformation was unlikely. Rather, pericytes, the cells surrounding the vasculature in the kidney, were associated with α-smooth muscle actin–positive fibroblasts (reviewed in ref. 20).

Additional support comes from gene expression studies of mouse and human kidney allografts with IF/TA with upregulation of connective tissue growth factor and TGF-β, matrix metalloproteinases, collagens, and α-smooth muscle actin (21–23). In human kidney allograft biopsies, investigators have identified signatures in the whole-kidney cortex associated with progressive fibrosis detected in the early course of transplantation that are predictive of later injury (24,25). Such studies indicate the importance of IF/TA in the progression of late allograft injury. Recent examination of mouse kidneys following acute kidney ischemia with single-cell RNA sequencing demonstrates a “failed-repair proximal tubule cell state,” which is also demonstrated in human kidney allografts over time (26). These transcriptional studies indicate regional variation of cells to ischemic injury and suggest that the dynamic nature of the repair response may be a new target for mitigating graft failure.

In spite of such results, the prevalence of IF/TA is debated. In a large prospective cohort of kidney and kidney/pancreas transplant recipients monitored closely with surveillance biopsy, 66% of transplants demonstrated atrophy and fibrosis by 5 years post-transplantation (27). More recent studies indicate that only 17% of transplants have moderate to severe IF/TA detected by 5 years (28), and stability of GFR over time and less frequent graft loss (29). The success of this cohort was attributed in part to more effective immunosuppression with tacrolimus, with less subclinical and clinical inflammation as well as the notion that tacrolimus may be “less fibrogenic” compared with the use of cyclosporin (27). Regardless of the prevalence of IF/TA, there is agreement that the extent of tubular atrophy and interstitial scarring correlates to allograft failure (4).

Allograft Inflammation Is an Important Mediator of Chronic Graft Injury

The presence of inflammation has been associated with higher risk of graft failure. Surveillance biopsy studies associated subclinical cellular rejection with progression of IF/TA (30,31). In the absence of randomized control trials of treatment and with a disconnect between severity of inflammation and outcomes (32), treatment of subclinical inflammation remains debated (reviewed in ref. 18).

Although such studies focused on inflammation in nonatrophic and nonscarred kidney tissue, investigators soon demonstrated the negative effect of inflammation in areas of IF/TA, an area of the biopsy not originally part of the Banff scoring schema. Specifically, total inflammation (total I; “ti”), including inflammation in both scarred and unscarred tissue, was identified as an independent risk factor for graft failure and added as a component score in 2008 (33). Further work from two large cohort studies identified that inflammation in areas of scarring and atrophy (“i-IFTA”) was an independent risk factor for allograft failure in both for-cause biopsies (34,35) and surveillance biopsies (26,36), leading to the incorporation of i-IFTA into the Banff schema (37). These findings were independently validated by other clinical cohorts, with correlation of these lesions to prior T cell–mediated rejection (38,39) or under-immunosuppression (38). Not surprisingly, i-IFTA is associated with the extent of inflammation and severity of IF/TA. Importantly, i-IFTA is not specific and may be seen in BK virus nephropathy, recurrent glomerular disease, antibody-mediated rejection, and pyelonephritis. This has led to considerable disagreement of the specificity of this finding and whether it truly represents a form of chronic active T cell–mediated rejection. In the latter diagnostic category, i-IFTA must be at a threshold level of moderate severity accompanied by moderate tubulitis. Interestingly, gene expression of allografts with i-IFTA lesions was more frequently associated with antibody-mediated rejection gene transcripts and eventual graft loss (40). Thus, questions remain about appropriate therapy (if any) and the effect of those treatments, including the role of molecular tissue analysis.

Calcineurin Inhibitors: Friends and Foes. The introduction of calcineurin inhibitors in kidney transplantation had an immediate effect by reducing allograft rejection and improving graft survival. However, their use was associated with nephrotoxicity both with acute and with long-term exposure. The mechanisms of calcineurin inhibitor nephrotoxicity are complex and associated with vascular (arteriolar), tubular, and glomerular dysfunction (41). Strongly implicated has been the activation of the renin–angiotensin system, with effects on kidney vasculature as well as on juxtaglomerular cells (42). Additionally, adverse remodeling has been implicated through direct effects on the epithelium and interstitium, with release of reactive oxygen species (17), mitochondrial dysfunction and HMGB1 release by tubular epithelial cells, and apoptosis (43). In vitro, cyclosporin treatment of proximal tubular epithelial cells results in a loss of epithelial phenotype (44,45) with endoplasmic reticulum stress (46). Such studies suggest that intervention in some of these signaling pathways may mitigate the nephrotoxicity, supporting tissue repair and correction of metabolic maladaptation. In spite of significant advances in transplantation and better mechanistic insights, there are no specific therapies that ameliorate calcineurin inhibitor nephrotoxicity. Furthermore, minimization or avoidance of these agents has resulted in cellular and antibody-mediated allograft rejection (47). Indeed, minimization of these agents to avoid toxicity may provoke subclinical and clinical alloimmune activation (7). Effective management strategies that limit calcineurin inhibitor injury while facilitating therapeutic levels are an unmet need in the transplant recipient.

Viral Nephropathy with BK Virus. BK polyomavirus nephropathy can cause significant allograft injury, leading to graft failure (48). BK virus, with a tropism for uroepithelium, undergoes replication under the immunosuppressive milieu resulting in a marked inflammatory response, leading to tubular epithelial cell injury and, ultimately, IF/TA (49). In spite of our knowledge of this entity for 2 decades, there are no approved antiviral treatments, with empirical therapies either untested or unproven by randomized trials. The mainstay of intervention includes proactive
monitoring for viral DNA with immunosuppressive reduction upon detection of BK viremia and/or viruria.

The progressive fibrosis and inflammation are not unlike that of other injuries and are unremitting in the context of continued viral replication. Histopathology is unable to distinguish alloimmune versus antiviral inflammation. Indeed, molecular analysis of allograft biopsies with BK nephropathy indicated similar gene expression to that of acute T cell–mediated rejection (50). Moreover, BK virus nephropathy was associated with a profibrogenic milieu, although whether this was due directly to viral invasion or related to the antiviral immune response is not clear. Recent studies quantifying gene expression in formalin-fixed kidney biopsy sections and the NanoString 800-gene panel to detect immune response and BK viral genes have also demonstrated an overlap of transcripts in BK virus nephropathy and T cell–mediated rejection, with excellent diagnostic performance of BK-specific genes to detect viral pathology. However, these transcript profiles were unable to predict outcomes in the BK virus nephropathy cohort, such as disease resolution, persistence, or subsequent T cell–mediated rejection. Further evaluation of the predictive value of these gene expression targets will require a larger cohort with discrete outcomes and a platform for therapeutic development.

**Targets of Injury: The Endothelium**

The allograft endothelium is the interface between the recipient and donor and serves as a target for innate and adaptive immunity. The injured endothelium responds by increased vasoconstriction, inflammation, and hypercoagulation (51), as well as upregulation of adhesion molecules and class 2 MHC expression, increasing graft immunogenicity. Furthermore, endothelial cell apoptotic death may release apoptotic exosome-like vesicles, which, in turn, promote further endothelial dysfunction, autoantibody production, and complement deposition (52). Additionally, endothelial cell activation leads to recruitment of inflammatory cells and proliferation of vascular smooth muscle cells, resulting in neointima formation.

Recently, Valenzuela and Reed (53) demonstrated that ligation and croslinking of HLA class I molecules induce endothelial cell activation and proliferation, with cytoskeletal alterations leading to vascular smooth muscle proliferation. Long term, this results in vascular remodeling and matrix deposition with intimal hyperplasia and arteriopathy (53). As such, chronic antibody-mediated rejection may be characterized by peritubular capillary injury, ultimately resulting in basement membrane duplication or laminations. Injury may also occur in the glomerular capillaries, leading to transplant glomerulopathy, a diagnosis associated with progressive allograft dysfunction, proteinuria, and graft loss (54). Recent studies utilizing archetype analysis have identified clusters of histology and clinical features, with five variants with differing outcomes (55,56). Archetypes with more advanced tubulointerstitial inflammation, vascular lesions, and microcirculation changes or high levels of proteinuria and more advanced cg lesions had the poorest graft survivals. Such analyses allow more specific phenotypic identification of subgroups of perhaps treatable patients. Similarly, the Deterioration of Kidney Allograft Function study, which created a prospective and cross-sectional cohort from seven transplant centers in North America using central pathology and central HLA antibody detection, used cluster analysis of clinical features and histology scores to identify grafts that are higher risk of failure after biopsy and least likely to respond to any therapeutic maneuver (4).

Chronic active antibody-mediated rejection has developed into one of the most difficult entities to manage clinically, with no prescribed and effective therapy, although many agents are used empirically. The frequency varies depending on the patient population, ranging from 3.5% in conventional recipients to as high as 50% in HLA-incompatible transplant kidneys, preceded commonly by microvascular injury (57). After diagnosed, median graft survival is 3.25 years, with a three-fold higher risk of graft failure (58). Risk factors for graft failure include proteinuria and reduced allograft function, as well as class 2 HLA donor-specific antibody (DSA) and de novo DSA compared with preformed/preexisting donor antibody (reviewed in ref. 59). Recent international consensus guidelines for treatment of chronic active antibody-mediated rejection with de novo DSA include optimizing immunosuppression with supportive care, such as reintroduction of steroids (if on a steroid-free regimen), maintaining trough tacrolimus levels >5 ng/ml, and optimizing medical management with a focus on BP, blood glucose, and dyslipidemia (60). Past studies with complement inhibition and proteasome inhibitors have had no effect on outcomes, and newer trials are underway, including the use of neutralizing IL-6 antibody, targeting natural killer and plasma cells (reviewed in ref. 61). As noted earlier, identifying treatable phenotypes is critical to define effective therapeutics.

Thrombotic microangiopathy of the glomerulus is another important endothelial injury that can lead to graft loss. Etiologies include primary genetic syndromes with complement activation as well as secondary causes, including antidonor HLA antibody, calcineurin inhibitor, and viral infections such as HIV, CMV, and parvovirus. With the therapeutic potential to inhibit complement activation, more attention has been paid in the recognition of this lesion and its etiology (62). Regardless of the cause, the presence of microcirculation occlusion with platelet thrombi, complement activation, and terminal membrane attack complexes causing endothelial cell death is a highly inflammatory microenvironment leading to progressive kidney damage with graft loss.

**Target of Injury: The Glomerulus**

Entities that cause chronic glomerular injury include recurrent glomerular disease, secondary diseases, and microvascular injury to the endothelium, such as thrombotic microangiopathy and chronic active antibody-mediated rejection as discussed above. Although primarily glomerular disease accounts for approximately 25% of kidney failure, recurrent GN following kidney transplant may account for up to 15% of graft failures. The diagnosis and management of recurrent GN depend on the underlying disease and are beyond the scope of this review. Notably, the natural history and presentation of recurrent GN in an allograft are often modified by global post-transplant...
immunosuppression. This limits the ability to extrapolate native kidney disease protocols to post-transplant recurrence, highlighting the need for development of transplant-specific responses to recurrent disease.

Unmet Needs and Future Directions in Chronic Kidney Injury Biomarkers
The diversity of pathologic and clinical entities in late graft failure, spanning the many conditions that we have discussed, has made therapeutic discovery a nightmare. Critical to this discussion is the timing of detection of chronic injury. Although serum creatinine is used to monitor allograft function and detect injury, it lacks specificity and sensitivity for early allograft injury. Indeed, as noted in native kidney diseases, considerable nephron damage and loss can occur before a significant change in creatinine is detected. Thus, by the time there is detection of functional change, biopsy reveals more advanced processes, often with limited reversibility and diminished opportunity to mitigate chronic injury. There is a clear need for biomarkers to detect the onset and etiology of chronic allograft injury for the entities we have discussed. For example, surveillance biopsies at specified time points post-transplant may detect “subclinical” rejection, but benefits of therapeutic implementation are not certain. Moreover, the cost and time-consuming and invasive nature make their routine implementation challenging in most transplant centers.

Gene expression profiles may be useful in terms of predicting graft failure and progression as already noted, and further clinical validation awaits (25). Other alternatives include detection of donor-derived cellfree DNA to detect allograft injury (63) or gene transcripts in PBMCs associated with subclinical inflammation (64). Such assays have potential to guide patient management, and with the long-term goal of extending allograft survival, need to be more carefully studied prior to implementation.

Recent reports suggest that a composite measure called the integrated risk prediction score (iBOX) might provide risk prediction of graft failure. Based on data derived from both surveillance and medically indicated biopsies in a large cohort of kidney transplants, machine learning algorithms have identified independent risk factors for graft loss. These include allograft function, proteinuria, the level of donor-specific HLA antibody, and the histopathologic variables of severity of IF/TA, microvascular injury, inflammation, and tubulitis (56). This multiparameter risk score has been extensively validated with predictable accuracy. As such, the iBOX may assist in risk assessment of patient’s clinical course and is under consideration in clinical trial design as a surrogate end point of late graft failure.

Therapeutic Management of Fibrosis
There has been intense investigation into antifibrotic treatments, primarily in native kidney diseases, with some work in preclinical transplant models. With the recognition that fibrosis is perpetuated by immune injury, removing the insult is of primary importance to ameliorate graft injury and subsequent failure. To this end, an initial approach to limit fibrosis and graft failure would be on prevention; such strategies would limit alloimmune and innate injuries, including improved matching using molecular typing between donor and recipient (65), improved donor selection with an understanding of donor quality, and organ preservation methods that mitigate innate injury. Preemptive approaches include detection and management of cellular and humoral rejection prior to clinical detection, the tailoring of immunosuppressive therapies on the basis of immune risk profiles, and addressing medication nonadherence. The final aspect is antifibrotics, a topic that is worthy of an entire review (66). These therapies, however, may work best as “anticipatory” and used concurrently with immunosuppression prior to advanced disease. An example is the use of SGLT2 inhibitors in diabetic glucose management in kidney transplant recipients (67). These agents demonstrate renoprotective effects in native kidneys (68) and may have relevance to improved long-term kidney function in transplantation as well.

The frequency of late graft failure improves slowly over time, with substantial gains in reducing patient death with a functioning graft. However, the incremental improvements in long-term function continue to be a challenge. The etiologies are multifactorial, but our better understanding of the pathways to failure demonstrates common themes. These include better detection prior to clinical manifestation and opportunities for improved therapeutics.

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Recurrence Glomerular Disease after Kidney Transplantation
Diagnostic and Management Dilemmas

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Abstract
Recurrence of glomerular disease after kidney transplant remains an important cause of allograft failure. Many of the different entities post-transplant still suffer from incomplete knowledge on pathophysiology, and therefore lack targeted and effective therapies. In this review, we focus on specific clinical dilemmas encountered by physicians in managing recurrent glomerular disease by highlighting new insights into the understanding and treatment of post-transplant focal segmental glomerulosclerosis, membranous nephropathy, atypical hemolytic uremic syndrome, C3 glomerulopathy, amyloid light-chain (AL) amyloidosis, and IgA nephropathy.

Introduciton
Glomerular disease is one of the leading causes of kidney failure, representing the third most common reason for kidney transplantation in the United States (1). After kidney transplantation, glomerular disease has been identified as an important contributor to allograft failure in registry studies worldwide (2–4). Glomerular disease after transplantation includes a variety of disease entities and has already been subjected to many high-quality reviews. This review will address specific dilemmas that clinicians face in the management of post-transplant glomerular disease and highlight emerging evidence that may help guide management.

FSGS
Recurrence of primary FSGS after kidney transplant is immensely challenging. Recurrence rates after transplant vary from 30%–60% between studies (5), due to variability in study size, study design, and the criteria used for the selection of patients with presumed primary FSGS, including methods used for exclusion of secondary and genetic FSGS, and the definition of recurrent FSGS. The pathogenesis of recurrent FSGS is still largely unknown, although the presence of a circulating factor toxic to podocytes is highly suggestive (6). Despite the use of multiple treatment approaches, resistant disease and graft loss remain common.

Dilemma: How Do the Clinic-Pathologic Features of Native FSGS Inform the Risk of Recurrence after Transplant? FSGS describes a histologic pattern found on kidney biopsy caused by a heterogeneous group of etiologies that lead to podocyte injury. Identifying the different causes of FSGS is pivotal in counseling patients because there is a high risk of recurrence in patients with primary FSGS, but negligible risk in patients with secondary (7) and genetic forms.

One important clinical clue about the risk of recurrence is the presence or absence of nephrotic syndrome in the patient’s presentation of native FSGS. Patients without nephrotic syndrome at disease manifestation seem to have a very low risk of recurrence after kidney transplantation (8). This was endorsed by our own data from the Post-Transplant Glomerular Disease (TANGO) cohort in which 22 patients with biopsy-proven FSGS without clinicopathological signs of secondary FSGS, and no nephrotic syndrome at manifestation, did not experience a recurrence after kidney transplantation (5). FSGS histologic variants (collapsing, tip lesion, cellular, perihilar lesion, not otherwise specified) have no effect on the risk of recurrence (9), and there is no literature supporting an association between the degree of podocyte foot process effacement on electron microscopy and risk of recurrence after transplant.

Many studies have attempted to identify clinical factors that are associated with higher or lower risk of recurrence, resulting in associations between recurrence and older age, White race, faster time to kidney failure, living (related) donation, and nephrectomy of native kidneys. However, most studies relied on univariable analysis and did not mention methods to exclude genetic and secondary FSGS. Because a distinction between primary and secondary FSGS is difficult, and greatly influences recurrence risk, the found associations are likely confounded by misclassification of secondary FSGS and lack of genetic testing, including APOL-1 high-risk variants in recipients and donors. Overall, specific histologic changes on native biopsy are not associated with FSGS recurrence, and the absence of nephrotic syndrome at disease presentation is associated with nonrecurrence.
Dilemma: Should Patients with Primary FSGS Undergo Genetic Testing before Kidney Transplantation? More than 50 genes have been associated with FSGS. Children with FSGS have a higher prevalence of monogenic or familial genetic FSGS (approximately 30%) versus adults, and most pathogenic variants are podocyte specific (kidney intrinsic) (10). Studies of FSGS recurrence in patients with monogenic or familial FSGS have revealed a low recurrence rate, as low as 0% in a large pediatric cohort (11). One exception is a specific NPHS1 mutation (Fin-major/Fin-major type) that has a recurrence rate of 25%-34%, but this mutation is rare outside Finland (12,13). Given the availability of comprehensive and low-cost genetic testing panels for FSGS (14), and the increasing number of identified genes associated with adult-onset FSGS, such as the COL4A genes, we believe genetic testing should be considered an important tool for the risk stratification of FSGS recurrence.

APOL1 high-risk variants found among individuals with sub-Saharan ancestry have been associated with augmented risk of several kidney diseases, including FSGS (15). Our understanding suggests that APOL1-related FSGS should not recur after transplant because kidney-specific expression of APOL1 high-risk variants is a crucial driver of podocyte injury (16). Indeed, 5-year graft survival of recipients with APOL1 high-risk alleles was similar to patients without risk alleles (17), whereas donor APOL1 status was associated with higher risk of graft failure (18). The important question of how donor APOL1 status should influence organ allocation is beyond the scope of this review and is being explored by the APOL1 Long-term Kidney Transplantation Outcomes Network (19).

Dilemma: Should Patients with Primary FSGS Undergo Prophylactic Treatment around Kidney Transplantation? The treatment of recurrent FSGS remains empirical because no randomized controlled trials have ever been performed. Although various agents have been described to treat recurrent FSGS (Table 2), international cohorts and surveys reveal most patients receive treatment with plasmapheresis, in many patients combined with rituximab (5,22). Plasmapheresis is used with the goal of removing the elusive circulating factor, whereas rituximab may act by a direct effect on podocytes or by its depletion effect on immune B cells (23). The remission rates in studies with plasmapheresis, rituximab, and/or other treatments for recurrent FSGS vary widely (listed in Table 2), likely due to varying treatment regimens, definition of partial and complete remission, and the possibility of publication bias. In some centers, especially in France, intravenous cyclosporine is part of the standard care after recurrence of FSGS because it has been reported to have a function in stabilization of the podocyte cytoskeleton (24). However, this treatment is not widely used, possibly due to the concern for nephrotoxicity and logistical challenges with continuous intravenous infusion, and the available alternative treatments.

In a minority of centers, plasmapheresis has been replaced by immunoadsorption, apheresis method that enables more selective removal of immunoglobulin, with the advantage that no substitution fluid is needed and no coagulation factors are lost. The efficacy of the more expensive and less available immunoadsorption method compared with plasmapheresis has never been assessed in a trial, although average remission rates between both treatment modalities seem similar (25–27). The crucial limitation is that it is unclear what circulating factor that drives the podocyte injury is being removed with either therapy. In patients without response to pheresis/rituximab, other treatments have been proposed, such as LDL apheresis, abatacept, adrenocorticotropic hormone on recurrent FSGS (NCT02683889, NCT02921789, and NCT03763643, respectively).
Table 1. Selected studies of prophylactic treatment before kidney transplantation in patients with primary FSGS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Total (n)</th>
<th>Genetic Testing</th>
<th>Dosage</th>
<th>Recurrence Rate Per Group</th>
<th>Recurrence/No Remission (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis</td>
<td>Ohta et al. 2001 (75)</td>
<td>Children</td>
<td>Retrospective PPP versus none</td>
<td>21</td>
<td>No info</td>
<td>2–3 sessions PP pre-transplant</td>
<td>PPP: 5 out of 15 (33%)</td>
<td>None: 4 out of 6 (67%)</td>
<td>No information on exclusion of genetic FSGS</td>
</tr>
<tr>
<td></td>
<td>Gohh et al. 2005 (76)</td>
<td>Adults + 1 child</td>
<td>Retrospective Single group (PPP)</td>
<td>10</td>
<td>No info</td>
<td>8 sessions PP peri-Tx</td>
<td>PPP: 3 out of 10 (30%)</td>
<td></td>
<td>No control group</td>
</tr>
<tr>
<td></td>
<td>Hickson et al. 2009 (77)</td>
<td>Adults + children</td>
<td>Retrospective PPP versus none</td>
<td>30</td>
<td>Not performed Familial FSGS excluded</td>
<td>1 or more sessions PP pre-Tx</td>
<td>PPP: 6 out of 7 (86%)</td>
<td>None: 7 out of 23 (30%)</td>
<td>Large differences in time point PP was started</td>
</tr>
<tr>
<td></td>
<td>Gonzalez et al. 2011 (78)</td>
<td>Children</td>
<td>Retrospective PPP versus none</td>
<td>34</td>
<td>NPHS2 tested in 10 patients</td>
<td>1–10 sessions PP pre-Tx</td>
<td>PPP: 9 out of 17 (53%)</td>
<td>None: 10/17 (59%)</td>
<td>Study was designed to define patients with high-risk for FSGS recurrence, not to assess effects of PPP</td>
</tr>
<tr>
<td></td>
<td>Verghese et al. 2018 (79)</td>
<td>Children</td>
<td>Retrospective PPP versus none</td>
<td>51</td>
<td>NPHS2 tested in PPP group</td>
<td>1–3 sessions PP pre-Tx, 5 sessions post-Tx</td>
<td>PPP: 7 out of 26 (27%)</td>
<td>None: 8 out of 31 (26%)</td>
<td>1 patient had a heterozygous NPHS2 mutation</td>
</tr>
<tr>
<td>Plasmapheresis + rituximab</td>
<td>Alasfar et al. 2018 (80)</td>
<td>Adults</td>
<td>Prospective PPP + PRTX and PRTX versus none</td>
<td>66</td>
<td>Genetic FSGS excluded, no info on number of patients tested</td>
<td>3–10 sessions PP peri-Tx, 1–2 doses RTX</td>
<td>PRTX and PPP + PRTX: 23 out of 37 (62%)</td>
<td>None: 14 out of 27 (52%)</td>
<td>Prophylactic treatment on the basis of high/low risk</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Fornoni et al. 2011 (23)</td>
<td>Children</td>
<td>Retrospective PRTX versus none</td>
<td>41</td>
<td>No info</td>
<td>1 dose RTX (375 mg/m²)</td>
<td>PRTX: 8 out of 27 (30%)</td>
<td>None: 10 out of 14 (71%)</td>
<td>No differentiation between PRTX only and combined PRTX + PPP</td>
</tr>
<tr>
<td>LDL-apheresis + rituximab</td>
<td>Sannomiya et al. 2018 (81)</td>
<td>Adults</td>
<td>Retrospective Single group (RTX + LDL-apheresis)</td>
<td>5</td>
<td>No info</td>
<td>1 dose RTX (100 mg) and 2 sessions LPL-apheresis pre-Tx</td>
<td>PRTX + LDL: 0 out of 5 (0%)</td>
<td></td>
<td>No control group Exclusion of secondary FSGS not mentioned</td>
</tr>
</tbody>
</table>

PPP, prophylactic plasmapheresis; PP, plasmapheresis; Tx, transplant; PRTX, prophylactic rituximab.

*aNo clear definition of FSGS recurrence; numbers are on the basis of treatment with plasmapheresis within 1 month after transplant.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Total (n)</th>
<th>Dosage</th>
<th>Response Rate Complete Remission + Partial Remission (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis</td>
<td>Ponticelli <em>et al.</em> 2010 (82)</td>
<td>Children and adults</td>
<td>Review of case series and case reports</td>
<td>144</td>
<td>Variable</td>
<td>98 out of 144 (68%)</td>
<td>Review of case reports, therefore publication bias</td>
</tr>
<tr>
<td></td>
<td>Gonzalez <em>et al.</em> 2011 (78)</td>
<td>Children</td>
<td>Retrospective, single center</td>
<td>17</td>
<td>Unknown</td>
<td>15 out of 17 (88%)</td>
<td>Treatment of recurrent FSGS not described in methods</td>
</tr>
<tr>
<td></td>
<td>Schachter <em>et al.</em> 2010 (83)</td>
<td>Children and adults</td>
<td>Retrospective, single center</td>
<td>12</td>
<td>PP: 4-48 sessions</td>
<td>8 out of 12 (75%)</td>
<td>Patients also received high dose steroids (70%) Some patients also received RTX (16%)</td>
</tr>
<tr>
<td></td>
<td>Mansur <em>et al.</em> 2019 (84)</td>
<td>Children and adults</td>
<td>Retrospective, single center</td>
<td>61</td>
<td>PP: median 20 sessions</td>
<td>22 out of 61 (36%)</td>
<td>Many other treatments used: iv CsA, CP, RTX, high dose steroids, ABT, galactose Not all participants received RTX (50%) No definition of recurrent FSGS</td>
</tr>
<tr>
<td></td>
<td>Francis <em>et al.</em> 2018 (85)</td>
<td>Children</td>
<td>Retrospective, single center</td>
<td>20</td>
<td>PP: 10–92 sessions</td>
<td>15 out of 20 (75%)</td>
<td>Not all patients received RTX (50%)</td>
</tr>
<tr>
<td>Plasmapheresis + rituximab</td>
<td>Alasfar <em>et al.</em> 2018 (80)</td>
<td>Adults</td>
<td>Prospective, multicenter</td>
<td>40</td>
<td>PP; &gt;10 sessions RTX: 1–2 doses (375 mg/m²)</td>
<td>35 out of 40 (87%)</td>
<td>Large differences between treatment regimen between patients Not all patients received RTX (57%) Some patients also received iv CsA (26%)</td>
</tr>
<tr>
<td></td>
<td>Uffing <em>et al.</em> 2020 (5)</td>
<td>Adults</td>
<td>Retrospective, multicenter</td>
<td>61</td>
<td>Variable</td>
<td>35 out of 61 (57%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Garroute <em>et al.</em> 2017 (86)</td>
<td>Adults</td>
<td>Retrospective, multicenter</td>
<td>19</td>
<td>PP: unknown RTX: 1–4 doses (375 mg/m²)</td>
<td>12 out of 19 (63%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alachkar <em>et al.</em> 2013 (87)</td>
<td>Adults</td>
<td>Retrospective, single center</td>
<td>24</td>
<td>PP: median 15 sessions RTX: 1–2 doses (375 mg/m²)</td>
<td>19 out of 24 (79%)</td>
<td>Not all patients received RTX (54%)</td>
</tr>
<tr>
<td></td>
<td>Staeck <em>et al.</em> 2015 (88)</td>
<td>Adults</td>
<td>Retrospective, single center</td>
<td>12</td>
<td>PP: median 11 sessions RTX: unknown</td>
<td>11 out of 12 (92%)</td>
<td>Not all patients received RTX (50%) Other treatments used: iv CsA, high dose steroids Many other treatments used: PP, iv CsA, RTX, ABT, BTZ, CP, saquinavir, galactose</td>
</tr>
<tr>
<td></td>
<td>Allard <em>et al.</em> 2018 (25)</td>
<td>Children</td>
<td>Retrospective, single center</td>
<td>12</td>
<td>IA: median 129 sessions</td>
<td>10 out of 12 (83%)</td>
<td>All patients also received high dose oral steroids</td>
</tr>
<tr>
<td>Immunoadsorption</td>
<td>Canaud <em>et al.</em> 2010 (89)</td>
<td>Children and adults</td>
<td>Prospective, single center</td>
<td>10</td>
<td>PP: 25–39 sessions CsA iv: 14 days (target level 200–400)</td>
<td>10 out of 10 (100%)</td>
<td>All patients also received high dose iv steroids</td>
</tr>
<tr>
<td></td>
<td>Shishido <em>et al.</em> 2013 (90)</td>
<td>Children</td>
<td>Prospective, single center</td>
<td>10</td>
<td>CsA oral: target level 4500–5500 ng/h/ml</td>
<td>9 out of 10 (90%)</td>
<td>All patients also received high dose iv steroids</td>
</tr>
<tr>
<td></td>
<td>Grafals <em>et al.</em> 2019 (91)</td>
<td>Adults</td>
<td>Retrospective, two centers</td>
<td>14</td>
<td>ACTH: 80 units twice a week</td>
<td>5 out of 14 (36%)</td>
<td>Many other treatments used: PP, high-dose steroids, ABT, Bela, RTX ACTH used as “last resort.” In patients without PP, ACTH did not result in response Study sponsored by pharmaceutical company ACTH used as “last resort” if PP and RTX did not work. Divergent definition of CR and PR Researcher funded by pharmaceutical company</td>
</tr>
<tr>
<td></td>
<td>Alhamad <em>et al.</em> 2019 (92)</td>
<td>Adults</td>
<td>Retrospective, two centers</td>
<td>20</td>
<td>ACTH: 40–80 units twice a week</td>
<td>10 out of 20 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

PP, plasmapheresis; RTX, rituximab; CsA, cyclosporine; CP, cyclophosphamide; ABT, abatacept; iv, intravenous; BTZ, bortezomib; ACTH, adrenocorticotropic hormone; Bela, belatacept; IA, immunoadsorption; CR, complete remission; PR, partial remission.

*CR and PR were differently defined in different studies.*
Membranous Nephropathy

Testing for serum antibodies against the podocyte M type phospholipase A2 receptor (PLA2R Ab) has revolutionized the understanding and management of membranous nephropathy. PLA2R-associated membranous nephropathy accounts for 70%–80% of patients with primary membranous nephropathy (28). Trends in PLA2R Ab titers correlate with proteinuria, changes in antibody levels precede changes in proteinuria by weeks to months (29), and the presence of PLA2R Ab is associated with developing native membranous nephropathy (31). PLA2R-associated membranous nephropathy also requires mention. Risk alleles in HLA and donor pairs, have been linked to disease. Berchtold et al. investigated 105 kidney transplant recipients with membranous nephropathy and donor pairs, finding that donor single-nucleotide polymorphisms in between HLA-DRB1 and HLA-DQA1, and three single nucleotide polymorphisms in PLA2R1, were associated with post-transplant membranous nephropathy (38). Although this deserves further study, it is likely that combining biopsy, serologic, and genetic testing will improve the understanding, prediction, and management of post-transplant membranous nephropathy.

Dilemma: What Is Best Practice for Treating Post-Transplant Membranous Nephropathy? There is a lack of evidence for risk stratifying patients with post-transplant membranous nephropathy. Studies conducted in the pre-PLA2R/rituximab era showed the burden of post-transplant membranous nephropathy on graft survival (39–41). However, when an effective therapy is administered, disease recurrence does not appear to correlate with worse graft survival (34). It seems clear that renin-angiotensin-aldosterone blockade should be prescribed for all patients with post-transplant membranous nephropathy,

Dilemma: How Can PLA2R Testing Be Used to Improve the Management of Patients with Membranous Nephropathy in the Transplant Setting? In the largest cohort to date (n=63), Grupper et al. showed that detectable PLA2R Ab before transplantation was significantly associated with recurrent membranous nephropathy by protocol or clinically-indicated kidney biopsies (hazard ratio, 3.76; 95% confidence interval, 1.64 to 8.65) (34). Other studies have supported that positivity of PLA2R Ab testing shortly before or at the time of transplant is associated with recurrent disease (35,36). However, some studies have not found this association (37). Studies on monitoring PLA2R Ab post-transplant are limited but support that persistent or reemerging PLA2R Ab is associated with an increase of proteinuria and, in some patients, resistant disease (35,37).

In the study by Grupper et al., one third of patients with negative pretransplant PLA2R Ab experienced recurrent disease (34), and a study by Kattah et al. found the negative predictive value of pretransplant PLA2R Ab was only 42% (35). Quintana et al. found a much higher negative predictive value of 92% when using a lower cutoff value of 45 RU/ml on ELISA, highlighting that the pretransplant PLA2R Ab titer may be important (36). Nonetheless, as other autoantibodies have emerged as potential culprits in membranous nephropathy, more research will be needed to assess their individual predictive value at time of transplant.

There is important clinical heterogeneity in these data that precludes a “one-size-fits-all” approach to care. Moreover, most research available so far came from a single center (34). Replication by other centers would give greater validity to these results. We advocate for trending serum PLA2R Ab levels using indirect immunofluorescence and ELISA at the time of initial transplant evaluation, and at the time of transplant, in all patients with membranous nephropathy to establish baseline values.

In patients with stable PLA2R-associated membranous nephropathy post-transplant, following PLA2R Ab levels every 3–6 months is likely to detect trends to guide further monitoring. Additionally, PLA2R staining of previous native and/or allograft biopsies can help guide the use of PLA2R Ab testing for patients with a prior diagnosis of membranous nephropathy with unknown PLA2R status (evidence grade for above recommendations: expert opinion/not graded) (32). Furthermore, the use of PLA2R Ab as a diagnostic biomarker (i.e., to replace kidney biopsy) in the transplant setting requires study.

Recent discoveries in the genetics of membranous nephropathy also require mention. Risk alleles in HLA and PLA2R1 have been linked to disease. Berchtold et al. investigated 105 kidney transplant recipients with membranous nephropathy and donor pairs, finding that donor single-nucleotide polymorphisms in between HLA-DRB1 and HLA-DQA1, and three single nucleotide polymorphisms in PLA2R1, were associated with post-transplant membranous nephropathy (38). Although this deserves further study, it is likely that combining biopsy, serologic, and genetic testing will improve the understanding, prediction, and management of post-transplant membranous nephropathy.
and additional immunosuppression prescribed in the setting of worsening kidney function, overt nephrotic syndrome, and/or thromboembolic complications of nephrotic syndrome, unless contraindicated. However, data are lacking for other clinical phenotypes. The study by Grupper et al. used a threshold of 1000 mg of proteinuria, despite the use of angiotensin-converting enzyme inhibitors and/or aldosterone receptor blockers to qualify for rituximab treatment (34), a cutoff some experts have advocated for (42).

In patients with post-transplant membranous nephropathy who require immunosuppression, rituximab is the drug of choice because patients are usually already taking calcineurin inhibitors, and it is desirable to avoid alkylating agents due to risk of malignancy. Rituximab leads to complete or partial remission in most patients with recurrent membranous nephropathy (Table 3). The optimal dosing for rituximab in recurrent membranous nephropathy is not established, but it is reasonable to prescribe two doses of 1000 mg separated by 2 weeks, as used in the Rituximab or Cyclosporine for the Treatment of Membranous Nephropathy (MENTOR) study (43). After rituximab therapy, we advocate for routine laboratory monitoring including CD19 counts and PLA2R antibody levels (in PLA2R-associated membranous nephropathy). Repeated rituximab dosing may be required, particularly in patients who have not achieved immunologic remission (i.e., PLA2R Abs still detectable) (all above recommendations: expert opinion/not graded). Additional therapies such as bortezomib targeting plasma cells and other anti-CD20 antibodies (obinutuzumab and ofatumumab) have been described in case reports for resistant membranous nephropathy pre- and post-transplant, and deserve further study in treatment of post-transplant membranous nephropathy (44–46).

Pretransplant antibody depletion strategies (i.e., anti-B cell therapy, plasmapheresis) are likely not necessary for most patients with membranous nephropathy because recurrent membranous nephropathy is often slowly progressive and responds well to therapy. Preemptive antibody depletion deserves further study in patients who previously lost their allograft due to recurrent membranous nephropathy who have persistently positive PLA2R antibody titers (47).

Atypical Hemolytic Uremic Syndrome

Dilemmas: Should Patients with Atypical Hemolytic Uremic Syndrome Who Are Planning for Kidney Transplant Receive Eculizumab Prophylactically, and How Does Complement Testing Inform Management of These Patients? Recurrence of atypical hemolytic uremic syndrome (aHUS) occurs in 20%–100% of patients, strongly influenced by genetic background. Patients with mutations in complement factor genes have a three-fold risk of recurrence compared with patients without mutations (48), with the highest risk in patients with mutations in genes encoding complement regulatory proteins (such as CFH, CFI, C3, and CFB). Risk haplotypes for aHUS have been identified in the CFH and MCP genes with varying recurrence rates, whereas the recurrence of anti-FH associated aHUS has been shown to depend on the antibody titer (49).

The 2015 Kidney Disease Improving Global Outcomes Controversies Conference for aHUS and C3 glomerulopathy summarized a risk stratification for prescribing prophylactic eculizumab, on the basis of clinical phenotype and specific complement testing (49) (Table 4). The Global aHUS Registry found the highest mean eGFR at 6 months, and lowest risk of dialysis for patients treated prophylactically (n=88) versus no prophylaxis in patients with (n=52) or without (n=48) a previous diagnosis of aHUS (50). A recent systematic review and meta-analysis comprising 380 adult kidney transplant recipients who received eculizumab for prevention or treatment of aHUS revealed a pooled estimated rate of allograft loss of 6% in the prophylaxis group compared with 23% in those treated after disease recurrence (51). In the French atypical hemolytic uremic syndrome cohort (52), no patient who received eculizumab prophylaxis developed recurrent disease (n=52, 75% high risk and 25% moderate risk for recurrence) versus a clinical recurrence of 41% in the nonprophylactic group (n=74, 47% high risk, 41% moderate risk, 12% low risk). Furthermore, death-censored graft loss was significantly more common in the nonprophylaxis group (38% versus 4%, P<0.001). The Kidney Disease Improving Global Outcomes Controversies Conference recommends starting prophylactic eculizumab at the time of transplant, but noted there were no studies comparing prophylactic or pretransplant strategies of treatment or monitoring (49).

Conversely, a smaller case series from The Netherlands demonstrated good allograft outcomes in 17 patients who were high risk and underwent living donor kidney transplantation without prophylactic eculizumab (53). With a mean follow-up of 25 months, only one patient experienced disease recurrence that was successfully treated with eculizumab. The authors hypothesized that these impressive outcomes in a high-risk group could be related to living donation and the use of lower dose calcineurin inhibitor regimens compared with previously published studies. The same group also found that kidney transplantation with use of eculizumab upon recurrence of aHUS (as opposed to prophylactically) was more cost effective, and that use of prophylactic eculizumab did not result in more quality-adjusted life years (54).

Taken together, these data support that genetic complement testing should be performed in all patients with aHUS who are undergoing kidney transplant evaluation, and large registry studies indicate that graft survival may be improved by using prophylactic eculizumab, particularly in patients who are high and moderate risk. However, further study is required to understand additional donor and recipient characteristics, and aspects of post-transplant management, to further optimize patient outcomes. More data are also required to help guide decisions around stopping eculizumab treatment in patients with aHUS after kidney transplant.

C3 Glomerulopathy

Dilemma: How Should Patients with C3 Glomerulopathy Be Managed before Transplant and after Disease Recurrence? Does Complement Testing Inform Management of Patients with C3 Glomerulopathy Undergoing Evaluation for Kidney Transplantation? Recurrent C3 glomerulopathy after kidney transplant is common. The two largest case series exploring C3 glomerulopathy and transplantation are from the Mayo Clinic (n=21) and Columbia
### Table 3. Case series and retrospective cohort studies on rituximab for recurrent membranous nephropathy

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Total n</th>
<th>Recurrence Treatment</th>
<th>Dose of Rituximab</th>
<th>Clinical Condition At Last Follow-up</th>
<th>Follow-up (Months)</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Zoghby et al. 2009</td>
<td>Retrospective, single center</td>
<td>8</td>
<td>RTX</td>
<td>2 doses of 1000 mg 2 weeks apart</td>
<td>PR/Cr: 6 out of 8 (75%) Relapse: 1 (13%) For 1 patient, no long-term data were available</td>
<td>Mean 37 (SD ± 31)</td>
<td>2 patients required hospitalization for infection 9 and 12 months after treatment</td>
</tr>
<tr>
<td>Sprangers et al. 2010</td>
<td>Case series</td>
<td>4</td>
<td>RTX + steroids</td>
<td>4 weekly doses of 375 mg/m² or 2 doses of 1000 mg 2 weeks apart</td>
<td>Proteinuria decreased from 4 g/24 h to 1.8 g/24 h</td>
<td>Mean 81 (SD ± 41)</td>
<td>No</td>
</tr>
<tr>
<td>Spinner et al. 2015</td>
<td>Part of retrospective cohort study</td>
<td>3</td>
<td>RTX</td>
<td>Single dose of either 200 mg or 500 mg</td>
<td>Cr: 3 out of 3 patients (100%)</td>
<td>Median 25 (IQR 12–43)</td>
<td>N/A</td>
</tr>
<tr>
<td>Makhdooimi et al. 2015</td>
<td>Case report</td>
<td>2</td>
<td>RTX</td>
<td>4 doses of either 600 mg or 900 mg every 2 weeks</td>
<td>CR: 2 out of 2 patients (100%)</td>
<td>36, 18</td>
<td>No</td>
</tr>
<tr>
<td>Kattah et al. 2015</td>
<td>Case series</td>
<td>11</td>
<td>RTX</td>
<td>Not stated</td>
<td>Cr: 5 out of 11 (45%) Pr: 2 out of 11 (18%) Nr: 4 out of 11 (36%)</td>
<td>Median 88 (IQR 64–122)</td>
<td>N/A</td>
</tr>
<tr>
<td>Quintana et al. 2015</td>
<td>Case series</td>
<td>6</td>
<td>RTX (n=3)</td>
<td>RTX: 4 weekly doses of 375 mg/m² PP: 7 exchanges over the course of 14 days</td>
<td>Cr: 1 out of 6 (17%) Pr: 3/6 (50%) Nr: 1 out of 6 (17%) For 1 patient, no long-term data were available</td>
<td>Median 141</td>
<td>No</td>
</tr>
<tr>
<td>Gupta et al. 2016</td>
<td>Case series</td>
<td>6</td>
<td>RTX</td>
<td>1–2 doses of 375 mg/m² 2 weeks apart</td>
<td>Pr: 5 out of 6 (83%) For 1 patient, no long-term data were available</td>
<td>Median 70 (IQR 12–108)</td>
<td>No</td>
</tr>
<tr>
<td>Grupper et al. 2016</td>
<td>Retrospective cohort study</td>
<td>17</td>
<td>RTX + steroids</td>
<td>2 doses of 1000 mg 2 weeks apart</td>
<td>Cr: 9 out of 17 (53%) Pr: 5 out of 17 (29%) Nr: 3 out of 17 (18%)</td>
<td>Median 87.5 (IQR 42.7–139)</td>
<td>5 patients required hospitalization due to infection within 2 years after treatment</td>
</tr>
</tbody>
</table>

RTX, rituximab; Cr, complete remission (defined as proteinuria ≤0.3 g/24 h with a stable kidney function); Pr, partial remission (defined as reduction of 50% in baseline proteinuria <3.5 g/24 h with a stable kidney function); SD, standard deviation; IQR, interquartile range; N/A, not available; Nr, no remission; PP, plasma exchange.

*Relapse was defined as proteinuria ≥3.5 g/24 h after a period of Cr or Pr.
Table 4. Risk stratification and recommendations for prophylactic treatment in patients with atypical hemolytic uremic syndrome undergoing kidney transplant evaluation

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk (50%–100%)</td>
<td>Previous early recurrence of aHUS</td>
<td>Prophylactic eculizumab recommended</td>
</tr>
<tr>
<td></td>
<td>Pathogenic mutation in aHUS gene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gain-of-function mutation</td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>No mutation identified</td>
<td>Prophylactic eculizumab or plasma exchange recommended</td>
</tr>
<tr>
<td></td>
<td>Isolated mutation in CFI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variant of unknown significance in complement gene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent low titer anti-FH antibody</td>
<td></td>
</tr>
<tr>
<td>Low risk (&lt;10%)</td>
<td>Isolated MCP mutation</td>
<td>No prophylaxis recommended</td>
</tr>
<tr>
<td></td>
<td>Persistently negative anti-FH antibodies</td>
<td></td>
</tr>
</tbody>
</table>

aHUS, atypical hemolytic uremic syndrome. Adapted from ref. 49, with permission.

Table 5. Considerations for transplantation in patients with C3 glomerulopathy

<table>
<thead>
<tr>
<th>Risk stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid transplantation during acute period of kidney loss and acute inflammation, as</td>
</tr>
<tr>
<td>limited data suggest that rapid progression to kidney failure in the native kidneys</td>
</tr>
<tr>
<td>is associated with a higher risk for recurrence</td>
</tr>
<tr>
<td>No data exist to support whether serum complement abnormalities predict risk of recurrent disease after transplant</td>
</tr>
<tr>
<td>Monoclonal gammopathy-associated C3G has a high rate of recurrence</td>
</tr>
<tr>
<td>Treatment of recurrent C3G</td>
</tr>
<tr>
<td>There are no known strategies to reduce the recurrence risk of C3G</td>
</tr>
<tr>
<td>The use of anticomplement therapy is on the basis of small open-label trial and case reports with unknown effect of publication bias</td>
</tr>
</tbody>
</table>

C3G, C3 glomerulopathy. Adapted from ref. 49, with permission.

University (n=19) and observed recurrent disease in 67%–84% patients, with a median time to recurrence of 14–28 months (55,56). In the Mayo Clinic series, half of the patients with recurrent disease developed allograft failure at a median of 18 months after diagnosing recurrent C3 glomerulopathy. No data exist to support an association between complement testing and recurrent disease and treatment after transplantation (49) (Table 5).

A recent systematic review of the literature on the treatment of C3 glomerulopathy after kidney transplant included 12 studies comprising 122 patients (57), half of whom did not receive treatment due to stable kidney function or clinical discretion. For treated patients, the pooled rate of allograft loss was 33% with eculizumab, 42% with therapeutic plasma exchange, and 81% with rituximab. When stratified by disease subgroup, eculizumab was associated with lower rates of graft loss in C3 glomerulonephritis (22% versus 56% for TPE and 70% for rituximab), with limited data in dense deposit disease (53% rate of allograft loss with eculizumab). The pooled risk of allograft loss for those who did not receive treatment was 32%. Data on the soluble membrane attack complex (sMAC) were available for only seven patients. In total, 80% of those with elevated sMAC levels responded to eculizumab, and all responders normalized sMAC levels after treatment. These data must be interpreted with caution due to publication bias.

With these data in mind, we advocate performing genetic and functional complement testing before transplant in all patients with C3 glomerulopathy from kidney failure in the clinical research setting, but these results should not guide decisions on transplantation status or peri-transplant management. Ideally, longitudinal complement testing (such as sMAC levels) should be followed to observe trends that may inform associations with clinical phenotype and disease management. The use of eculizumab for posttransplant C3 glomerulopathy remains controversial, but in the absence of other treatment options, can be considered for patients at high risk of graft loss, such as those with worsening or high-grade proteinuria and/or progressive decline in kidney function.

**AL Amyloidosis**

**Dilemma: Should Patients with Kidney Failure Due to AL Amyloidosis Undergo Kidney Transplant?** Management of amyloid light-chain (AL) amyloidosis relies on diagnosing the underlying clonal cell disorder followed by treatment with clone-directed therapy to achieve hematologic response (*i.e.*, reduction or normalization of paraprotein levels in the blood and urine), which is associated with improved kidney outcomes, morbidity, and mortality. Autologous stem cell transplant and/or antiplasma cell therapies, including bortezomib and daratumumab, have led to tremendous improvements in hematologic response, organ response, and survival for patients with AL amyloidosis.

Two of the largest amyloidosis programs have published data supporting kidney transplant in selected patients with AL amyloidosis. In a study by Angel-Korman *et al.* comprising 49 patients at Boston University, graft survival at 1, 3, and 5 years was 94%, 89%, and 81%, respectively (58). Achieving a complete or very good partial hematologic response before kidney transplant was associated with improved patient and graft survival, and resulted in lower
rates of clinical or pathologic indicators of disease recurrence in the allograft (15% versus 69% in patients with partial or no remission). Heybeli et al. described 60 patients with AL amyloidosis treated at the Mayo Clinic, of whom 51 had undergone treatment before kidney transplant (59). The estimated median overall survival for the group was >10 years, with best survival occurring in patients with complete or very good partial hematologic response and in those who were treatment naive at the time of kidney transplant, but who were treated after kidney transplantation. Sawinski et al. also used United Network of Organ Sharing data to show that patients with amyloidosis (all types) who underwent kidney transplant had similar overall and graft survival compared with patients with diabetes-associated kidney failure and patients over age 65 who underwent transplant (60).

There is limited experience describing the use of anti-plasma cell agents after solid organ transplant for relapsed AL amyloidosis or maintenance of hematologic response. Case reports of patients who developed acute cellular rejection during treatment with lenalidomide may give pause to using this agent in the post-transplant setting (61,62). Bortezomib has been studied for the treatment of antibody-mediated rejection and does not require dose adjustment for kidney function. There are limited descriptions for the use of bortezomib for multiple myeloma and AL amyloidosis after kidney transplant (63,64). The anti-CD38 antibody daratumumab has shown efficacy as an add-on therapy for AL amyloidosis (65). One recent case series described the use of daratumumab as part of salvage therapy in five patients with plasma cell neoplasms after solid organ transplant, four of whom had AL amyloidosis, and three of whom experienced infectious complications (66).

In aggregate, these data suggest patients with kidney failure and AL amyloidosis who do not have cardiac involvement and who otherwise meet criteria for transplantation should be considered for kidney transplantation, particularly those who have achieved complete or very good partial hematologic responses. Multidisciplinary collaboration with hematology and cardiology is essential for appropriate evaluation, risk stratification, and management of these patients.

IgA Nephropathy

The incidence of recurrent IgA nephropathy increases with time after transplant (67). Its manifestation is variable, and recurrence rates vary from 10% to 30% in studies with for-cause biopsies, and 25%-53% in studies with protocol biopsies (68). Recurrence of IgA nephropathy seems to have no effect on short-term graft survival, although in studies with longer follow-up, graft outcomes seem to be worse compared with patients without recurrence.

An important concern with registry studies that investigate IgA recurrence is misclassification of graft loss due to a lack of kidney biopsy. In the setting of graft dysfunction, patients receiving a steroid-free regimen may be more likely to receive a kidney biopsy than patients on steroids, and thus more likely to receive a diagnosis of recurrent IgA. Supporting this concern, two registry studies (United Network of Organ Sharing/Organ Procurement and Transplantation Network [OPTN] and Australian and New Zealand Dialysis and Transplant Registry [ANZDATA]) found a reduced risk of graft losses due to IgA nephropathy with continued steroid use, and also reported a higher number of graft loss due to chronic allograft nephropathy and rejection. Furthermore, these studies only investigated recurrences that led to graft loss, and the immunosuppressive regimens used in the ANZDATA study are not comparable to current standard of care transplant immunosuppression. Contrarily, two United States Renal Data System registry studies did not find an association of steroid withdrawal with graft loss due to recurrent IgA nephropathy (69) or overall graft loss (70).

Two single-center studies evaluating IgA nephropathy recurrence and steroid withdrawal have similar limitations, such as large differences in groups at baseline (including immunosuppression), no or limited multivariable analysis, IgA deposits that were not defined as recurrence when rejection was present in the biopsy, a higher risk of rejection in the steroid group, and possible selection bias of which patients received the steroid free regimen (71,72). Unfortunately, there are no prospective studies that look at early steroid withdrawal and recurrent IgA with protocol biopsies, although a retrospective study with protocol biopsies by Ortiz et al. found an overall IgA nephropathy recurrence rate of 32%, with no association between IgA recurrence and steroid withdrawal (73). In TANGO, early steroid withdrawal was prescribed in 76 out of 504 patients with native IgA nephropathy and was not associated with recurrence of IgA nephropathy after kidney transplantation in a multivariable analysis.

In conclusion, the evidence for an association between early steroid withdrawal and IgA nephropathy recurrence has significant limitations. Because there is some evidence that the incidence of recurrent disease has decreased over time (74), newer trials are required to investigate the association between steroid withdrawal and recurrent IgA nephropathy in the modern era.

Exciting advances over the last decade have clearly improved our insight and treatment for many post-transplant glomerular diseases, yet significant dilemmas still exist for both clinicians and patients. International collaborative research efforts hold great promise to revolutionize our understanding, management, and, most importantly, patient outcomes for these rare and challenging conditions.

Disclosures

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References
effacement closely links to suPAR levels at time of posttransplantation focal segmental glomerulosclerosis occurrence and improves with therapy. Transplantation 96: 649–656, 2013

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Thinking Outside the Box: Novel Kidney Protective Strategies in Kidney Transplantation

Hassan N. Ibrahim,1 Dina N. Murad,1 and Greg A. Knoll2

Abstract
Despite the reduction in the incidence of acute rejection, a major risk factor for graft loss, there has been only modest improvement in long-term graft survival. Most cases of kidney graft loss have an identifiable cause that is not idiopathic fibrosis/atrophy or calcineurin inhibitor nephrotoxicity. Distinct immunologic and nonimmunologic factors conspire to lead to a common pathway of allograft fibrosis. It remains plausible that mitigating nonimmunologic damage using strategies proven effective in native kidney disease may yield benefit in kidney transplantation. In this review, we will focus on nonimmunologic aspects of kidney transplant care that may prove to be valuable adjuncts to a well-managed immunosuppression regimen. Topics to be addressed include the roles of hypertension and agents used to treat it, lipid lowering, sodium and water intake, elevated uric acid, metabolic acidosis, and the use of sodium-glucose cotransporter 2 inhibitors on long-term kidney transplant health.

Introduction
Avoidance of premature graft failure remains a key goal in the management of kidney transplant recipients. Graft loss is associated with a nearly four-fold higher risk of death compared with those with a functioning graft (1,2). The Standardized Outcomes in Nephrology—Kidney Transplantation group has identified kidney transplant survival as the most important priority for both patients and health care providers (3). Preventing graft loss was the top priority, even over death, as transplant recipients were more concerned with quality rather than quantity of life. Kidney transplant outcomes vary by program and region. Registry data from 1988 to 2014 on over 350,000 kidney transplant recipients from the United States, the United Kingdom, Australia, and New Zealand are instructive (4). Long-term adjusted graft failure risk (conditional on 1-year function) was significantly higher in the United States compared with Australia, New Zealand, and the United Kingdom. Long-term kidney graft outcomes were, however, approximately 25% worse in the United States compared with the three other developed nations, perhaps due to major differences in health care delivery systems and extent of immunosuppressive medications coverage. If the reasons behind these inferior outcomes in the United States can be firmly determined, appropriate changes may result in substantial benefits to both patients and the health care system in the United States.

Many strategies have been used with the intended goal of preserving kidney function and prolonging graft survival. These include adjustments in immunosuppression to prevent and treat rejection as well as prevent the development of donor-specific antibody. In addition to these immunologic approaches, nonimmunologic strategies, often explored and used first in the nontransplant setting, remain important options for the management of kidney transplant recipients. In this review, we will focus on nonimmunologic aspects of kidney transplant care that may be overlooked and perhaps overshadowed by the focus on immunosuppression-based interventions.

Hypertension and Allograft Outcome
BP lowering in both the general and CKD populations has been associated with many beneficial effects, including reduction in cardiovascular events and death. Data from the Systolic Blood Pressure Intervention Trial (SPRINT) suggest that even lower BP targets (i.e., <120 mm Hg) may be associated with improved clinical outcomes, even for those with CKD (5). Although the supportive data for BP lowering are more consistent for cardiovascular events and death, there are also beneficial effects of BP lowering on kidney outcomes. In the nontransplant CKD population, a meta-analysis of 11 randomized trials found that more intensive BP lowering was associated with a significant reduction in kidney failure events (defined as either a composite of doubling of serum creatinine level and 50% decline in GFR or kidney failure) (6). In the kidney transplant population, unfortunately, we do not have similar supportive data. There are observational data showing that a lower BP 1 year after transplantation is associated with an improvement in long-term graft survival, but perhaps the best available evidence comes from the Folic Acid for Vascular Outcome Reduction study, which showed a direct graded relation between systolic BP and future risk of...
cardiovascular disease and all-cause mortality (7,8). Unfortunately, there have been no interventional trials evaluating whether lowering BP, to a specific target, is associated with improvement in any clinically important outcomes, such as allograft survival. Despite the lack of strong evidence from randomized trials in transplant recipients, it seems reasonable to target a BP level similar to other high-risk patients. A target BP of <130/80 mm Hg has been recommended in the Kidney Disease Improving Global Outcomes (KDIGO) guideline on post-transplant management (9). A similar target for kidney transplant recipients was suggested in the 2012 KDIGO clinical practice guideline for the management of BP in CKD as well as in the recently published American College of Cardiology/American Heart Association BP guidelines (10,11). Until further evidence accumulates, a lower “SPRINT-like” target of <120 mm Hg may not be an appropriate goal given the higher risk of AKI and GFR decline seen with more intensive BP control (12,13). These concerns may conceivably be more serious in the setting of lack of robust autoregulation of renal blood flow in the denervated allograft.

Choice of Antihypertensive Agent

Although there is no direct randomized trial-driven evidence to support a certain BP target in kidney transplant recipients, there are data suggesting that calcium channel blockers (CCBs) may be the preferred antihypertensive in this population (14). In a systematic review of 60 trials (n=3802 patients), with 29 trials (n=2262 recipients) comparing CCBs with placebo or no treatment, ten trials involving 445 recipients comparing angiotensin-converting enzyme inhibitors (ACEis) with placebo or no treatment, and seven trials (n=405) comparing ACEis with CCBs, Cross et al. (14) found that CCBs compared with placebo or no treatment were associated with a 25% lower risk of graft loss (relative risk [RR], 0.75; 95% confidence interval [95% CI], 0.57 to 0.99) and an improvement in GFR (mean difference, 4.5 ml/min per 1.73 m^2, 95% CI, 2.2 to 6.7). Although this supports the notion that CCBs are the preferred antihypertensive agents in preventing allograft failure, it is worth noting that <900 recipients in these trials received a non-CCB, which possibly limits the robustness of this conclusion.

Renin-Angiotensin-Aldosterone System Blockade in Kidney Transplantation

In the nontransplant setting, ACEis and angiotensin receptor blockers (ARBs) have been shown to prolong kidney survival in patients with proteinuric kidney diseases. In the transplant setting, three relatively contemporary, well-done randomized trials in kidney transplantation have been published (15–17). Collectively, these placebo-controlled trials randomized 867 recipients to candesartan (for 1.7 years), losartan (for 5 years), or ramipril (for 4 years). None of these trials demonstrated a favorable effect on all-cause mortality, graft failure, or the conventional end point of creatinine doubling. Furthermore, in a systematic review of eight randomized trials (n=1502 patients) examining ACEi or ARB use in the kidney transplant population, Hiremath et al. (18) found no beneficial effect on kidney transplant loss (RR, 0.76; 95% CI, 0.49 to 1.18) or doubling of serum creatinine (RR, 0.84; 95% CI, 0.51 to 1.39) compared with controls. The major limitations of this systematic review are the relatively short follow-up of the included trials (five trials with <2-year follow-up and overall range of follow-up of 1–10 years), low death events (n=71), and a low number of transplant failure events (n=72). KDIGO is currently updating its BP guidelines for CKD. In a draft that was circulated for public comment, an updated systematic review suggested that ARB use, but not ACEi, is associated with a reduction in kidney allograft loss. This finding suggests that in addition to CCBs, ARB use for the management of hypertension may be preferred over other agents given this salutary effect on graft survival. At the end of the day, however, a trial with >10,000 recipients would be needed to prove superiority of renin-angiotensin-aldosterone system (RAAS) blockade in transplant recipients.

Although RAAS blockade has been shown to prevent progression of proteinuric kidney disease, it has never been shown to reduce structural damage or kidney failure in patients with preserved kidney function akin to that of a newly transplanted kidney. In fact, neither losartan nor enalapril prevented expansion of the mesangial glomerular volume in normoalbuminuric, normotensive, normal, or high GFR type 1 diabetic subjects who were treated for 5 years (19). The failure of RAAS blockade to show benefit in transplantation similar to that observed in native kidney disease may reflect the small sizes of the trials conducted and the low overall event rate, but it is also conceivable that RAAS is not overly activated in kidney transplantation (20–22). In the 5-year-long randomized trial of losartan versus placebo, we measured plasma renin activity (PRA) and plasma aldosterone annually in 153 kidney transplant recipients. PRA and aldosterone were in the normal range the entire duration of the trial; those on losartan exhibited higher PRA but similar plasma aldosterone levels (16,22). Furthermore, PRA and plasma aldosterone levels did not vary by immunosuppressive agents used, and neither baseline nor serial PRA or aldosterone were associated with GFR decline, proteinuria, or cortical interstitial expansion. A higher serial aldosterone level, however, was associated with higher risk of kidney failure (hazard ratio, 1.01; 95% CI, 1.00 to 1.02; P=0.02).

Blood Pressure Measurement: Role of Ambulatory Blood Pressure Monitoring

Of relevance to the discussion of hypertension management in transplant recipients is the current dependence on office BP measurement to diagnose and make treatment decisions regarding hypertension. In an elegant study by Mallamaci et al. (23), 260 stable kidney transplant recipients underwent both routine office BP measurement and 24-hour ambulatory BP monitoring (ABPM). Over a median follow-up of 3.9 years, 25% of patients’ visits triggered initiation or modification of their antihypertensive regimen for office BP >140/90 mm Hg, whereas ambulatory BP was actually normal. In contrast, 12% of visits revealed normal office BP, whereas ABPM was in the hypertensive range. Collectively, 37% of office BP measurements triggered inappropriate therapeutic interventions. These data suggest that white coat hypertension and masked hypertension are prevalent in
kidney transplant recipients and that perhaps wider use of ABPM is needed to guide diagnosis and treatment in this population. In the KDIGO CKD BP guideline recently sent out for public review, the use of out of office BP measurements (ABPM and home BP monitoring) is suggested to complement office BP readings in both nontransplant and transplant populations. The feasibility of a wider adoption of ABPM remains a challenge for most, if not all, providers and clinic personnel.

**Sodium Intake and Allograft Function**

There have been relatively few randomized trials examining the role of salt restriction in CKD and kidney transplantation (24–26). Collectively, nontransplant trials have noted a favorable effect of sodium restriction on BP, but the effect on proteinuria and GFR change is not consistent. In kidney transplant recipients, van den Berg et al. (27) compared sodium intake in 660 recipients with that of 201 healthy controls. The average daily urinary sodium excretion was 156 mmol/d compared with 195 mmol/d in controls, and the association between sodium intake and both systolic BP and diastolic BP was modest. Interestingly, Moeller et al. (28) noted no relationship between 24-hour urinary sodium excretion and antihypertensive medications use in 129 kidney transplant recipients with stable kidney function. Two trials randomized 55 kidney transplant recipients to daily sodium intake of 50–80 versus 100–150 mmol/d demonstrated an 11- to 30-mm Hg reduction in systolic BP and a roughly 10 mm Hg in diastolic BP after 1.5–3 months on the low-sodium diet (29,30). On the basis of the available data, there seems to be no distinct advantage of salt restriction in kidney transplant recipients or known benefit regarding allograft outcome. Clinical considerations such as volume overload and BP control, however, would be logical indications for sodium restriction.

**Uric Acid and Allograft Outcome**

Uric acid has been implicated in endothelial dysfunction, vascular smooth muscle proliferation, and stimulation of profibrotic and inflammatory cytokines (31). Moreover, a higher serum uric acid level has been linked to incident hypertension, cardiovascular disease, incident CKD, and accelerating established CKD (32). Two randomized, placebo-controlled trials in diabetic and nondiabetic patients with CKD, however, found that allopurinol did not slow the decline in eGFR compared with placebo (33,34). In the transplant setting, the evidence linking elevation in uric acid to allograft survival is mixed. Meier-Kriesche et al. (35) reported no difference in GFR decline between high, medium, and low levels of uric acid obtained at the time of transplantation in 852 participants of the Symphony trial. The Angiotensin II Blockade in Chronic Allograft Nephropathy trial assessed both baseline and time-varying uric acid level on iothalamate GFR change, proteinuria development, and histologic changes (36). Men, higher body mass index, diuretic use, and lower GFR were associated with a higher uric acid, whereas older age, fewer than three HLA matches, and receipt of a kidney from a woman donor were associated with lower levels. In multivariable analysis adjusted for baseline GFR, uric acid was associated with doubling of cortical interstitial volume on biopsy or kidney failure from interstitial fibrosis/tubular atrophy at 5 years (odds ratio [OR], 1.83; 95% CI, 1.06 to 3.17; \( P = 0.03 \)). A 1-mg/dl higher time-varying uric acid was associated with a 2.39-ml/min-lower iothalamate GFR (\( P < 0.001 \)) at 5 years but not with the secondary outcome of creatinine doubling, kidney failure, or death. Uric acid level is highly influenced by GFR. In an elegant analysis addressing uric acid and graft failure in 1170 recipients, Kim et al. (37) demonstrated no higher risk of graft failure with increasing uric acid level after accounting for kidney function as a time-varying confounder that is affected by prior uric acid levels. Collectively, these data suggest a possible opportunity to study uric acid lowering as a potential intervention in kidney transplant recipients. However, the prevalence of hyperuricemia is lower today with the more widespread use of tacrolimus compared with the earlier days of cyclosporin predominance, and the negative trials of uric acid lowering in native kidney disease certainly dampen enthusiasm regarding uric acid lowering being a reasonable target for future trials in kidney transplant recipients.

**Metabolic Acidosis and Allograft Function**

Kidney transplant recipients frequently have a mild metabolic acidosis that stems from defective acid handling as a result of reduced nephron mass and persistence of hyperparathyroidism early after transplantation (38). Furthermore, calcineurin inhibitors impair tubular acid secretion and cause a type 4 renal tubular acidosis. The prevalence of metabolic acidosis following kidney transplantation can be as high as 50%, particularly in those with a GFR <30 ml/min per 1.73 m² (39). Metabolic acidosis can lead to enhanced ammonia genesis, which through complement activation, can lead to tubulointerstitial injury (40). This has engendered a great deal of interest in whether alleviating acidosis in native CKD would slow kidney function decline. Studies in nontransplant settings seem to suggest benefit from alkali supplementation, but a critical appraisal of 14 studies (1394 study subjects) suggests that the strength of the evidence linking alkali supplementation to slowing GFR decline is of moderate certainty and the effect on urinary albumin lower as very low certainty (41). Importantly, there have been no large-scale randomized trials that demonstrated less kidney failure with alkali supplementation. Whether acidosis can lead to kidney allograft dysfunction is uncertain, and the evidence has generally been mixed. In one multicenter, retrospective cohort study of 2318 adult kidney transplant recipients, serum bicarbonate <22 mEq/L at 3 months was associated with a 74% higher risk of allograft loss (hazard ratio, 1.74; 95% CI, 1.26 to 2.42) (38). More recently, Gojowy et al. (42) showed that metabolic acidosis was present in 12% of 486 recipients and that those with HCO₃<sub>-</sub> <22 mEq/L had a 3-year graft survival of 74% compared with 93% for those without metabolic acidosis after adjusting for baseline eGFR. The Preserve-Transplant study is an ongoing prospective, single-blind, multicenter, randomized controlled trial of sodium bicarbonate versus placebo in 240 kidney transplant recipients (43). The primary end point is GFR change over 2 years, and the trial is expected to be completed in June 2021. Until these data are available, maintaining serum
bicarbonate above 22 mmol/L, which is suggested for native CKD, should perhaps be the goal in kidney transplantation not only for its potential positive effect on kidney function but also for preservation of bone health.

**Sodium-Glucose Cotransporter 2 Inhibitors in Kidney Transplantation**

In patients with type 2 diabetes, sodium-glucose cotransporter 2 (SGLT-2) inhibitors reduce the risk of hospitalization for heart failure and the risk of serious adverse kidney events (reviewed in ref. 44). The role of SGLT-2 inhibitors in nondiabetic kidney disease was addressed in two trials (45,46). In a 6-week randomized, double-blind, crossover trial of 53 nondiabetic subjects with a mean GFR of 58.3 ml/min and median proteinuria of 1110 mg/24 h, dapagliflozin 10 mg daily did not reduce proteinuria and resulted in an acute 6.6-ml/min decline in GFR that was reversible after discontinuation of the drug (45). The Dapagliflozin in Patients with CKD (DAPA-CKD) trial randomized 4304 patients (approximately one third were not diabetic) with a GFR between 25 and 75 ml/min and proteinuria to dapagliflozin or placebo (46). After a median follow-up of 2.4 years, participants assigned to dapagliflozin were 39% less likely to experience the primary outcome of declining kidney function, kidney failure, or death. Important cardiovascular end points were similarly reduced.

The experience with SGLT-2 inhibitors in kidney transplantation is limited to a few patient series and one randomized trial, summarized in Table 1 (47–52). Halden et al. (52) reported the results of their single-center, prospective, double-blind study of empagliflozin versus placebo in 49 kidney transplant recipients who developed posttransplant diabetes mellitus, had an eGFR>30 ml/min per 1.73 m², and were at least 1 year post-transplantation. Empagliflozin resulted in a significant reduction in hemoglobin A1c, body weight, and uric acid compared with placebo. There was no difference between the groups with respect to GFR, but data on proteinuria were not reported. Importantly, it does not seem that these agents interfere with calcineurin inhibitor levels.

In all, SGLT-2 inhibitors have emerged as major therapeutic options for both diabetic and nondiabetic kidney disease. Their use in the setting of kidney transplantation is minimal, but it appears that they are safe to use in those with preserved GFR. Certainly, the possibility that these agents may make urinary tract infections more common in transplant recipients needs to be considered carefully. Interestingly, the incidence of urinary tract infection was similar in dapagliflozin- and placebo-treated participants in the DAPA-CKD trial (46). Considering that cardiovascular disease is the leading cause of death after kidney transplantation, a large trial of SGLT-2 inhibitors in kidney transplant recipients would be greatly welcomed. A consideration should also be given to test these agents as a primary prevention strategy for post-transplant diabetes mellitus.

**Water Intake and Allograft Function**

The general public is inundated with messages to drink eight glasses of water daily for good health. The rationale for the need for higher water intake has included augmented clearance of toxins, better skin health, and possibly aiding in weight loss. Certainly, none of these have proven to be true. The origin of this recommendation is hard to trace, but some raised the possibility that Jane Brody of the New York Times may have been responsible for promoting this concept (53). This has been propagated further, and a prime example is the “Drink-Up” campaign sponsored by the Partnership for a Healthier America in collaboration with former First Lady Michelle Obama (54).

It is thought that high fluid intake may confer a kidney protective effect on kidney function in disease states. Work supporting this notion has been primarily on the basis of rat models that attribute the beneficial effects of generous fluid intake on suppressing antidiuretic hormone, which has been linked to hyperfiltration-mediated injury. Hebert et al. (55) reported accelerated GFR decline in those with CKD stages 3 and 4, with increasing urine volume potentially explained by pressure-induced glomerulosclerosis. In contrast, Clark et al. (56) demonstrated a beneficial effect of urine volume above 3 L on the rate of change in GFR in an observational study of patients with CKD. His group later went on to perform the Chronic Kidney Disease Water Intake Trial, which enrolled 631 subjects with a mean GFR of 43 ml/min per 1.73 m², the majority of whom had micro- or macroalbuminuria (57). The group randomized to higher water intake was able to increase water intake by 0.6 L/d, but that did not translate into any positive effect on the 1-year change in GFR when compared with the usual hydration group.

The issue of water intake has also been studied in kidney transplant recipients. Gordon et al. (58) interviewed 88 recipients 2 months after receiving a kidney transplant regarding adherence to the center-recommended >3 L/d fluid intake. The cohort was followed prospectively for 12 months, and multivariable regression models were used to determine the effect of adherence to recommended fluid intake on eGFR change. This study found no relationship between high fluid intake and eGFR at 6 or 12 months. Similar observations were made by Magpantay et al. (59), who randomized 62 kidney transplant recipients to >4 or 2 L/d for 12 months and found that higher fluid intake resulted in no improvement. Lastly, Weber et al. (60) studied the relationship between urinary volume and functional and structural kidney end points in the previously mentioned Angiotensin Blockade in Chronic Allograft Nephropathy trial. The highest urinary volume tertile (>2.56 L/d) was not associated with the development of cortical interstitial volume doubling on biopsy or kidney failure from interstitial fibrosis/tubular atrophy (OR, 3.5; 95% CI, 0.4 to 38.1; P=0.26); interstitial volume doubling or all-cause kidney failure (OR, 7.04; 95% CI, 0.66 to 74.8; P=0.10); or doubling of serum creatinine, all cause kidney failure, or death. Collectively, data from patients with native CKD and the small observational studies in kidney transplantation do not support the need for high fluid intake in these populations.

**Hyperlipidemia**

Perhaps as many as 50%–80% of kidney transplant recipients have dyslipidemia (61). Interest in lipid lowering with the intention of reducing cardiovascular deaths, which
<table>
<thead>
<tr>
<th>Authors</th>
<th>Design/Duration</th>
<th>No. of Participants / Agent Used</th>
<th>Timepoint</th>
<th>Hemoglobin A1c</th>
<th>Systolic BP, mm Hg</th>
<th>Diastolic BP, mm Hg</th>
<th>eGFR, ml/min per 1.73 m²</th>
<th>Body Mass Index, kg/m², or Weight, kg</th>
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<tr>
<td>Rajasekaran et al. (47)</td>
<td>Patient series 23 mo</td>
<td>6 KT, 4 SPK; canagliflozin</td>
<td>Baseline</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Mean change</td>
<td>0.07</td>
<td>0.13</td>
<td>0.30</td>
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<td>-2.14</td>
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<tr>
<td>AlKindi et al. (48)</td>
<td>Patient series 24 mo</td>
<td>8 KT; type 2 diabetes mellitus: 2, PTDM: 6; empagliflozin: 6; dapagliflozin: 2</td>
<td>Baseline 12 mo</td>
<td>9.3±1.3</td>
<td>135±9.59</td>
<td>80.6±10.1</td>
<td>76±13</td>
<td>32.7±7.2</td>
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<tr>
<td>Mahling et al. (49)</td>
<td>Prospective observational study 12 mo</td>
<td>10 KT with type 2 diabetes mellitus; empagliflozin</td>
<td>Baseline 112 mo</td>
<td>7.3%</td>
<td>135</td>
<td>80</td>
<td>57</td>
<td>75</td>
</tr>
<tr>
<td>Schwaiger et al. (50)</td>
<td>Prospective, interventional pilot study 12 mo</td>
<td>14 KT with PTDM; empagliflozin</td>
<td>Baseline 12 mo</td>
<td>6.7%</td>
<td>150</td>
<td>86</td>
<td>54</td>
<td>29.3</td>
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<tr>
<td>Attallah and Yassine (51)</td>
<td>Patient series 12 mo</td>
<td>8 KT; type 2 diabetes mellitus: 4</td>
<td>Baseline</td>
<td>7.1</td>
<td>145</td>
<td>76</td>
<td>61</td>
<td>59</td>
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<tr>
<td>Halden et al. (52)</td>
<td>Double-blind, placebo-controlled, randomized trial 6 mo</td>
<td>44 KT, all with PTDM; empagliflozin: 22, placebo: 22</td>
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<td>66</td>
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<td></td>
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<td>76</td>
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KT, kidney transplant; SPK, simultaneous kidney-pancreas; NA, not available; PTDM, post-transplant diabetes mellitus; E, empagliflozin; P, placebo.
account for the majority of deaths in kidney transplant recipients, is long-standing. The Assessment Lescol in Renal Transplantation Trial (ALERT) is the only prospective randomized trial in transplant recipients comparing fluvastatin with placebo and demonstrated a significant 35% reduction in the incidence of nonfatal myocardial infarction or cardiac deaths in fluvastatin-treated recipients but a nonsignificant reduction in the primary end point of cardiac death, nonfatal myocardial infarction, or coronary intervention (RR, 0.83; 95% CI, 0.64 to 1.06; P = 0.14) (62). An extension of ALERT with 1652 patients from the original study also demonstrated a 21% reduction of major cardiac events (P = 0.01) (63). However, there was no difference in graft survival between groups.

Amlodipine is the most commonly used antihypertensive agent in kidney transplant recipients, and its concomitant use with simvastatin at >20 mg daily for the latter should be avoided to avoid myositis. Rosuvasatin at higher doses has been associated with increased proteinuria and kidney failure in postmarketing studies. The Prospective Evaluation of Proteinuria and Renal Function in Diabetic and Non-Diabetic Patients with Progressive Renal Disease trials demonstrated a decline in urine protein-creatinine ratio by 12.6% with atorvastatin 80 mg (P = 0.03) and a nonsignificant <5% reduction in the rosuvastatin 10 and 40 mg in diabetic subjects with baseline proteinuria between 0.5 and 5 g/d (64). In nonpatients with diabetes, there was a 24.1% reduction in urinary protein with atorvastatin 80 mg (P = 0.003) and a nonsignificant <10% reduction with 10 and 40 mg rosuvastatin (65). In all, there is no evidence that lipid lowering is associated with improvement in allograft survival, but their use for cardiovascular disease reduction should follow national guidelines. The choice of a specific agent in transplant recipients should be highly individualized considering pharmacologic interactions and possible advantage of atorvastatin over others in terms of reducing proteinuria.

Strategies proven beneficial in native kidney disease, such as a lower BP target and RAAS blockade, have not been studied extensively, and neither yielded similar results in transplant recipients. At this time, a BP target of 130/80 mm Hg is recommended, and CCBs followed by ARBs are the preferred agents. The future research agenda should include trials targeting acidosis treatment and studying SGLT-2 inhibitors for reducing death from cardiovascular disease and possibly prevention of post-transplant diabetes.

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References
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Post-Transplant Cardiovascular Disease

Kelly A. Birdwell and Meyeon Park

Abstract
Cardiovascular disease remains a leading cause of death and morbidity in kidney transplant recipients and a common reason for post-transplant hospitalization. Several traditional and nontraditional cardiovascular risk factors exist, and many of them present pretransplant and worsened, in part, due to the addition of immunosuppression post-transplant. We discuss optimal strategies for identification and treatment of these risk factors, including the emerging role of sodium-glucose cotransporter 2 inhibitors in post-transplant diabetes and cardiovascular disease. We present common types of cardiovascular disease observed after kidney transplant, including coronary artery disease, heart failure, pulmonary hypertension, arrhythmia, and valvular disease. We also discuss screening, treatment, and prevention of post-transplant cardiac disease. We highlight areas of future research, including the need for goals and best medications for risk factors, the role of biomarkers, and the role of screening and intervention.

Introduction
Kidney transplantation is the preferred treatment for kidney failure, affording significant survival and quality of life advantages over long-term dialysis (1). This lower mortality is seen in populations with higher risk for cardiovascular disease at the time of transplant, including individuals with diabetes, older age, and obesity (2). Although short-term kidney graft and patient survival is excellent, long-term outcomes have been limited. Death with a functioning graft is the leading cause of graft loss in kidney transplant recipients, and a major cause of death is cardiovascular disease, accounting for about one third of known causes (3). Even though kidney transplantation reduces cardiovascular disease risk compared with staying on dialysis, kidney transplant recipients experience a higher risk of cardiovascular disease outcomes, including death, compared with the general population. These higher odds of cardiovascular death approach a 50-fold increase in patients in the fifth decade of life (4). In addition, cardiovascular disease is an increasingly common reason for post-transplant hospitalization, accounting for about 30% of these hospitalizations with an associated 4% mortality (5).

Cardiovascular Outcomes Post-Transplant
The spectrum of cardiovascular disease seen after kidney transplant includes coronary artery disease (CAD), heart failure, cardiac arrhythmias, and pulmonary hypertension. The risk for cardiovascular disease is affected by traditional and nontraditional cardiovascular disease risk factors, some of which are present prior to transplant and others that occur in the post-transplant period. The goal of this review is to elaborate on cardiovascular disease risk factors present after kidney transplant and their metabolic effect, their screening and prevention, and cardiovascular disease outcomes experienced by this population in the post-transplant period.

Cardiovascular Risk Factors
Kidney transplant recipients enter the post-transplant period with several preexisting cardiovascular disease risk factors, particularly hypertension and diabetes, which are highly prevalent in the CKD population and known to be associated with higher cardiovascular disease burden (6,7). These established risk factors include hypertension, tobacco use, dyslipidemia, and diabetes. In addition to these traditional cardiovascular disease risk factors, nontraditional risk factors, including some unique to the post-transplant state, also contribute to the higher cardiovascular disease burden. Patients with CKD experience several conditions to exacerbate vascular disease, including volume overload that may lead to left ventricular hypertrophy, anemia, and mineral bone disease (8,9).

Even though traditional cardiovascular disease risk factors are easily identified, studies have shown that control of these factors in kidney transplant recipients is often poor. For example, in a study by Kasiske et al. (10), only 56% of recipients had a systolic BP <140 mm Hg at 1 year. Another study found that a BP target of >130/80 mm Hg was not met in 69% of kidney transplant recipients, with uncontrolled hypertension (>140/90 mm Hg) observed in 44% on medications. In addition, 18% had borderline to elevated LDL, with 60% of those not treated (11). Furthermore, standard cardiovascular disease risk calculators may not be applicable to the kidney transplant population, and prior efforts made to construct relevant ones have not been widely adopted (12). The paragraphs below provide additional details of cardiovascular disease risk...
factors in relation to kidney transplant and strategies to modify them.

**Traditional Risk Factors**

**Hypertension.** The prevalence of post-transplant hypertension in the kidney transplant population is 80%–90% as observed in a retrospective cohort of 1666 kidney transplant recipients followed 5 years post-transplant (10). At 1 year, only 4% of recipients had normal BP without any use of antihypertensive medications. In this cohort, hypertension was independently associated with graft failure, death-censored graft failure, and death after adjusting for kidney function, acute rejection, and other transplant variables. For each 10-mm Hg higher systolic BP, the adjusted relative risk of death was 1.18 (95% confidence interval [95% CI], 1.12 to 1.23) (10). Similarly, in the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) cohort, a randomized control trial of 4110 stable kidney transplant recipients receiving a high- versus low-dose multivitamin of folic acid, vitamin B6, and vitamin B12 followed for 4 years, a follow-up study showed that each 20-mm Hg higher systolic BP was associated with a 32% higher risk of cardiovascular disease (hazard ratio [HR], 1.32; 95% CI, 1.19 to 1.46) (13). This study also showed that lower levels of diastolic BP (<70 mm Hg) were associated with higher risk of cardiovascular disease and death.

Despite the association of hypertension with worsened cardiovascular disease outcomes in kidney transplant recipients, the ideal BP target remains unknown, although experts often recommend <130/80 mm Hg (14,15). One retrospective study of 815 kidney transplant recipients stratified by mean office systolic BP values (<130, 130–139, or ≥140 mm Hg) showed a better composite graft and patient survival for a systolic BP <130 and 130–139 mm Hg compared with ≥140 mm Hg (P<0.001) with up to 120 months of follow-up (16). The best choice of antihypertensive medication is also unknown, although experts often recommend dihydropyridine calcium channel blockers for general use or angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) when proteinuria ≥1 g/d is present (14,15). The benefit of ACEIs and ARBs on cardiovascular disease outcomes is not well supported. In the Collaborative Study cohort, a retrospective study of approximately 39,000 kidney transplant recipients, no difference in cardiovascular disease outcomes was observed in recipients taking ACEIs or ARBs versus other medications, a similar finding to another meta-analysis study of eight trials (17,18).

**Tobacco.** Most kidney transplant centers do not require cessation of tobacco for kidney transplant listing, and the prevalence of tobacco users usually reflects that of the general population. Several studies support an association of ever tobacco use and worse graft and patient survival, with one study showing an adjusted HR of 1.60 (95% CI, 1.06 to 2.41) for mortality in ever smokers (19,20). One study that looked at incident smokers post-transplant reported that 5% of recipients become new smokers, and after excluding chronic obstructive pulmonary disease, adjusted higher risks of death-censored allograft loss (HR, 1.43; 95% CI, 1.16 to 1.76; P=0.001) and death (adjusted HR, 2.26; 95% CI, 1.91 to 2.66; P<0.001) were observed (21). Clearly, tobacco cessation should be encouraged pre- and postkidney transplant.

**Dyslipidemia.** Dyslipidemia is frequent post-transplant on the basis of common comorbid conditions like obesity, diabetes, and metabolic syndrome. Another risk factor is immunosuppression, including mammalian target of rapamycin (mTOR) inhibitors, calcineurin inhibitors (especially cyclosporin), and steroids. Treating dyslipidemia after kidney transplant is recommended. In the randomized control study Assessment of Lescol in Renal Transplantation (ALERT), 2106 kidney transplant recipients were randomized to fluvastatin versus placebo, with LDL lowered 32% in the statin group, but no difference was observed in the primary composite end point of adverse cardiac events after mean follow-up of 5.1 years (relative risk, 0.83; 95% CI, 0.64 to 1.06) (22). In a follow-up study with 2 more years of data, however, a 35% relative reduction in the risk of cardiac death or definite nonfatal myocardial infarction was observed (HR, 0.65; 95% CI, 0.48 to 0.88), supporting use of statins (23). Minimal data are available for the use of proprotein convertase subtilisin/kexin-9 inhibitors. The ideal LDL target is unknown, although Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest treating kidney transplant recipients with a statin regardless of LDL concentrations (24). It must be kept in mind the drug interaction of statin drugs with calcineurin inhibitors, particularly cyclosporin, when dosing these medications.

**Diabetes, Including Post-Transplant Diabetes.** Abnormalities in glucose metabolism are common post-transplant in patients without preexisting diabetes and represent a spectrum of disorders of impaired fasting glucose, impaired glucose tolerance, and post-transplant diabetes mellitus (25). Impaired fasting glucose is observed as early as the first week post-transplant in up to 45% of patients, whereas post-transplant diabetes develops in 16% at 1 year and 24% at 3 years (26,27). Diagnosis is made using American Diabetic Association guidelines, but post-transplant diabetes is recognized as a distinct form of type 2 diabetes caused by underlying insulin resistance combined with an insulin secretion defect (28). Given the many metabolic stressors immediately post-transplant affecting glucose, it is suggested that post-transplant diabetes should not be diagnosed until 46 days post-transplant (28). Post-transplant diabetes incidence has been declining over the past 10 years, although it remains a prevalent problem (29). The major consequence of abnormal glucose metabolism is higher risk of fatal and nonfatal cardiovascular disease events (26), with one study showing with an approximately three-fold higher risk of cardiac death or nonfatal acute myocardial infarction as compared with that in nondiabetic patients (HR, 3.27; 95% CI, 1.22 to 8.80; P=0.02) (30). Transplant recipients have fixed factors that increase their risk of post-transplant diabetes, including age >45 years, men, and Black or Hispanic heritage, but one modifiable factor, immunosuppression, plays a direct role in post-transplant diabetes through several mechanisms (31). Corticosteroids contribute to insulin resistance, and mTOR inhibitors decrease insulin sensitivity (32). Calcineurin inhibitors, especially tacrolimus, affect pancreatic β-cells and insulin secretion (33). Several studies have established tacrolimus as an independent risk factor for post-transplant diabetes in kidney transplant recipients, including a large retrospective study of 11,569 patients (27). A 6-month randomized, multicenter trial of 682 patients
showed that tacrolimus was significantly more likely than cyclosporin to cause post-transplant diabetes, with 34% of tacrolimus-treated patients developing impaired fasting glucose or post-transplant diabetes versus 26% of cyclosporin users (34). A separate study confirmed this finding even for patients where steroids were withdrawn on day 2 post-transplant (35). Increasing doses of tacrolimus (corrected by body weight) are independently associated with higher risk of post-transplant diabetes (36).

Treatment strategies for post-transplant diabetes include immunosuppression modification, lifestyle changes, and medications. Wissing et al. (37) showed in a randomized, prospective study that converting tacrolimus to cyclosporin use in kidney transplant recipients resulted in less need for diabetes treatment at 12 months, with 39% of patients in the cyclosporin group off glucose-lowering medication versus 13% of patients in the tacrolimus group ($P=0.01$). However, any change in immunosuppression must be balanced with whether it might increase the risk for rejection. Avoiding use of calcineurin inhibitors is another strategy, with a meta-analysis of trials using belatacept versus calcineurin inhibitors showing a lower odds of post-transplant diabetes at 12 months with belatacept (odds ratio, 0.43; 95% CI, 0.24 to 0.78) (38). Although it seems logical that steroid avoidance would be helpful, it has not been clearly shown that steroid avoidance improves post-transplant diabetes, and it might increase risk of rejection (39). A study by Sharif et al. (40) showed that an intensive lifestyle intervention in kidney transplant recipients with impaired fasting glucose led to 44% reverting to normal glucose metabolism as measured by oral glucose tolerance tests. For medications, hyperglycemia <45 days post-transplant is generally managed with insulin. After that, a combination of lifestyle changes, oral antiglycemic agents, and insulin is suggested (28).

The most used oral agents for post-transplant diabetes in kidney transplant recipients are the sulfonylureas and meglitinides, with metformin use frequently avoided due to safety concerns, although some promote its use (41). Newer oral agents have not been well studied in the kidney transplant population, but of interest are the inhibitors of sodium-glucose cotransporter 2 (SGLT2), which work by inhibiting glucose reabsorption at proximal renal tubules. SGLT2 inhibitors are associated with improved cardiovascular disease outcomes in patients with type 2 diabetes in randomized control trials (42–44). The Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial specifically examined patients with type 2 diabetes and kidney dysfunction (eGFR of 30 to <90 ml/min per 1.73 m² body surface area and albuminuria), finding that the relative risk of the kidney-specific composite outcome was lower by 34% (HR, 0.66; 95% CI, 0.53 to 0.81; $P<0.001$) as well as lower risks of cardiovascular death, myocardial infarction, or stroke (HR, 0.80; 95% CI, 0.67 to 0.95; $P=0.01$) and hospitalization for heart failure (HR, 0.61; 95% CI, 0.47 to 0.80; $P<0.001$) (45). Given their mechanism of action, potential adverse events related to SGLT2 inhibitors include volume depletion and urinary tract infection, which are concerning for use in kidney transplant recipients where both conditions already commonly occur. The Empagliflozin in Post-Transplant Diabetes Mellitus pilot study from Vienna was the first study published on the use in kidney transplant recipients; a pilot study of 14 recipients examined glycemic control using empagliflozin in place of insulin, finding that empagliflozin monotherapy resulted in worse glucose control (46). A single-center, prospective, randomized, double-blind study of empagliflozin versus placebo in 49 kidney transplant recipients in Oslo showed improved hemoglobin A1C and body weight with no higher risk for adverse events (47). To date, additional small patient series using SGLT2 inhibitors in kidney transplant recipients have also shown that use of these medications may be safe, with a meta-analysis of eight studies including 132 patients reaching the same conclusion (48–50). However, studies are needed to confirm safety and to see if SGLT2 inhibitors reduce cardiovascular mortality and improve graft survival in this population.

Nontraditional Risk Factors

Obesity. The potentially protective effect of obesity seen on dialysis is lost with transplant. Obesity at the time of transplant is a unique risk factor in that it is independently associated with higher cardiovascular disease risk and death in kidney transplant recipients, but that it also contributes directly to several other cardiovascular disease risk factors (hypertension, post-transplant diabetes, dyslipidemia, metabolic syndrome, physical inactivity, and graft dysfunction), which likely compounds its effect on cardiovascular disease outcomes. In one study, each 5-unit higher body mass index was associated with a 25% higher risk of the cardiac composite (HR, 1.25; 95% CI, 1.07 to 1.47; $P=0.005$), largely driven by heart failure and atrial fibrillation (51). Additional weight gain post-transplant is also a problem, with an average weight gain of 5%–10% in the first 12 months (52). As such, weight gain prevention strategies should be prioritized. These include lifestyle changes, but increasingly, bariatric surgery is being used as safety concerns in individuals with kidney disease are being abated. Turgeon et al. (53) showed in one study that patients undergoing bariatric surgery with CKD stages 3–5 had significantly more diabetes, hypertension, peripheral vascular disease, treated CAD, and prior strokes compared with those without CKD, but overall 30-day mortality was not significantly different, despite longer length of stay and higher percentage of return to the operating room in the CKD group. Another study of a larger population of patients undergoing bariatric surgery comparing groups of no CKD, CKD, and kidney failure showed higher mortality in the kidney failure group (odds ratio, 11.59; 95% CI, 6.71 to 20.04) but not the CKD group (odds ratio, 1.00; 95% CI, 0.32 to 3.11), although 30-day reoperation, readmission, and complication rate were higher in patients with CKD or kidney failure compared with those without (54). Pretransplant laparoscopic sleeve gastrectomy has shown to be safe and effective in providing weight loss, getting candidates on the kidney transplant waiting list, and decreasing comorbidities, including diabetes and hypertension, resulting in less delayed graft function and allograft dysfunction post-transplant compared with control groups (55,56). Similarly, individuals who undergo bariatric surgery after kidney transplant have been shown to have lower mortality, improved kidney function, and fewer obesity-related comorbidities compared with those who do not undergo surgery (57).

Left Ventricular Hypertrophy. In kidney transplant recipients, left ventricular hypertrophy prior to transplant...
is associated with more cardiovascular disease. In a study of 1063 individuals with pretransplant echocardiography, left ventricular hypertrophy (HR, 1.58; 95% CI, 1.07 to 2.35, \( P=0.02 \)) and high relative wall thickness (HR, 1.44; 95% CI, 1.02 to 2.01, \( P=0.04 \)) were associated with cardiovascular disease events in a multivariable survival regression analysis independently of common pretransplant cardiovascular disease risk factors (58). Transplantation leads to regression in left ventricular hypertrophy, with one study showing a significant decrease in left ventricular mass index (\( P<0.001 \)) and left atrial volume index (\( P<0.001 \)), with a significant increase in ejection fraction (\( P=0.009 \)) over 24 months of follow-up (59). Improvement in left ventricular hypertrophy may lead to better post-transplant outcomes, as shown by Paoletti et al. (60) in a prospective observational extension of two randomized controlled trials where left ventricular hypertrophy regression (HR, 0.41; 95% CI, 0.22 to 0.79; \( P=0.01 \)) was protective from the cardiovascular end point and associated with improved cardiac event-free survival.

**Mineral Bone Disease, Inflammation, and Oxidative Stress.** Changes in the mineral bone metabolism seen in CKD have long been associated with adverse vascular health and higher cardiovascular disease risk (61). Hyperparathyroidism frequently persists after kidney transplant as tertiary hyperparathyroidism and may be associated with lower graft and patient survival (62). Pretransplant treatment with these options has not been shown to be associated with better long-term graft or patient survival (63,64). The best treatment option post-transplant, surgical parathyroidectomy versus use of calcimimetics, is unknown, with one trial showing improved parathyroid hormone and calcium levels but no clear better long-term outcomes (65). However, a retrospective study from Sweden that included 156 kidney transplant recipients who underwent parathyroidectomy versus 736 matched control recipients who did not found lower risk of cardiovascular events in the parathyroidectomy group (HR, 0.53; 95% CI, 0.34 to 0.84) (66). Data on how tertiary hyperparathyroidism and its treatment affect cardiovascular outcomes after kidney transplant are needed.

Likewise, inflammation and oxidative stress are also associated with vascular disease and endothelial dysfunction in kidney disease, with C-reactive protein shown to be independently associated with cardiovascular disease and mortality in kidney transplant recipients (67). Post-transplant, with improvement in kidney function, several of these markers of inflammation change considerably, which may affect cardiovascular disease risk. Yilmaz et al. (68) showed that carotid intima media thickness improves significantly after kidney transplantation, with changes in C-reactive protein and fibroblast growth factor 23 the strongest independent correlates of carotid intima media thickness. Endothelial function improves rapidly following kidney transplantation, with this improvement maintained at 48 months (69).

**Immunosuppression.** Although current immunosuppression used in transplant has afforded excellent short-term outcomes, the off-target effects of these medications may contribute to cardiovascular disease risk as noted in the paragraphs above. These include increased hypertension (calcineurin inhibitors and steroids), dyslipidemia (steroids and mTOR inhibitors), post-transplant diabetes (calcineurin inhibitors, steroids, and mTOR inhibitors), and anemia (mycophenolate and azathioprine). Studies have examined if adjustment of immunosuppression regimens may improve cardiovascular disease risk factors, but often, one factor is helped at the exacerbation of another. For example, a meta-analysis looking at conversion studies from calcineurin inhibitors to mTOR inhibitors after kidney transplant found no changes in post-transplant diabetes risk but a significant increase in hypercholesterolemia (relative risk, 2.15; 95% CI, 1.35 to 3.41), acute rejection, proteinuria, and anemia (70). Belatacept, a costimulation blocker and one of the newer options for maintenance immunosuppression, may be beneficial in the context of cardiovascular risk. In a retrospective study of belatacept alone, belatacept and tacrolimus, or tacrolimus alone, the risk of post-transplant diabetes was lower with belatacept plus or minus tacrolimus versus tacrolimus alone (71). In the belatacept 5-year extension trial, belatacept was associated with fewer cardiac disorders (2%) than cyclosporin (12%) (72).

**Cardiovascular Disease in the Kidney Transplant Recipient**

**Coronary Artery Disease**

Considering the comorbidities of CKD and kidney failure, CAD is expected and prevalent among kidney transplant recipients. Screening and surveillance of kidney transplant candidates for CAD are standards of care at activation and during time spent on the waiting list (73). However, noninvasive cardiac stress testing may not be sufficiently accurate to exclude significant CAD in high-risk kidney transplant candidates (74). Only coronary angiography improves prediction of post-transplant mortality (75), but it is not routinely pursued due to concern about precipitating dialysis in pre-dialysis kidney transplant candidates, especially those with a possible preemptive transplant from a living donor available. Coronary revascularization has not been shown to improve mortality or adverse cardiovascular outcomes in individuals with stable coronary disease and advanced CKD (76); the role of preoperative revascularization and the preferred method (percutaneous coronary intervention or coronary artery bypass grafting) are also unclear in kidney transplant recipients and, thus, are not currently recommended for asymptomatic patients (77). The outcomes of the CKD substudy of the Ischemia Trial also do not clearly support an initial invasive strategy relative to initial conservative management with medical therapy, and whether kidney transplant alters the course of coronary disease is not known (76).

The role of post-transplant risk stratification is even less clear. Mortality in kidney transplant recipients after hospitalization for acute coronary syndrome may be as high as 24% at 1 year to >45% at 4 years (78). Recipient characteristics associated with post-transplant myocardial infarction include older age, history of angina, peripheral vascular disease, dyslipidemia, and pretransplant myocardial infarction and arrhythmia (79). KDIGO guidelines suggest managing cardiovascular disease “at least as intensively in kidney transplant recipients as in the general population, with appropriate diagnostic tests and treatments” (80). Use of stress tests post-transplant for primary or secondary prevention is not established, but use of revascularization by coronary artery bypass grafting or percutaneous transluminal coronary angioplasty has been found to be effective in
kidney transplant recipients and not associated with kidney allograft loss or allograft injury (81).

Measurement of biomarkers of cardiac ischemia both pre- and post-transplant may help with risk stratification. Elevated cardiac troponin T was found to be associated with higher risk of post-transplant death and major adverse cardiac events in high-risk patients at the Mayo Clinic (82). Troponin T levels that remained elevated after transplant (without normalization following restoration of normal kidney function from a healthy allograft) were found to be associated with high risk of death and cardiac events at up to 5 years follow-up.

Treatment of CAD has not been extensively studied exclusively in kidney transplant recipients. The ALERT trial demonstrated no difference in its primary end point (combined cardiovascular end point) but a favorable reduction in the separate outcomes of cardiac death and nonfatal myocardial infarction with fluvastatin therapy (22). Subsequent meta-analyses including ALERT suggested a likely benefit for statin use in reducing the outcome of major vascular event, coronary revascularization or stroke, and mortality. Overall, given the likely benefit and little harm, initiation and continuation of statin therapy in patients with functioning kidney transplants are recommended (83). The benefit of aspirin for primary prevention of CAD has not been studied in a randomized controlled trial of kidney transplant recipients. A secondary propensity score matching analysis of aspirin use in the FAVORIT trial showed no benefit from baseline aspirin use on cardiovascular disease or mortality outcomes (84). Given these limited data in general kidney transplant recipients, guidelines generally recommend aspirin use be considered in patients with diabetes or known atherosclerotic cardiovascular disease, unless contraindicated (80). KDIGO guidelines for treatment of triglycerides (often caused by immunosuppression) recommend primarily lifestyle modification, although fibric acid derivatives (i.e., ezetimibe; dose adjusted for kidney function) may be indicated for levels persistently >1000 mg/dl (24). Use of proprotein convertase subtilisin/kexin-9 inhibitors has not yet been established in kidney transplant recipients, although they seem to be safe in eGFR as low as 20 ml/ min per 1.73 m² (85).

Heart Failure

Heart failure is highly prevalent in patients with kidney failure, and heart failure is a leading cause of cardiovascular disease–related hospitalizations after kidney transplant (5). Although kidney transplant is associated with improvement in ejection fraction over time in most individuals (86), rates of de novo heart failure after transplant are as high as 10%–18% at 12 and 36 months, and de novo heart failure is independently associated with higher mortality and graft loss (87). Although improvement in left ventricular systolic and diastolic volumes and reduction in ventricular masses are also observed after transplant, the effects of the cardiorenal axis dysfunction pre- and post-transplant contribute to ongoing ventricular dilation, arrhythmia, and myocardial infarction in patients with heart failure (88). Prevalence of heart failure with preserved ejection fraction in kidney transplant recipients is not well known (89), but data using echocardiographic strain measurements suggest that subtle abnormalities in global longitudinal strain, a sensitive measure of left ventricular function, exist after transplant (mean follow-up time 338 days) even among individuals with normal left ventricular ejection fraction (90). Peritransplant reduction in global longitudinal strain may also be associated with higher risk of cardiovascular disease events or death after kidney transplant (91).

Evidence for screening and surveillance for heart failure in transplant candidates is limited, but KDIGO guidelines suggest that obtaining a screening echocardiogram is reasonable if symptoms of heart failure, history of cardiovascular disease, or hemodynamic instability on dialysis exists (89). Post-transplant de novo heart failure diagnosis should follow the approach in the general population, including evaluation for CAD. Risk stratification strategies using sensitive measures, like strain, may eventually be incorporated into clinical practice, although therapies for abnormal strain and heart failure with preserved ejection fraction do not yet exist outside preclinical studies. N-terminal prohormone B-type natriuretic peptide (NT-proBNP) measured pretransplant is independently associated with post-transplant mortality, whereas post-transplant NT-proBNP associates with left ventricular hypertrophy (92,93). Use of NT-proBNP to guide diagnosis or treatment of de novo heart failure post-transplant is not established.

Treatment of heart failure should be pursued as in the general population (89). Concern about hyperkalemia and reduction in eGFR often lead to withholding of otherwise beneficial treatments, and this is discouraged. Safety of the use of patiromer or sodium zirconium cyclosilicate to counteract hyperkalemia is unknown due to potential for reducing absorption of other medications, but evaluation of these strategies in conjunction with existing heart failure therapies should be pursued. Anemia is a risk factor for heart failure in the general population (94) and in kidney transplant recipients (87) in most studies, but treatment with erythropoiesis-stimulating agents for anemia in CKD has no role for prevention or treatment of heart failure (95). Although treatment of chronic heart failure and iron deficiency with or without anemia using parenteral iron improves symptoms, functional capacity, and quality of life, the specific use in kidney transplant recipients of parenteral iron or of hypoxia-inducible factor prolyl hydroxylase inhibitors has not been evaluated (89).

Pulmonary Hypertension

Pulmonary hypertension is present in up to 13%–33% of patients with CKD and kidney failure and develops as the result of several underlying factors common in CKD (96). The current World Health Organization (WHO) classification of pulmonary hypertension comprises five groups: group 1, pulmonary arterial hypertension; group 2, due to left heart disease; group 3, due to lung/respiratory disease; group 4, due to chronic pulmonary emboli; and group 5, due to unclear or multifactorial mechanisms or systemic diseases (96). Pulmonary hypertension (defined as a mean pulmonary artery pressure of >25 mm Hg at rest) may manifest in the kidney transplant recipient as a result of any one or more of these categories, but a specific consideration exists for kidney transplant recipients with high-flow arteriovenous fistulas previously used for dialysis. Compared with
patients with peritoneal dialysis or catheter-based dialysis, patients on hemodialysis with an arteriovenous fistula have higher prevalence of pulmonary hypertension (97).

Although right heart catheterization is the gold standard for diagnosis, transthoracic echocardiography is noninvasive, less expensive, and adequate to assess pulmonary pressures. Limitations of echocardiography-based diagnosis include dependence on patient volume status and image quality. Estimated pulmonary artery systolic pressure is an important metric that classifies severity of pulmonary hypertension as normal (<35 mm Hg), mild pulmonary hypertension (35–45 mm Hg), moderate (45–60 mm Hg), and severe (>60 mm Hg). Diagnosis and evaluation of pulmonary hypertension in kidney transplant candidates are important because pulmonary hypertension both is prevalent and likely has an independent effect on post-transplant outcomes. Following transplant, pulmonary hypertension may improve due to improvement in underlying heart failure and volume overload, but few studies have assessed post-transplant pulmonary hypertension prevalence, and none have assessed incidence. In patients with symptoms, echocardiography is a reasonable screening test. For patients with arteriovenous fistulas, assessing hemodynamics of the arteriovenous fistula in the resting state with the arteriovenous fistula occluded and not occluded is recommended to distinguish the relative contribution of the arteriovenous fistula to a high-flow state and elevated pulmonary pressures (96).

Evidence-based treatment of pulmonary hypertension in kidney transplant recipients is challenging due to exclusion of patients with kidney failure and kidney transplant recipients from clinical trials of pulmonary hypertension. In general, therapy on the basis of the pulmonary hypertension WHO group can be considered. Ligation of high-flow arteriovenous fistulas may lead to improvement of symptomatic pulmonary hypertension on the basis of small series (68,98).

Arrhythmia and Structural Heart Disease

Patients with CKD have a higher risk for both cardiac arrhythmias and sudden death due to electrolyte and volume disturbances, uremia, and abnormalities in myocardial structure and function. Atrial fibrillation is the most common arrhythmia in CKD. Preexisting atrial fibrillation is associated with higher mortality risk and graft failure after transplant (99), whereas post-transplant atrial fibrillation occurs in up to 7% by 35 months and is also associated with death (adjusted HR, 3.25; 95% CI, 2.92 to 3.63) and both death-censored and all-cause graft loss (adjusted HR, 2.88; 95% CI, 2.6 to 3.12) (100).

Age, men, White race, kidney failure caused by hypertension, and extended pretransplant dialysis duration are risk factors for post-transplant atrial fibrillation. As the age of kidney transplant recipients grows older, optimal risk stratification and prevention of atrial fibrillation and stroke will become increasingly important. Treatment with anticoagulation on the basis of stroke risk should be continued but poses challenges for drug interactions, and optimal use of new direct oral anticoagulants is uncertain in post-transplant patients (101). As use of novel direct oral anticoagulants rises, specific risks and benefits in kidney transplant recipients should be carefully observed.

Structural heart disease, particularly valvular disease, is common in CKD, and prevalence is higher with lower eGFR due to accelerated calcification and volume overload (101). Severe valvular disease is often a reason for the ineligibility of patients with kidney failure for kidney transplant, whereas severe heart failure with valve disease may be an indication for combined heart-kidney transplant (102). Whether kidney transplantation stabilizes disease progression is uncertain, although data suggest that hospitalizations for valvular disease are less frequent following kidney transplantation (102). Nevertheless, intervention for valvular disease in kidney transplant recipients is often required and commonly involves the aortic valve (103). Whether transcatheter aortic valve implantation is superior or noninferior to an open surgical approach is not certain in this population (104,105).

Special Populations

In studies comparing etiologies of kidney failure and associations with outcomes after kidney transplant, autosomal dominant polycystic kidney disease (ADPKD) is associated with better graft outcome overall but higher risk for metabolic complications (106). ADPKD is a nonmodifiable risk factor for post-transplant diabetes, which in turn, is a risk factor for cardiovascular complications (107). Death from cardiovascular disease is the leading cause of mortality relative to any other extra kidney manifestation of ADPKD (108). Cardiovascular disease is also the leading cause of death in patients with kidney failure across subtypes of glomerular disease (109). Although transplant improves the risk of cardiovascular disease death among patients with lupus nephritis relative to other waitlisted patients with lupus nephritis and kidney failure (110), cardiovascular disease is the most common cause of death in kidney transplant recipients with lupus nephritis (111). This is true for other subtypes of GN, including FSGS, membranous nephropathy, and membranoproliferative GN (111).

Prevention

As discussed above, aggressive management of preexisting cardiovascular disease is an important mainstay of preventing adverse cardiovascular disease outcomes, as kidney transplant recipients are undertreated with respect to cardiovascular risk factor modification (11). Because weight gain following transplant is a risk factor for adverse patient and graft outcomes, avoiding weight gain may be one method to prevent cardiovascular disease post-transplant, although this has not been proven prospectively (112). Belatacept may also provide a benefit to reduce cardiovascular disease risk after kidney transplant in eligible candidates via a lower risk of post-transplant diabetes (38).

Vascular arterial calcification is associated with cardiovascular and all-cause mortality in the general population and in kidney transplant recipients, and although progression of calcification appears to slow after transplant, it is not reversible (113). Methods to reduce and reverse the burden of arterial calcification are not yet available, although different immunosuppressive agents may differentially aggravate
vascular calcification (114). Other strategies to treat subclinical cardiovascular disease should be areas of focus for future research.

Preemptive Transplant

Preemptive transplant saves lives and is the basis for the “Transplant First” initiative in kidney failure care. Preemptive kidney transplantation is associated with improved allograft and patient survival (115). In a large study from France, preemptive kidney transplant was associated with a lower risk of graft failure than kidney transplant performed after initiation of dialysis, regardless of the duration of dialysis (even <6 months) (116). Identification of eligible living donors and reducing barriers to preemptive kidney transplant should be the focus for nephrologists and patients who are approaching KRT.

Future Directions and Conclusions

As in other areas of nephrology research, novel biomarkers of kidney injury have been evaluated as predictors of outcomes in kidney transplant, including graft loss (117) and cardiovascular outcomes (118). Although these biomarkers represent distinct kidney injury patterns from that of albuminuria, urine albumin-creatinine ratio remains one of the strongest predictors of allograft failure, cardiovascular disease events, and death (119).

Genetic risk may also be an important consideration for kidney transplant recipients. Associations between a genetic risk score comprising 27 single-nucleotide polymorphisms predictive of risk in the general population were analyzed in the ALERT trial. In analyses adjusted for cardiovascular risk factors, genetic risk score was significantly associated with major adverse cardiovascular event (HR, 1.81; 95% CI, 1.18 to 2.77, \( P = 0.006 \)) when comparing genetic high-risk patients (quartile 4) with genetic low-risk participants (quartile 1). Refining the score to better fit the transplant population may be feasible and incorporated in future clinical care (120).

As kidney transplantation continues to be the best option for patients requiring KRT, inclusion of kidney transplant recipients in cardiovascular disease trials will be important for improving outcomes in this population. Multidisciplinary clinical care models with an understanding of the risk of care fragmentation in cardiovascular disease management before and after kidney transplant should become standard (101).

In conclusion, several traditional and nontraditional cardiovascular risk factors have been identified in kidney transplant recipients, who experience a high burden of cardiovascular disease and related hospitalizations and death. Current management is largely on the basis of experience and expert
opinion. High-quality evidence is needed in this population to better understand risk and strategies to improve outcomes. On the basis of this review, it seems reasonable to target a systolic BP of <140 mm Hg, place kidney transplant recipients on a statin drug regardless of LDL unless a major contraindication is present, screen for and treat post-transplant diabetes, address weight gain and obesity with consideration of gastric bypass surgery for severe obesity, and individualize immunosuppression medication regimens. In addition, clinicians need to readily identify cardiovascular disease when present, working with a multidisciplinary team to provide comprehensive care. Treatment options are generally like what is used in the general population, with additional consideration of effect of kidney-specific factors, like arteriovenous fistula, on heart failure. Many opportunities for research are present (Figures 1 and 2, Table 1). Being more proactive regarding cardiovascular risk will hopefully lead to the better outcomes we desire for all our kidney transplant recipients.

Disclosures

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Table 1. Immunosuppression and off-target effects on cardiovascular risk factors

<table>
<thead>
<tr>
<th>Immunosuppression Medication</th>
<th>Cardiovascular Risk Factor</th>
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<tr>
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<td>Hypertension</td>
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<td>Tacrolimus</td>
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<tr>
<td>Cyclosporin</td>
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<tr>
<td>mTOR inhibitor</td>
<td>✓</td>
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<td>Steroids</td>
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mTOR, mammalian target of rapamycin.

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References

conditions with a calcifying medium. Ann Transplant 23: 112–118, 2018


Post-Transplant Pregnancy and Contraception

Christina L. Klein and Michelle A. Josephson

Abstract
Placed in a historical context, this overview focuses on post-transplant pregnancy, fatherhood, and contraception in women and men. The critical importance of early reproductive counseling because of improved sexual function and the early return of ovulation and menses post-transplant is emphasized. We explain the decision making regarding contraception choices. The available data on the safety of immunosuppressive drugs in pregnancy, and for men desiring fatherhood, are detailed. The risk of maternal ingestion of mycophenolate products on the in utero fetus is considered and contrasted with the lack of concern for their use by men fathering children. Pregnancy risks to the allograft, baby, and mother are discussed. An infant’s exposure to specific immunosuppressant medications through breastfeeding is reviewed. The ethics and realities of post-transplant parenthood are explored.

History
The first pregnancy in a transplant recipient occurred >60 years ago. Edith Helm, a 21-year-old woman with kidney failure, received a living-donor kidney transplant from her identical twin on May 24, 1956. She was the third person to receive a successful kidney transplant, the first woman to receive a successful kidney transplant, and the first to become pregnant. Her son, born in March 1958, was full term, 3300 g, and delivered by caesarian section. Mrs. Helm went on to have a daughter 2 years later, also delivered by caesarian section (1). When she died at the age of 76 in 2011, she was the world’s longest-surviving transplant recipient. Her transplanted kidney was functioning at the time of her death, illustrating that pregnancy need not interfere with graft longevity (2). Mrs. Helm’s pregnancies taught us that fertility could be restored in women with kidney failure. Of all women on dialysis, 1/20 will become pregnant. Her son, born in March 1958, was full term, 3300 g, and delivered by caesarian section. Mrs. Helm’s pregnancies taught us that fertility could be restored in women with kidney failure. Of all women on dialysis, 1/20 will become pregnant. Her son, born in March 1958, was full term, 3300 g, and delivered by caesarian section.

Reproductive Counseling
Reproductive counseling ideally begins before transplant and is repeated in the immediate post-transplant period and at follow-up visits during child-bearing years. Counseling should include assessment of a woman’s desire to achieve or avoid pregnancy, discussion of fertility, education regarding pregnancy risks and ideal timing of pregnancy, and explanation of contraceptive options. Women with kidney failure who desire motherhood have options, including pregnancy during dialysis or post-transplant, surrogate pregnancy, and adoption. There are considerations affecting risks for mother, baby, and graft that are specific for each woman. Outcomes are affected by maternal age, genetic causes of kidney failure, sensitization, maternal comorbidities and life expectancy, infection history, medications, social support, and medical resources available. For women desiring pregnancy, the general recommendations are to be at least 1 year post-transplant, have stable allograft function with no proteinuria, no recent episodes of rejection or infection, and well-controlled medical conditions (hypertension, diabetes) to achieve optimal pregnancy outcomes (4,5).

Fertility
Dysregulation of the hypothalamic-pituitary-gonadal axis causes low levels of sex hormones, oligo- or amenorrhea, reduced vaginal lubrication, difficulty achieving orgasm, loss of libido, and infertility in women with kidney failure. Of all women on dialysis, >90% have irregular or absent menstrual cycles. Restoration of fertility and improved sexual function can occur within the first year post-transplant, with return of ovulation and menses as early as the first month after transplantation (6,7).
Pregnancy rates are low on dialysis, potentially distorting women’s perception of fertility post-transplant. In a US study of recipients of solid organ transplants, nearly half of women aged 19–49 years were unaware that pregnancy was possible after transplant (8). In a Norwegian study of 118 recipients of kidney transplants of reproductive age, 37% reported not receiving contraceptive counseling early post-transplant, 84% were sexually active, and 78% had no intention of pregnancy (9). Similarly, in a Polish study including recipients of kidney transplants, only 34% reported receiving effective post-transplantation contraception counseling. Nearly half of these patients used condoms (a method with a high failure rate) for birth control. Contraceptive counseling was associated with significantly greater use of effective contraception (10). Unplanned pregnancy rates in recipients of kidney transplants ranging from 49% to 93% have been reported (11).

Attitudes regarding reproductive counseling were recently studied in candidates for liver transplant (n=14), recipients of liver transplants (n=60), and their health care providers (n=43) (12). Family planning was a high priority in 86% of the study group, with preference for in-person discussions with the providers. Of the health care providers, 96% voiced an interest in additional reproductive education; misconceptions about the safety of estrogen and intrauterine devices (IUD) were observed in 53% and 42% of providers, respectively. In the immediate post-transplant period when fertility may become restored quickly, females of reproductive age may not realize the importance of accessing reproductive health services. Transplant team members must become adept at reproductive and contraceptive counseling, or ensure early referral to an obstetrician or primary care provider comfortable with reproductive counseling and contraception in medically complex women. In addition to providing accurate information regarding medical risks and pregnancy outcomes, incorporating the wishes, values, and patient-level acceptance of pregnancy risks are vital in shared decision making.

Infertility and In Vitro Fertilization

Infertility rates after kidney transplant are poorly described, and reports of pregnancy achieved by in vitro fertilization (IVF) in recipients of transplant are limited. In a single-center report, eight of 13 recipients of transplants who had infertility for an average of 2 years achieved 11 pregnancies, with a live birth rate per procedure of 25% (13). In a population-based retrospective study crosslinking the IVF registry with the Medical Birth Registry in Sweden, pregnancy outcomes were compared in recipients of kidney transplants undergoing IVF with those experiencing spontaneous conception. Although small numbers of pregnancies occurred with IVF, preterm births, low birth weight, and preeclampsia were comparable (14).

Immunosuppression Considerations

Recipients of transplants require education on the potential teratogenic effects of immunosuppression. Women desiring pregnancy should review medications with their provider several months before attempting conception. Due to exclusion of pregnant females from immunosuppression trials, safety data are limited to animal studies and epidemiologic data from transplant pregnancy registries and case reports. Prednisone, azathioprine, and calcineurin inhibitors are generally considered safe, whereas mycophenolate mofetil and mycophenolic acid (mycophenolate products) are contraindicated. There are limited data on safety and outcomes with the mammalian target of rapamycin inhibitors, belatacept, basiliximab, anti-thymocyte globulin, and rituximab (4–7).

The use of mycophenolate products in female recipients of transplants is associated with spontaneous abortion and fetal malformations. Spontaneous abortions occur in nearly half of pregnancies conceived on these agents, and up to 26% of infants exposed in utero have birth defects, including microtia, cleft palate, and esophageal, cardiac, and kidney abnormalities (7,15,16). Women should be counseled to discontinue mycophenolate products at least 6 weeks preconception; when this is done, the observed birth defect rates are similar to the general population. Due to the incidence and severity of birth defects, all women of childbearing potential must be advised to use either an IUD or two alternative contraceptive agents while taking mycophenolate products. The US Food and Drug Administration–mandated Mycophenolate Risk Evaluation and Mitigation Strategy program collects outcome data on pregnancies conceived on or within 6 weeks of stopping mycophenolate products. Azathioprine is commonly substituted for mycophenolate products in women attempting conception. Although teratogenic in animal models, the human fetal liver does not convert azathioprine from its inactive to active form. Substantial observational data support azathioprine safety in pregnancy (7).

Corticosteroids freely cross the placenta, where 90% is metabolized to inactive forms, resulting in low fetal exposure. Fetal exposure to calcineurin inhibitors is greater, at approximately 70% of maternal tacrolimus and between 37% and 64% of maternal cyclosporine concentration (7,17). Despite this, initial concerns of higher risks of birth defects have not been supported by larger studies. Additionally, obstetric complications, including prematurity and low birth weight, in patients on calcineurin inhibitors are similar to other immunosuppressive regimens, and may relate to underlying comorbidities (7).

Recipients of kidney transplants warrant intensified clinical and laboratory monitoring to include assessment of BP, kidney function, proteinuria, blood glucose, urine culture, and calcineurin inhibitor trough levels. Follow-up is recommended every 2–4 weeks during the first and second trimesters, and every 1–2 weeks thereafter (5). Increased activity of the drug-metabolizing enzyme cytochrome P4503A, increased maternal blood volume, and decreased albumin and hemoglobin concentrations during pregnancy can result in lower whole-blood calcineurin-inhibitor concentrations, with relatively unchanged unbound (active) drug concentrations. Clinically, tacrolimus concentrations are measured in whole blood; dose increases required to maintain therapeutic levels may result in elevated unbound concentrations and possible toxicity in women with significant hypoalbuminemia or anemia. Trough concentrations should be followed postpartum, particularly for those in...
whom tacrolimus dose increases were made during pregnancy (17).

Other potential fetotoxic drugs, including valganciclovir hydrochloride and angiotensin-converting enzyme inhibitors, should be discontinued before or at time of pregnancy confirmation.

**Pregnancy Risks to the Allograft**

Although pregnancy was historically considered an immunosuppressed condition, our understanding has evolved because studies depict it as a modified and active state in which rejections can occur (18–20). Monitoring of allograft function is complicated by the hyperfiltration of pregnancy, which decreases creatinine and can mask a decline in GFR (21). Serum creatinine should decrease by 4–6 weeks gestation, remain stable during the second trimester, and increase to near prepregnancy values in the third trimester. Failure to decrease in the first trimester, or an increase in serum creatinine above prepregnancy baseline, is concerning and should prompt investigation, including ultrasound, measurement of proteinuria, donor-specific antibodies, and possible allograft biopsy. With the recent introduction of new immune-monitoring tools, the difficulty of assessing graft injury may lessen in the future. Data from the TPR registry for conception years 1967–2016 indicate that biopsy-proven acute rejection rates in pregnant recipients with transplant rejection are approximately 0.9%–1% postpartum. A recent meta-analysis demonstrated that acute rejection rates were similar in pregnant and nonpregnant recipients of transplants (18).

According to TPR data, 6% of kidney grafts are lost within 2 years of pregnancy. A 2009 Australian study compared 120 transplanted women after first live birth with control patients who were nonpregnant, nulliparous, and had received a transplant. History of delivering a live birth was not associated with a higher 20-year risk for graft loss (22). Mohammadi et al. (23) examined 56 pregnancies in 35 women who had received a transplant. They stratified the patients by kidney function: those with serum creatinine >140 μmol/L had a higher likelihood of worsening kidney function and allograft loss. A Norwegian registry study compared outcomes in recipients of transplants with and without pregnancies. The pregnancy group had better graft survival. However, this group was younger, had shorter dialysis time, more living donors, less antihypertensives, better HLA matches, and lower ischemic times (24). These studies demonstrate that graft outcomes depend on graft function before pregnancy.

Small studies on the children of recipients of kidney transplants have not demonstrated a higher incidence of intellectual impairment or abnormalities in neurologic development, beyond what would be expected for their gestational age (26–28). Stillbirths and early perinatal deaths (<24 hours after birth) occur more frequently than in the nontransplant population (29). Cytomegalovirus, a common post-transplant viral infection, can cause congenital malformations or congenital liver disease in 10%–15% of infected pregnancies, with risk being highest during early pregnancy. The incidence of congenital cytomegalovirus in infants born to recipients of transplants is not well described. Planning conception at least 1 year post-transplant decreases this risk (6).

**Risks to the Baby**

In contrast to Edith Helm’s full-term babies, most babies born to mothers with kidney transplants are born early (average, 35.9±3.4 months): 51% are born earlier than 37 weeks, compared with 10% in the general population, and 21% are born before 34 weeks. Consequently, average birth weights are lower in this group than in babies born to mothers who have not received a transplant: 10% are reported to have a very low birth weight (<1500 g), compared with 1% in the general population (25).

Small studies on the children of recipients of kidney transplants have not demonstrated a higher incidence of intellectual impairment or abnormalities in neurologic development, beyond what would be expected for their gestational age (26–28). Stillbirths and early perinatal deaths (<24 hours after birth) occur more frequently than in the nontransplant population (29). Cytomegalovirus, a common post-transplant viral infection, can cause congenital malformations or congenital liver disease in 10%–15% of infected pregnancies, with risk being highest during early pregnancy. The incidence of congenital cytomegalovirus in infants born to recipients of transplants is not well described. Planning conception at least 1 year post-transplant decreases this risk (6).

**Breastfeeding**

Breastfeeding has many benefits (31). For mothers on immunosuppression, it also has the potential unwanted side effect of exposing the infant to immunosuppression (7). Corticosteroid use has been deemed safe with infant exposure of 0.35%–0.58% of maternal prednisone dose. For cyclosporine, it has been estimated that the infant would receive at most 2% of the mother’s weight-adjusted dose. Cyclosporine is generally not detectable in the infant’s blood, although rarely has it been (32). For tacrolimus, estimates of the ingested dose are 0.06%–0.5% of maternal weight-adjusted dose (33). Blood levels of tacrolimus in bottle- and breastfed infants are comparable (34). Data are lacking for breast milk concentration and infant exposure to mycophenolate products and mammalian target of rapamycin inhibitors. Without dismissing the potential significance of immunosuppression exposure, decisions regarding whether to breastfeed should consider that the infant’s exposure to immunosuppression with breastfeeding is lower than in utero exposure.

A 2002 survey of transplant providers uncovered that 67% of providers advised female recipients of transplants to avoid nursing (35). In contrast, the 2003 American Society of Transplantation (AST) consensus conference issued the opinion that “breast feeding need not be viewed as absolutely contraindicated” (4). This professional proclamation lagged behind the one made in the court of public opinion, or perhaps reflected it, because women with kidney transplants were more frequently breastfeeding, with rates increasing since 1995 (36).
Special Considerations

Chronic hypertension, presence of anti-phospholipid antibodies, gestational hypertension, and obesity are risk factors for preeclampsia in the general public (37). Although not specifically studied in recipients of transplants, these associations likely affect recipients of kidney transplants and contribute to the elevated incidence of preeclampsia.

Limited information has been published on the safety and outcomes of pregnancy in recipients of transplants who are sensitized. The higher number of individuals who are sensitized and are successfully transplanted makes knowing these outcomes important. One may speculate that switching from mycophenolate to azathioprine in a patient who is sensitized may disproportionately pose a rejection risk. Ajami et al. (38) described pregnancies in 11 recipients of kidney transplants, eight of whom were considered sensitized. The sensitized group had worse pregnancy outcomes, including one stillbirth and two second trimester miscarriages. Three women who were sensitized developed preeclampsia. Babies born to women who were sensitized were more likely to be born preterm. Three of the eight patients who were sensitized developed antibody-mediated rejection within a year of delivery, resulting in graft loss. Because the study was retrospective, noncontrolled, and from a single center, it is not definitive; rather, it serves as an indicator that risks to the mother, baby, and graft are higher in pregnancies of recipients who are sensitized.

Fatherhood after Kidney Transplantation

Male infertility in kidney failure is common and multifactorial. Dysregulation in the hypothalamic-pituitary-gonadal axis leads to low testosterone and hypogonadism in >50% of men with kidney failure. Additionally, young males may have congenital or hereditary kidney conditions associated with impaired fertility. For example, autosomal dominant polycystic kidney disease is associated with asthenozoospermia, prune belly syndrome is characterized by undescended testicles and infertility, and posterior urethral valves are associated with erectile dysfunction. Men with kidney failure commonly experience impaired spermatogenesis, lower semen volume, and reduced sperm motility and viability, with severity correlating with dialysis duration. Additionally, erectile dysfunction is reported in over half of the kidney failure population, resulting from underlying conditions such as diabetes, medications, poor body image, anxiety, and depression. As a result of infertility, spontaneous pregnancies fathered by men with kidney failure occur at significantly lower rates than in the general population (39).

Transplant surgery poses reproductive risks because the retroperitoneal exposure can result in damage to the spermatic cord structures, including the vas deferens, and testicular blood supply. However, successful transplant can result in overall improved male fertility and pregnancy rates for many. In one series, hypogonadism resolved in over half of patients within the first post-transplant year, with normalization of testosterone levels as early as 3 months after transplant (40). Improved sperm morphology and motility has additionally been reported in a subset of patients. Post-transplant improvement of erectile dysfunction can lead to higher paternity rates. For male recipients of transplants with persistent oligoasthenozoospermia, successful paternity-assisted reproduction with intracytoplasmic sperm injection has been reported (39).

In contrast to female recipients of kidney transplants, data from the TPR illustrate that outcomes of the offspring fathered by kidney transplant recipients on mycophenolate at the time of conception have been comparable with those in the general public in terms of gestational age, weight, newborn complications, and incidence of birth defects (25,41). Conferring these findings, data from the Norwegian Renal Registry show that children fathered by men taking mycophenolate products, unlike offspring exposed in utero, are not at higher risk for malformations (42).

Registry data also suggest that paternal exposure to corticosteroids, calcineurin inhibitors, and azathioprine does not cause higher risk of obstetric complications or birth defects. Sirolimus may cause lower sperm counts, dysmotility, and reduced spontaneous pregnancy rates (43). Male recipients of transplants seeking paternity should be counseled regarding the potential effects of sirolimus on fertility. There are limited data on pregnancy rates and outcomes with fathers receiving basiliximab, anti-thymocyte globulin, and belatacept at the time of conception.

Ethics and Realities of Post-Transplant Parenthood

In 2006, McKay et al. (35) published results of a survey that questioned transplant surgeons and nephrologists about transplant pregnancy management. One survey item asked whether respondents advised recipients of transplants to avoid pregnancy. Of all respondents, 82% affirmed they did give such advice—although for most, it was for a limited time period, and 15% advised patients to completely avoid pregnancy. Hopefully, at approximately 15 years and thousands of births later, we have moved past that recommendation. Generalizations about pregnancy for all recipients of kidney transplants are no longer useful. Decisions should be made on the basis of known risks and the risk tolerance of the individual. It is important to think about the realities of life and survival with a kidney transplant, as illustrated in a retrospective Dutch study of 42 patients who had been transplanted between 1971 and 2016 (44). Their median transplant to first delivery time was 6.5 years, with median follow-up of 12.5 years. Graft survival in these women was better than the rest of their transplant cohort. Nevertheless, five (12%) patients died 1–20 years after childbirth. They did not see their children reach adulthood. This rate is higher than the general Dutch population, in which 4% of children lose a parent before adulthood. Furthermore, 40% of the women who had received a transplant were back on dialysis before their child attended elementary school. Ross (45) spoke to the issue of expected life span of recipients of transplants, arguing that, although there are never guarantees that any prospective parents will remain healthy until their children reach adulthood, “the greater likelihood of a lower maternal life expectancy is morally relevant in that physicians have an obligation to encourage women to consider their
reproductive decisions both from their own perspective and from that of the child-to-be.”

Contraception

Consensus recommendations for contraceptive use in recipients of solid organ transplants were published by the AST in 2005 (4). The Centers for Disease Control and Prevention (CDC) recommendations for contraception use in recipients of solid organ transplants were published in 2016 (46). Additional information on the safety and efficacy of contraceptive options in recipients of transplants, most notably the IUD, has been published since. Currently available contraceptive options, relative efficacy, and prescribing considerations are listed in Table 1.

The CDC contraception recommendations were separated by stable versus “complicated” graft function. Complicated graft function was defined as acute or chronic graft failure or rejection, without denoting a threshold of kidney impairment. CDC recommendations additionally exist for common transplant-associated conditions, including diabetes, hypertension, lupus, and prior deep venous thrombosis. All hormonal methods are categorized as safe in women with stable graft function. However, combined hormonal contraception is not recommended in women with complicated graft function, uncontrolled hypertension, history of stroke, thrombosis, or hypercoagulable state (46).

The copper and levonorgestrel IUD are designated safety grade 3 (theoretic or proven risks usually outweigh the advantages) for initiation of therapy in complicated graft function, but may remain in place (safety grade 2) if graft dysfunction develops after placement. Early concerns of IUD failure and the theoretic risk of pelvic inflammatory disease in recipients of transplants have not been supported by observational studies (47,48). Advantages of the IUD (including low failure rate, ease of use, and lack of immunosuppressive drug interactions and systemic side effects), along with restoration of fertility upon removal, have resulted in recommendations for its use among many transplant professionals (6,7,11).

Successful use of hysteroscopic sterilization in recipients of transplants is limited to case reports and can be confirmed by hysterosalpingography 3 months postprocedure (49). Use of emergency contraception (EC) in recipients of transplants has rarely been reported; in one study, 16% of 118 women reported EC use. The specific agents used and pregnancy rates after EC were not reported (9).

Conclusions

The thousands of successful pregnancies that have followed the birth of Edith Helm’s son >60 years ago make clear that pregnancy after kidney transplantation can occur safely and without negative effects on the mother, baby, or the kidney transplant. Nevertheless, it is high risk and safest when planned so that immunosuppression can be modified and risks are well understood.

Disclosures

M.A. Josephson reports serving as a scientific advisor or member of American Society of Nephrology, American Society of Transplantation, National Kidney Foundation, and Mycophenolate Pregnancy Exposure Registry Advisory Committee; receiving honoraria from American Society of Nephrology Highlights and Board Review Course and Update; receiving research funding from Bucksbaum Institute and Gift of Hope; having ownership interest in Seagen; having consultancy agreements with UBC Pharmaceutical Support Services for the Mycophenolate Pregnancy Registry and Labcorp; and being employed by the University of Chicago. C.I. Klein reports serving on the advisory board for CareDx and speakers bureau for CareDx, Sanofi, and Veloxis; having consultancy agreements with, and receiving honoraria from, CareDx, Sanofi, and Veloxis; serving as a scientific advisor or member of LifeLink Board of Governors; being employed by Piedmont Transplant Institute; and having patents and inventions with UpToDate.

Table 1. Contraceptive options and failure rates

<table>
<thead>
<tr>
<th>Agent</th>
<th>Failure Rates (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu-IUD</td>
<td>0.8</td>
<td>Effective approximately 10 yr, may cause heavy menses, anemia</td>
</tr>
<tr>
<td>LNG-IUD</td>
<td>0.2</td>
<td>Effective 3–5 yr, light menses or amenorrhea</td>
</tr>
<tr>
<td>Implant</td>
<td>0.05</td>
<td>Effective approximately 3 yr, irregular menses</td>
</tr>
<tr>
<td>DMPA</td>
<td>6</td>
<td>Can result in delayed return of fertility up to 18 mo, decline in bone mineral density</td>
</tr>
<tr>
<td>POP</td>
<td>9</td>
<td>Requires strict adherence, take at same time each day</td>
</tr>
<tr>
<td>CHC</td>
<td>9</td>
<td>Estrogen-containing agents may worsen hypertension and increase thrombosis risk</td>
</tr>
<tr>
<td>Hysteroscopic sterilization</td>
<td>0.02</td>
<td>Case reports in recipients of kidney transplants</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>0.5</td>
<td>Condoms provide protection against STDs, best used as adjunct therapy with other agent</td>
</tr>
<tr>
<td>Male partner vasectomy</td>
<td>0.5</td>
<td>Highest failure rates</td>
</tr>
<tr>
<td>Barrier methods*</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Rhythm method</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Withdrawal</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Emergency contraception</td>
<td></td>
<td>Progestin, progestin-receptor modulator, or copper IUD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Efficacy depends on method, time from unprotected intercourse, and patient BMI</td>
</tr>
</tbody>
</table>

*Barrier methods include condoms, diaphragm, cervical cap, and contraceptive sponge.

Data from references 6,7,11. Cu, copper; IUD, intrauterine device; LNG, levonorgestrel; DMPA, depot medroxyprogesterone acetate; POP, progestin-only pill; CHC, combined hormonal contraception (oral contraceptive pills, transdermal patch, vaginal ring); STD, sexually transmitted disease; BMI, body mass index.
References

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Bone and Mineral Disease in Kidney Transplant Recipients

Pascale Khairallah and Thomas L. Nickolas

Abstract

After kidney transplantation, mineral and bone disorders are associated with higher risk of fractures and consequent morbidity and mortality. Disorders of calcium and phosphorus, vitamin D deficiency, and hyperparathyroidism are also common. The epidemiology of bone disease has evolved over the past several decades due to changes in immunosuppressive regimens, mainly glucocorticoid minimization or avoidance. The assessment of bone disease in kidney transplant recipients relies on risk factor recognition and bone mineral density assessment. Several drugs have been trialed for the treatment of post-transplant mineral and bone disorders. This review will focus on the epidemiology, effect, and treatment of metabolic and skeletal derangements in the transplant recipient.

Introduction

After kidney transplantation, disorders of mineral and bone metabolism are common and are important causes of morbidity and mortality (1–4). Post-transplantation mineral and bone disease (MBD) is defined by clinical features that are similar to, but distinct from, MBD occurring prior to transplantation. Hypophosphatemia, hypercalcemia, and hypovitaminosis D are highly prevalent (5–8). Over the past 2 decades, high-dose glucocorticoids have become less integral to maintenance immunosuppression regimens, resulting in relatively stable central skeleton (i.e., spine and hip) bone mineral density (BMD). In contrast, worsening BMD at the peripheral skeleton (i.e., forearm and leg) continues to be seen (9–11). This is associated with ongoing fractures that have important contributions to morbidity and mortality in post-transplant recipients (4,11). This review will focus on the epidemiology, pathogenesis, and potential therapeutics for disordered mineral and bone metabolism occurring after kidney transplantation.

Disorders in Calcium and Phosphorus

Hypercalcemia and hypophosphatemia are major mineral abnormalities occurring post-transplantation (12). Hypercalcemia affects up to 59%, 45%, and 21% of recipients at 3 and 12 months and 5 years, respectively (5,13). Serum calcium levels peak by 2 months post-transplant and remain elevated in 18% of recipients by 12 months post-transplant, and in 6%, levels remain high even by 10 years post-transplantation (14,15). Hypercalcemia is related to a combination of increased urinary calcium absorption secondary to hyperparathyroidism in a well-functioning kidney, vitamin D repletion, and calcium release from the skeleton (16). It is unclear from bone biopsy studies whether bone turnover is related to hypercalcemia (13,17).

Importantly, hypercalcemia may be associated with the development of calcifications in the allograft that consequently affect graft survival (18).

Hypophosphatemia develops in up to 90% of post-transplant recipients (6,8). It typically develops in the first 3 months post-transplant and improves in approximately 86% of recipients by 12 months post-transplant (14,19,20). Hypophosphatemia develops secondary to high fibroblast growth factor 23 (FGF-23) levels (6), hyperparathyroidism-induced urinary phosphate wasting (6), and immunosuppressant effects (19). Beyond the first year post-transplantation, some recipients continue to experience urinary phosphate wasting despite normalization of serum phosphate levels (20).

Vitamin D Deficiency

Vitamin D deficiency, defined as 25-hydroxyvitamin D levels <30 ng/ml, is highly prevalent following transplantation, occurring in up to 80% of recipients by 3 months post-transplantation (6) and persisting in the short- and long-term periods post-transplantation (6,21). Vitamin D deficiency results in hypocalcemia and subsequent bone loss (22). Additionally, in vivo studies suggest that vitamin D has an immunoregulatory role, including diminished dendritic cell maturation and antigen-presenting capacity, enhanced regulatory T cell differentiation, improved pathogen clearance, and differentiation of immune inhibitory cell proliferation (22). Therefore, it is postulated that vitamin D deficiency in immunosuppressed individuals may reduce transplant tolerance, increase infections, and be associated with higher risk of malignancies (22). Major risk factors for persistent vitamin D deficiency post-transplantation include decreased allograft function and elevated FGF-23 levels (6). The Kidney Disease Improving Global Outcomes (KDIGO) guidelines...
recommend that vitamin D deficiency and insufficiency be corrected in CKD G1T–G5T using treatment strategies recommended for the general population (23).

Hyperparathyroidism
Parathyroid hormone (PTH) levels improve quickly after transplantation (9,24). This improvement is due to involution of the parathyroid glands following the restoration of kidney function and the correction of most metabolic abnormalities that stimulate hyperparathyroidism (25). However, hyperparathyroidism completely resolves in only 30% and 57% of recipients within the first and second years post-transplantation, respectively (7). Drivers of persistent hyperparathyroidism include severe pretransplant hyperparathyroidism (26), poor allograft function, and low vitamin D levels (27). In some studies, hyperparathyroidism in the post-transplant period was associated with increased cortical and trabecular bone losses (9,28) and with higher fracture risk (29). Nevertheless, in recipients maintained on glucocorticoid-based regimens, PTH levels did not correlate with bone turnover (13) or BMD losses (24,30), emphasizing the complexity of bone disease post-transplantation.

Bone Disease
The Changing Epidemiology of Bone Strength after Transplantation
Bone strength is defined as the combination of bone density and quality. Bone density refers to the amount of bone mineral (hydroxyapatite) per centimeter squared of bone tissue (i.e., gmHA/cm²), and in the clinic, it is measured by dual energy x-ray absorptiometry. Bone quality refers to bone tissue material properties (i.e., microarchitecture, turnover, mineral content and structure, microcracks, collagen content, and structure) and is measured by tetracycline double-labeled bone biopsy with quantitative histomorphometry. Kidney transplant recipients come to transplant with significant impairments in bone strength, characterized by high rates of osteopenia and osteoporosis (32% and 15%, respectively) (31–33) and fractures (two- to 14-fold greater than that of the general population) (34–36). After kidney transplantation, the skeleton undergoes changes in the short and long term that are manifested by further impairments in bone strength. Historically, the first 12–18 months of transplantation were associated with dramatic decreases in bone density of up to 9% at the spine and hip (33,37,38). Over the long term, BMD was reported to stabilize between the third and fifth years post-transplant, increase by around 6% between the sixth and tenth years post-transplant, and increase by around 2% afterward (28). High rates of bone loss in the early transplant period were associated with high rates of fracture. Ball et al. (39) reported that hip fracture rates were three-fold higher among recipients than patients on dialysis during the first 3 years of transplantation; however, by the third post-transplant year, hip fracture incidence was equivalent between groups. Nikkel et al. (1) reported that 23% of recipients transplanted between 1988 and 1998 fractured within the first 5 years of transplantation. However, immunosuppression regimens have changed over the past several decades to favor either lower glucocorticoid doses or complete glucocorticoid withdrawal. Glucocorticoids are toxic to the skeleton, and exposure to glucocorticoids is an important risk factor for fracture. Thus, the epidemiology of bone disease and fractures after kidney transplantation has changed in parallel with the decreasing use of glucocorticoid-based immunosuppression. Several prospective studies conducted on recipients managed with low-dose or early glucocorticoid withdrawal regimens have reported that, over the first 12 months of transplantation, BMD at the central skeleton (i.e., spine and hip) remained stable or increased (9,10). In contrast, BMD at the peripheral skeleton (i.e., radius and tibia) decreased (9,10). Epidemiologic studies suggest that lower rates of bone loss have resulted in lower incidence of fractures. In a systematic review of fractures in kidney transplant recipients, Naylor et al. (11) reported that rates have been lower over the last decade, likely due to decreasing exposure to glucocorticoids. Using the United States Renal Data Systems (USRDS), Nikkel et al. (40) reported that patients discharged from the hospital without glucocorticoid-based immunosuppression compared with those with glucocorticoid-based immunosuppression experienced a 31% reduction in 5-year cumulative all-type fracture incidence, with yearly incidence rates of 5.8 and 8 per 1000 patient-years in recipients managed without and with glucocorticoids, respectively. In a Belgium cohort of 518 recipients managed with either glucocorticoid withdrawal or standard glucocorticoid-based immunosuppression followed for a median of 5.2 years, Evenepoel et al. (41) reported a cumulative fracture incidence rate of 7% with an incidence rate of 14.3 per 1000 patient-years. Even though there is lower fracture incidence among recipients, fractures remain an important cause of morbidity and mortality. In transplant recipients older than 55 years, incident fracture of the spine, hip, or extremity (i.e., hand, distal radius and ulna, and foot/ankle) was associated with 2.8-, 1.34-, and 1.85-fold higher mortality risk, respectively (4). Irrespective of mortality, the risk of graft loss was reported as 1.34- and 1.3-fold higher after a hip or extremity fracture, respectively (4).

Bone Biopsy Studies—New Insights into Bone Disease in the Era of Lower-Dose Glucocorticoid Regimens
Recent bone biopsy studies suggest that lower-dose glucocorticoid-based immunosuppression regimens are associated with less severe impairments in bone quality compared with those reported in older studies in patients managed with higher-dose glucocorticoid-based regimens. Older bone biopsy studies demonstrated more profound defects in bone volume. Monier-Faugere et al. (13) reported on 57 recipients followed for 5.6±0.8 years post-transplantation maintained on an average prednisone dose of 8.8±0.85 mg at the time of biopsy. Fifty-six percent had low trabecular bone volume, 60% had low bone turnover, and 87% had a mineralization defect (13). Cumulative prednisone dose described 36% and 20% of the heterogeneity in bone volume and turnover, respectively, and no clinical or demographic feature explained the mineralization defect. In recent studies, low bone turnover remains common, but bone volume is less severely impaired. In a placebo-controlled randomized clinical trial (RCT) of zoledronic acid given over the first year of kidney transplantation, 31 patients assigned to active
drug (n=15) or placebo (n=16) underwent bone biopsy pretransplantation and 12-months post-transplantation. There were no effects of zoledronic acid on static or dynamic indices of histomorphometry; thus, we report the combined results. At baseline, 48% had low turnover and 63% had a mineralization defect. After transplantation, 68% had low turnover and 61% had a mineralization defect. The distribution among normal−, low−, and high−trabecular volume groups before and after transplantation changed from 61%, 15%, and 24% to 74%, 26%, and 0%, respectively (P=0.01). Furthermore, trabecular microarchitecture worsened, characterized by decreases in trabecular number and spacing (10). In another study of 27 recipients managed with either glucocorticoid-sparing or glucocorticoid-based regimens, Keronen et al. (17) reported that, pretransplantation, 63% had high turnover, 26% had low turnover, and 33% had a mineralization defect. Follow-up biopsy at 2 years post-transplantation demonstrated that 19% had high turnover, 52% had low turnover, and 44% had a mineralization defect. Trabecular bone volume did not change, and information on trabecular microarchitecture was not provided. In summary, these data suggest that minimizing glucocorticoid exposure after transplantation has fewer deleterious effects on trabecular bone quality. In contrast, transplantation itself is associated with lowering bone turnover.

Assessment of Bone Disease and Risk Classification of Fractures after Transplantation

The 2017 KDIGO guidelines recommended BMD testing in kidney transplant recipients if the results will alter therapy. The guidelines did not mandate the need for a bone biopsy to start treatment, and it acknowledged that the guidance is limited to the first 12 months post-transplantation due to insufficient data to guide long-term recommendations (23). Our approach is to consider a full clinical risk factor assessment for osteoporosis and fractures. Risk factors for post-transplant osteoporosis and fractures can be divided into pre- and post-transplant factors (2,4,31,32,42,43) (Figure 1). Measurement of BMD by dual energy x-ray absorptiometry is the clinical gold standard to assess fracture risk. Using the World Health Organization T-score thresholds, limited but important prospective studies in kidney transplant recipients reported that osteopenia or osteoporosis at the spine and hip predicted fracture (41,44). Prior to starting treatment, we assess bone turnover by circulating markers of bone formation and resorption, and then, we use that information to decide upon treatment options (Figure 2). Both the fracture risk assessment tool and trabecular bone score are reported to have discriminatory ability to predict fractures in kidney recipients (45,46), but they need further validation in large and diverse cohorts of transplant recipients prior to their widespread application; therefore, they are not part of our algorithm.

Figure 1. | Pretransplant and post-transplant risk factors for osteoporosis. BMI, body mass index.
Treatment of Bone Disease and Fractures after Kidney Transplantation

KDIGO recommends that patients with eGFR >30 ml/min per 1.73 m² and low BMD receive vitamin D, calcitriol, or bisphosphonates in the first 12 months after transplantation (23). However, there are now several classes of pharmacologic agents to treat osteoporosis and prevent fractures that may have applicability to kidney recipients. In the following section, we will review the evidence supporting therapeutic strategies.

Glucocorticoid Minimization

The skeletal effects of glucocorticoids are well established (47). Most transplant recipients remain on lifelong glucocorticoids, but many recipients can have glucocorticoid doses reduced to less than the threshold associated with skeletal toxicity (i.e., <7.5 mg daily) (48). Several longitudinal studies of patients on glucocorticoid-sparing immunosuppressive regimens demonstrated that BMD at the spine and hip remained stable or increased during the first post-transplant year (9,10,49). Furthermore, a USRDS analysis of 77,430 kidney transplant recipients reported that recipients discharged from the hospital without glucocorticoids compared with those with glucocorticoids had a lower risk of fracture (2% versus 3%, respectively; P<0.001): a 26% lower risk of fracture at 1 year post-transplantation and a 70% lower risk of fracture at 3 years post-transplantation (40). Thus, limiting exposure to glucocorticoids (in accordance with transplant center protocols) should be a key consideration in the management of transplant recipients, particularly those at high fracture risk defined by either prior fragility fracture at any level of BMD or low bone density (i.e., T score ≤ -1.0) along with other clinical risk factors for fracture (e.g., older age, women, and diabetes).

Vitamin D and Analogs

Vitamin D deficiency is common following kidney transplantation (50). Treatment of kidney transplant recipients with cholecalciferol safely increases serum 25-hydroxy vitamin D levels and decreases PTH levels (51). Paricalcitol, a vitamin D receptor analog (VDRA), is similarly effective in decreasing PTH levels post-transplantation, although hypercalcemia and hypercalciuria are relatively frequent side effects (52,53). Transplant recipients randomized to calcium and a VDRA compared with recipients randomized to calcium or placebo had higher lumbar (total loss 2.6% versus 5.0±5%; P<0.002) and femoral BMD (total loss 0.001) at 6 months post-transplantation (54) and higher BMD at the femoral neck (5% increase versus 1% increase; P=0.03) and distal radius (33% increase versus 2% decrease; P=0.03) at 1 year post-transplantation (55). Supplementation for 6 months with paricalcitol compared with no supplementation decreased markers of bone turnover and increased BMD at the spine and femoral neck (53). Although a VDRA may be effective at improving BMD of kidney transplant recipients during

Figure 2. Risk-based approach to mineral and bone disease (MBD) management after kidney transplantation. *Parathyroidectomy should be preferred over cinacalcet in patients who require long-term (>12-month) management of MBD abnormalities, including persistent hypercalcemia, nephrocalcinosis/nephrolithiasis, or high bone turnover states resistant to medical therapies. Bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA) is performed at 2–4 months post-transplantation in accordance with Kidney Disease Improving Global Outcomes guidelines. The authors recommend that BMD evaluation by DXA should be repeated yearly until BMD has stabilized and as long as antiresorptive/anabolic agent is being administered. Following stabilization or discontinuation of treatment, BMD can be assessed every 3–5 years. Bone turnover markers in clinical practice are limited to the following: parathyroid hormone (PTH) and bone-specific alkaline phosphatase (BSAP). Low turnover markers refer to PTH less than two times the upper limit of normal and BSAP less than the lower limit of the reference range. High turnover markers refer to PTH greater than two times the upper limit of normal and BSAP greater than the median of the reference range. If PTH and BSAP are discordant, then a bone biopsy is recommended to guide therapy. LLN, lower limit of normal; ULN, upper limit of normal; VDRA, vitamin D receptor analog.
the first year post-transplantation, no study has examined the effect of vitamin D supplementation on either BMD beyond the first year after transplantation or antifracture efficacy.

Calcimimetics

Post-transplant MBD comprises biochemical (i.e., hyperparathyroidism, hypercalcemia, and hypophosphatemia) and skeletal (i.e., impaired bone strength) disorders. The pathogenesis of the biochemical disorders is related to the effects of circulating PTH and FGF-23 on kidney handling of phosphate and possible alterations in the kidney calcium-sensing receptors, mimicking a phenotype of familial hypocalciuric hypercalcaemia (6,16). Calcimimetics increase the sensitivity of the parathyroid gland calcium-sensing receptor to calcium, thereby suppressing PTH. A placebo-controlled RCT of cinacalcet following kidney transplantation demonstrated that 70% of the participants who received cinacalcet had normalization of calcium levels as compared with only 4% of the participants who received placebo (P<0.001) (56).

ParathyroidectomY

Calcimimetics increase the sensitivity of the parathyroid gland calcium-sensing receptor to calcium, thereby suppressing PTH. A placebo-controlled RCT of cinacalcet following kidney transplantation demonstrated that 70% of the participants who received cinacalcet had normalization of calcium levels as compared with only 4% of the participants who received placebo (P<0.001) (56). Phosphate levels increased following cinacalcet treatment (P<0.001 as compared with placebo). PTH levels decreased by a mean of 128 pg/ml in the cinacalcet group, a change that was considerably greater than the 10.6-pg/ml decrease in PTH in the placebo group (P=0.002) (56). A prospective observational study of kidney transplant recipients with persistent hyperparathyroidism similarly demonstrated normalization of calcium as well as a rise in phosphate levels toward normal shortly following treatment initiation and for up to 12 months of follow-up. PTH levels did not improve until 9 months following initiation and did not normalize (57). The normalization of hypercalcemia and hypophosphatemia and the improvement in PTH levels with cinacalcet can be seen for up to 60 months of follow-up (58,59). When cinacalcet was discontinued following 12 months of therapy in ten kidney transplant recipients, calcium levels increased but remained within the normal range in eight of the recipients. PTH levels rose to pretreatment levels in two recipients only (60). Larger studies are required to inform nephrologists about the ideal time to discontinue cinacalcet in transplant recipients with secondary hyperparathyroidism. An RCT by Evenepoel et al. (56) assessed the effects of cinacalcet versus placebo on spine, hip, and one-third radius BMD in 154 (57 per group) patients. There were no between-group differences in percentage change in BMD at any skeletal site or in bone turnover markers. Kidney function assessed by eGFR was stable and similar between groups, and even though cinacalcet therapy resulted in hyperparathyroidism, this did not translate into higher risk of calcium deposits in the kidney (56). Borchardt et al. (61) performed bone biopsies in ten kidney transplant recipients at baseline and after 18–24 months of treatment with cinacalcet. Bone formation decreased in seven patients, with four patients progressing to adynamic bone disease. However, the decrease in bone formation was accompanied by an increase in osteoblast number, which is not a characteristic of adynamic bone disease, suggesting mini modeling similar to after parathyroidectomy rather than true shutdown of bone turnover. No study to date has evaluated the effect of cinacalcet on fractures in kidney recipients. In summary, cinacalcet is useful for controlling MBD biochemical abnormalities. However, no study has demonstrated a benefit on bone density, fractures, vascular calcifications, or nephrocalcinosis after transplantation. As such, it is not currently approved by the US Food and Drug Administration for the treatment of post-transplant MBD. Long-term benefits on important clinical outcomes have not been established for cinacalcet, and it may be useful as either a bridge to parathyroidectomy or ongoing therapy in patients with persistent MBD biochemical abnormalities but with contraindications to surgery.

Parathyroidectomy

One RCT compared parathyroidectomy with cinacalcet in recipients ≥6 months from transplant who had secondary hyperparathyroidism, hypercalcemia, and hypophosphatemia (62). At 12 months after intervention, parathyroidectomy was superior to cinacalcet in reducing PTH and normalizing calcium. Beneficial skeletal effects of parathyroidectomy versus cinacalcet included increased BMD at the femoral neck and a reduction in bone resorption markers. There were no differences in vascular calcification changes. eGFR declined by 9 and 4 ml/min in the cinacalcet and parathyroidectomy groups, respectively, but the change was significant only in the cinacalcet group (P<0.01). Parathyroidectomy performed in an experienced center was associated with more severe hypocalcemia as compared with cinacalcet and was associated with health care economic cost benefit if treatment had been extended to >14 months. Parathyroidectomy can rarely be associated with complications, including wound-related complications and/or damage to nearby structures. Hence, parathyroidectomy should be preferred over cinacalcet in patients who require long-term management of MBD abnormalities, including persistent hypercalcemia, nephrocalcinosis/nephrolithiasis, or high bone turnover states resistant to medical therapies (63).

Bisphosphonates

Bisphosphonates are the most widely studied treatment for post-transplant bone disease. They increase BMD by suppressing bone turnover through inhibiting osteoclast function. Their suppressive effects on turnover and theoretical risk of inducing adynamic bone disease have led to considerable controversy regarding their use after kidney transplantation. Four small studies have used bone biopsy to determine if bisphosphonates are associated with adynamic bone disease in the early post-transplant period (10,64–66). The first study by Coco et al. (67) evaluated bone histomorphometry in six patients who received pamidronate for 12 months post-transplantation and 12 controls. All six patients who received pamidronate developed adynamic bone disease, as compared with half of the controls. It is important to note that three of the six patients who received pamidronate had adynamic bone disease at baseline. The findings of Coco et al. (67) were in contrast to those of Haas et al. (66), who found that no adynamic bone disease developed in seven patients who received zoledronic acid compared with six controls in the first 6 months post-transplantation. A later study by Coco et al. (64) included a larger number of patients; 16 patients received risendronic acid in the first 12 months of transplantation compared with 13 controls. The study found no increased risk for
Table 1. Available treatments for the management of mineral and bone disease post-transplantation

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Parameters Affected by Therapy</th>
<th>Indications</th>
<th>Risks and Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D analogs (51–55)</td>
<td>• Higher serum 25-hydroxy vitamin D levels</td>
<td>• Vitamin D insufficiency</td>
<td>• Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>• Lower PTH levels</td>
<td>• Osteopenia</td>
<td>• Hypercalciuria</td>
</tr>
<tr>
<td></td>
<td>• Higher BMD at the spine, femoral neck, and radius within a year of transplantation</td>
<td>• Osteoporosis</td>
<td>• No data beyond the first year post-transplantation</td>
</tr>
<tr>
<td></td>
<td>• Lower PTH levels</td>
<td>• Hypercalcemia</td>
<td>• No data regarding antifracture efficacy</td>
</tr>
<tr>
<td>Calcimimetics (56–59)</td>
<td>• Lower serum calcium levels</td>
<td>• Hypophosphatemia</td>
<td>• Hypercalciuria</td>
</tr>
<tr>
<td></td>
<td>• Higher serum phosphate levels</td>
<td>• Prolonged hypercalcemia/hypercalcemia resistant to medical therapy</td>
<td>• Unknown ideal time to discontinue the drug</td>
</tr>
<tr>
<td></td>
<td>• Lower PTH levels</td>
<td>• Nephrolithiasis</td>
<td>• No data showing effect on BMD</td>
</tr>
<tr>
<td></td>
<td>• Higher BMD at the femoral neck</td>
<td>• Nephrocalcinosis</td>
<td>• No data regarding antifracture efficacy</td>
</tr>
<tr>
<td>Parathyroidectomy (62,63)</td>
<td>• Higher serum calcium levels</td>
<td>• Severe hyperparathyroidism resistant to medical therapy</td>
<td>• Not FDA approved for treatment of post-transplant MBD</td>
</tr>
<tr>
<td></td>
<td>• Higher serum phosphate levels</td>
<td></td>
<td>• Surgical complications</td>
</tr>
<tr>
<td></td>
<td>• Lower PTH levels</td>
<td></td>
<td>• Hypocalcemia</td>
</tr>
<tr>
<td>Bisphosphonates (68,69)</td>
<td>• Higher femoral neck and lumbar spine BMD in some studies—data controversial</td>
<td>• Osteoporosis or worsening BMD with high turnover bone disease</td>
<td>• AKI with intravenous bisphosphonates</td>
</tr>
<tr>
<td></td>
<td>• Lower serum calcium levels</td>
<td>• Prolonged hypercalcemia/hypercalcemia resistant to medical therapy</td>
<td>• No antifracture efficacy</td>
</tr>
<tr>
<td></td>
<td>• Higher serum phosphate levels</td>
<td>• Nephrocalcinosis</td>
<td>• No data beyond the first year post-transplantation</td>
</tr>
<tr>
<td></td>
<td>• Lower PTH levels</td>
<td>• Severe hyperparathyroidism resistant to medical therapy</td>
<td>• Hypocalcemia</td>
</tr>
<tr>
<td></td>
<td>• Higher BMD at the femoral neck</td>
<td>• Osteoporosis or worsening BMD with high turnover bone disease</td>
<td>• Urinary tract infections</td>
</tr>
<tr>
<td>Denosumab (73,74,77)</td>
<td>• Higher lumbar spine and total hip BMD</td>
<td>• Osteoporosis or worsening BMD with high turnover bone disease</td>
<td>• No data regarding antifracture efficacy</td>
</tr>
<tr>
<td></td>
<td>• Higher serum calcium levels</td>
<td></td>
<td>• Rapid and significant bone loss and higher risk of vertebral fractures following discontinuation</td>
</tr>
<tr>
<td></td>
<td>• Higher serum phosphate levels</td>
<td></td>
<td>• Daily subcutaneous injection</td>
</tr>
<tr>
<td></td>
<td>• Lower PTH levels</td>
<td></td>
<td>• No data regarding antifracture efficacy</td>
</tr>
<tr>
<td></td>
<td>• Higher BMD at the femoral neck</td>
<td></td>
<td>• No data beyond the first 6 mo post-transplantation</td>
</tr>
<tr>
<td>Teriparatide (80)</td>
<td>• Higher femoral neck BMD</td>
<td>• Osteoporosis or worsening BMD with adynamic bone disease</td>
<td>• No antifracture efficacy</td>
</tr>
</tbody>
</table>

PTH, parathyroid hormone; BMD, bone mineral density; FDA, Food and Drug Administration; MBD, mineral and bone disease.

Adynamic bone disease or mineralization defects. Most recently, Marques et al. (10) performed the largest and most informative trial to date, further demonstrating that zoledronic acid did not result in the development of adynamic bone disease. It is important to note that in Marques et al. (10), bone turnover in both the placebo and treatment groups decreased, suggesting that the natural history of bone turnover in the first year of transplantation is to decrease.

The effects of bisphosphonates on skeletal outcomes are unclear. A 2016 meta-analysis of 12 studies that included 621 kidney transplant recipients who received a bisphosphonate (including pamidronate, alendronate, clodronate, ibandronate, zoledronic acid, and risedronate) concluded that bisphosphonates were associated with improvement in femoral neck BMD (mean difference 0.055 g/cm²; 95% confidence interval [95% CI], 0.01 to 0.10) and lumbar spine BMD (0.053 g/cm²; 95% CI, 0.03 to 0.07). The improvements in femoral neck and lumbar spine BMD were more pronounced when patients were started on bisphosphonates within the first 6 months following transplantation. However, rates of fractures were similar between groups. Bisphosphonate therapy was safe, with no adverse kidney effects noted (68). A 2019 Cochrane review searched for RCTs and quasi-RCTs evaluating treatments for bone disease among kidney transplant recipients (69). Bisphosphonates administered for a median of 12 months post-transplantation were not associated with significant increases in BMD at the spine or hip. Furthermore, there was low-certainty evidence that they prevented fractures (relative risk, 0.62; 95% CI, 0.38 to 1.01). Data on the use of bisphosphonates are limited to the first 12 months post-transplantation as no study evaluated BMD, histomorphometric changes, or fracture rates beyond that time period. These studies provide conflicting evidence as to whether bisphosphonates ameliorate bone disease in kidney transplant recipients.
Intravenous but not oral bisphosphonates have been associated with AKI (70,71); thus, many nephrologists are apprehensive to administer them to their patients. In such cases, referral to a kidney MBD expert or to endocrinology may be necessary. It is reasonable for nephrologists to administer oral bisphosphonates to transplant recipients at risk for fracture, as long as their limitations and risks are discussed with patients prior to initiating therapy.

Denosumab
Denosumab is a potent antiresorptive agent. It is an mAb against the receptor activator of the NF-κB ligand, and it inhibits osteoclast proliferation and development. In contrast to bisphosphonates, denosumab is not cleared by the kidney; therefore, there is no risk of oversuppressing bone turnover due to drug accumulation in CKD (72). Only one prospective, randomized trial by Bonani et al. (73) evaluated the use of denosumab versus placebo in de novo kidney transplant recipients. At 1 year following treatment, lumbar spine and total hip BMD significantly increased in the denosumab group compared with the placebo group (5%; P<0.001 and 2%; P=0.04, respectively). Urinary tract infections occurred more frequently in the denosumab-treated group, as did hypocalcemia events, although the latter events were asymptomatic and transient. Hypocalcemia events can be averted by ensuring adequate vitamin D repletion before denosumab initiation. The study was too small to assess effects on fractures. Randomized controlled trials evaluating the effect of denosumab beyond the first year of transplantation are lacking. However, a retrospective study of solid organ transplant recipients 6.4±6.3 years post-transplantation determined that denosumab use for 1.65±0.7 years resulted in improvements in lumbar spine and proximal femur BMD T scores in kidney transplant recipients (74). A phase 2 trial in long-term kidney recipients is currently enrolling (NCT03660554). Given the antiresorptive consequences of using denosumab, caution should be used in patients suspected of having adynamic bone disease. Furthermore, studies in postmenopausal women demonstrated rapid and significant bone loss (75) and higher risk of vertebral fractures (76) following denosumab discontinuation. Similarly, Kobel et al. (77) reported in follow-up to Bonani et al. (73) that significant bone loss at the spine and hip occurred after discontinuation of denosumab. Current recommendations are to initiate a several-year course of potent bisphosphonate therapy to preserve BMD and prevent vertebral fractures after denosumab discontinuation (78,79).

Teriparatide
Teriparatide is a recombinant peptide of the first 34 amino-terminal residues of PTH. It is an osteanabolic agent used to treat osteoporosis and prevent fractures in both age-related and glucocorticoid-induced osteoporosis (72). Only one randomized, double-blind, placebo-controlled trial has evaluated the efficacy of teriparatide in post-transplant bone disease (80). Twelve patients received teriparatide for 6 months, while 12 patients received placebo. BMD at the lumbar spine and the distal forearm did not differ between groups throughout the study period. Femoral neck BMD remained stable in the teriparatide group, whereas it decreased significantly in the placebo group. Bone biopsies were performed in six participants in each group. None of the histomorphometric parameters differed between the groups at baseline or at the end of the study. Of five patients with adynamic bone disease at the beginning of the study, teriparatide resulted in three patients converting to higher turnover states (80). Teriparatide is expensive, is cumbersome to use as a daily subcutaneous injection, and is without a significant proven benefit or superiority over current therapies. Consequently, its role is likely to be limited to patients with adynamic bone disease who are not candidates for other agents.

MBD post-transplantation is a complex syndrome including hypercalcemia, hypophosphatemia, hyperparathyroidism, and decreased bone quality and strength. MBD is ultimately associated with high risk of morbidity and mortality. MBD biochemical abnormalities require therapeutic interventions but will resolve in the majority of patients after the first year of transplantation, and then, long-term management should prioritize parathyroidectomy for persistent abnormalities in patients who are surgical candidates (Figure 2, Table 1). In regard to the skeleton, observational research has proven that high doses of glucocorticoids are linked to greater bone loss and fractures in recipients. Unfortunately, other than minimizing glucocorticoids, no other treatment has been definitively proven to be associated with MBD improvements or fracture risk reduction. As KDIGO points out, “data are insufficient to guide treatment after the first-year post-transplantation” (23) because even the few studies that showed some therapeutic benefit lacked long-term data. Future research in this area should focus on long-term evaluation of current therapies (i.e., beyond the first year post-transplantation) on the treatment of prevalent kidney transplant recipients and on the effects of treatment on fracture rates and cardiovascular calcification and events. In the meantime, using algorithms, such as the one we propose (Figure 2), can guide fracture risk assessment and the treatment of biochemical and skeletal derangements, possibly improving post-transplant outcomes.

Disclosures
P. Khairallah reports serving on the National Kidney Foundation (NKF) Spring Clinical Meetings Program Committee for 2021, serving as a member of NKF, and serving as a member of the International Society of Nephrology. T.L. Nickolas reports consultancy agreements with Pharmacosmos; receiving research funding from Amgen; and serving as a scientific advisor or member of Amgen and Pharmacosmos. Columbia University (T.L. Nickolas’s institution) has licensed patents on Neutrophil Gelatinase Associated Lipocalin to Abbott Diagnostics and Alere.

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Long-Term Infectious Complications of Kidney Transplantation

Akansha Agrawal,1,2 Michael G. Ison 3,4 and Lara Danziger-Isakov4

Abstract
Infections remain a common complication of solid-organ transplantation. Most infections in the first month after transplant are typically health care–associated infections, whereas late infections, beyond 6–12 months, are community-acquired infections. Opportunistic infections most frequently present in the first 12 months post-transplant and can be modulated on prior exposures and use of prophylaxis. In this review, we summarize the current epidemiology of postkidney transplant infections with a focus on key viral (BK polyomavirus, cytomegalovirus, Epstein-Barr virus, and norovirus), bacterial (urinary tract infections and Clostridioides difficile colitis), and fungal infections. Current guidelines for safe living post-transplant are also summarized. Literature supporting prophylaxis and vaccination is also provided.

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Introduction
The field of transplantation has been transformed since the first kidney transplant was performed (1). Significant advances in surgical technique and induction and maintenance immunosuppression regimens have improved allograft outcomes. Nonetheless, infections remain a leading cause of complications after kidney transplantation (2,3). Over time, the field of transplant infectious diseases has grown, and discovery and implementation of modern antimicrobial prophylaxis has contributed to delaying and reducing the incidence of post-transplant infections (3). This review summarizes the timing of infectious complications and discusses common post-transplant infections and tactics to minimize infectious risk, as well as approaches to safe living.

Timing of Infectious Complications in Kidney Transplantation
Infectious complications are categorized as occurring in one of three time periods post-transplant: early post-transplant infections, infections during peak immunosuppression, and late-onset infections (Figure 1) (3,4). A number of factors affect the timing of the infections, including specific donor and recipient factors such as a preexisting infection or immunity, the use of antimicrobial prophylaxis, and the net state of immunosuppression. Of these, the net state of immunosuppression is harder to assess because there are no direct measures. Instead, the clinician must assess a variety of factors, including current and past immunosuppression; underlying immunodeficiency; neutropenia; lymphopenia; a variety of complex metabolic conditions, such as presence of uremia, malnutrition, poorly controlled diabetes mellitus, and cirrhosis; and replication of immunomodulatory viruses. Net state of immunosuppression not only reflects the medications the patient is currently taking, but also agents, such as alemtuzumab or rituximab, which may be used as part of induction or in the treatment of rejection and may have long-standing effects on components of the immune system. Further, recent changes in immunosuppression may alter the assessment of the net state of immunosuppression. Taken together, these considerations allow a clinician to estimate if the patient is more or less immunosuppressed than the usual patient.

Early post-transplant infections are infections that occur in the first 30 days post-transplant (5). The majority of such infections (approximately 98%) are common post-surgical infections, including surgical site infections, pneumonias, urinary tract infections (UTIs), bacteremias, and Clostridioides difficile colitis. Management approaches for such infections are consistent with the local epidemiology and susceptibility of predicted pathogens and published guidelines (5).

Recipient-origin infections may manifest in the first 30 days. Examples of recipient-origin infections include respiratory viral infections or occult bacteremias that were incubating in the candidates at the time they present for their transplant procedures.

Donor-derived infections, although rare (approximately 0.2%), may present during the first 30 days post-transplant (6). Donor-derived infections are defined as any infection present in the donor that is transmitted to the recipient with the transplanted organ or vessels (6–9). Such infections can be categorized as either expected, where the pathogen is known to be present in the donor at the time of procurement regardless of whether steps are taken to mitigate the disease transmission (e.g., cytomegalovirus [CMV] and Epstein-Barr virus [EBV]), or unexpected, when the donor infection is not recognized and is identified.
after clinical disease presents in one or more of the transplant recipients. Most (76%) unexpected donor-derived infections present within 30 days of transplantation (6).

Clinicians should have a high index of suspicion for donor-derived infections in any patient with atypical early post-transplant course, unexplained sepsis, fever, or alteration in mental status in the first 30–45 days post-transplant. Those with early infections should always prompt review of donor cultures and history. Recognition and reporting of potential donor-derived infections are essential because they may potentially affect all of the recipients of organs from the same donor. In the United States, any documented or suspected unexpected donor-derived disease transmissions need to be reported to the Organ Procurement and Transplantation Network (OPTN) as soon as possible, but not >24 hours after initially suspecting transmission (OPTN Policy 15.4), through the Patient Safety Portal. Timely reporting of suspected transmissions is essential to facilitate communication and rapidly allow screening and treatment of recipients of organs from the same donor (10).

The second period of post-transplant infections occurring during peak immunosuppression are typically opportunistic infections or pathogens that reactivate from latent infection in the recipient, such as BK virus, CMV, herpes simplex virus (HSV), varicella zoster virus, hepatitis B virus, hepatitis C virus (HCV), tuberculosis, listeria, strongyloides, and Chagas disease, and generally occur between 30 days and 6 months post-transplant or within 3 months of treatment of rejection. Patients with potent induction therapy, particularly those with persistent lymphopenia, have an extended period of risk (3,4). Use of prophylactic antimicrobials may delay the infection onset, resulting in later than typical onset.

Late-onset infections typically present >6–12 months post-transplant or >3 months after treatment for a rejection episode (3,4). Most late-onset infections are community acquired, such as community-acquired pneumonia, respiratory viral infections, and UTIs. Patients may acquire infections from exposure to the environment or travel, which increases over time as the patient returns to normal function. Patients may also become less cautious, which can lead to a higher risk of community-acquired infections, as we have seen with coronavirus disease 2019 (COVID-19) (11). Rarely, opportunistic infections may present in this late period, including progressive multifocal leukoencephalopathy or Pneumocystis jirovecii (12).

Viral Infections

Although the remainder of this virology review will focus on some of the more common viral infections complicating kidney transplant, there are others that warrant discussion but already have excellent recent reviews. For example, there is a growing body of literature about HCV in kidney transplantation. Most patients are treated before transplantation, making post-transplant HCV management a rare issue, with the exception of intentional transmission of HCV from nucleic acid test-positive donors (13). Recent studies suggest the ability to treat HCV in this setting, with shorter course of therapy, but optimal approaches are yet to be defined (14).

Respiratory viral infections, including influenza, respiratory syncytial virus, and COVID-19, can result in severe infections in kidney transplant recipients, but frequently are self-limited (15). Vaccines for influenza are recommended in all transplant recipients and their close contacts. Antiviral therapy with neuraminidase inhibitors are

<table>
<thead>
<tr>
<th>Early Post-Transplant Infections 0–30 Days Post-Transplant</th>
<th>Period of Peak Immunosuppression 31–365 Days Post-Transplant</th>
<th>Late-Onset Infections &gt;365 Days Post-Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nosocomial Infections</strong></td>
<td><strong>With Prophylaxis</strong></td>
<td><strong>Opportunist Infections</strong></td>
</tr>
<tr>
<td>• MDRO: MRSA, VRE, ESBL/CRE</td>
<td>• Polymavirus</td>
<td>• When these occur, must consider why they are happening late</td>
</tr>
<tr>
<td>• C. difficile colitis</td>
<td>• HCV</td>
<td>• CMV</td>
</tr>
<tr>
<td>• Surgical site infections</td>
<td>• Cryptococcus neoformans</td>
<td>• JC/PML</td>
</tr>
<tr>
<td>• Urinary tract infection</td>
<td>• M. tuberculosis</td>
<td>• PTLD/EBV</td>
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<tr>
<td>• Catheter-related bloodstream infections</td>
<td>• Strongyloides</td>
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<td></td>
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<tr>
<td><strong>Donor-Derived Infections</strong></td>
<td><strong>After Prophylaxis Stops</strong></td>
<td></td>
</tr>
<tr>
<td>• Atypical post-transplant course</td>
<td>• Pneumocystis</td>
<td></td>
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<tr>
<td>- Examples: LCMV, WNV, T. cruzi, HCV, Bacteremia, endemic mycoses</td>
<td>• Herpesviruses (CMV, HSV, VZV)</td>
<td></td>
</tr>
<tr>
<td>• Incubating or colonization</td>
<td>• HBV</td>
<td></td>
</tr>
<tr>
<td>- Examples: influenza, Pseudomonas, Aspergillus</td>
<td>• Listeria, Nocardia, Toxoplasmosis</td>
<td></td>
</tr>
<tr>
<td><strong>Recipient-Derived Infections</strong></td>
<td>• Community-Acquired Infections</td>
<td></td>
</tr>
<tr>
<td>• Incubating or colonizing</td>
<td>- Urinary tract infection</td>
<td></td>
</tr>
<tr>
<td>- Examples: influenza, Pseudomonas, Aspergillus</td>
<td>- Pneumonia</td>
<td></td>
</tr>
<tr>
<td>• C. difficile colitis</td>
<td>- C. difficile colitis</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. | Common infections associated with time since kidney transplantation. C. difficile, Clostridoides difficile; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ESBL/CRE, extended spectrum beta-lactamase/carbapenem resistant enterobacteria; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; IC/PML, IC virus/progressive multifocal leukoencephalopathy; LCMV, lymphocytic choriomeningitis virus; MDRO, multi-drug resistant organism; MRSA, methicillin-resistant staphylococcus aureus; M. tuberculosis, mycobacterium tuberculosis; PTLD, post-transplant lymphoproliferative disease; T. cruzi, Trypanosoma cruzi; VRE, vancomycin-resistant enterococcus; VZV, varicella zoster virus; WNV, West Nile virus.
recommended for the treatment of influenza in kidney transplant recipients; baloxavir marboxil, a new anti-influenza antiviral, is approved but generally not recommended for transplant recipients because of the concern for emergence of resistance. Although the optimal therapy for COVID-19 has yet to be defined for kidney transplant recipients, most current guidelines recommend considering remdesivir, dexamethasone, and/or convalescent plasma (11).

**Epstein-Barr Virus**

EBV is a human herpesvirus infecting about 90% of adults. It is transmitted mainly via oropharyngeal secretions, and primary infection is commonly asymptomatic. EBV remains latent within the B lymphocytes, but can reactivate post-transplant. This can manifest as asymptomatic viremia, infectious mononucleosis syndrome, or other organ involvement such as hepatitis, myocarditis, and pancreatitis. The majority of symptomatic infections in kidney transplant recipients are primary infection, likely related to reactivation of donor virus. The most concerning presentation of EBV is post-transplant lymphoproliferative disorder (PTLD) (16,17).

Current guidelines recommend routine screening for EBV in high-risk kidney transplant recipients (donor EBV seropositive [D+/R–]/recipient EBV seronegative [R–]) by nucleic acid testing (18). Monitoring is performed at regular intervals in the first year post-transplant and after treatment of acute rejection. Reduction of immunosuppression should be considered in EBV-naïve recipients with an increasing EBV viral load (19). Subclinical EBV DNAemia has been reported in up to 40% of patients in the first post-transplant year and is associated with worse graft outcomes and increased opportunistic infections (20).

PTLD represents 21% of all cancers in solid-organ transplants recipients (21,22). Early-onset PTLD, occurring within the first post-transplant year, is commonly seen in younger individuals and is more frequently associated with EBV positivity and allograft involvement (22). The most common risk factors for PTLD are EBV D+/R– status and the degree of immunosuppression, with T cell-depleting induction a strong factor. A recent meta-analysis concluded that antiviral prophylaxis had no effect on PTLD incidence (23). Belatacept, a costimulation blocker approved in kidney transplant recipients, is contraindicated in EBV-seronegative recipients because of an estimated tenfold higher risk of PTLD reported during the phase 3 studies (24,25). If there is a clinical suspicion of PTLD, the quantitative blood EBV viral load should be assessed, although there are no specific diagnostic levels.

The cornerstone of EBV/PTLD management is immunosuppression reduction, which leads to disease regression in 20%–80% of cases. PTLD management should be done in consultation with an oncologist, who may recommend anti-B cell therapy (rituximab), chemotherapy, and/or radiation. Adoptive immunotherapy with EBV-specific T lymphocytes is an emerging therapeutic option (26). In the largest series of patients retransplanted after PTLD, only one of the 52 patients developed recurrent PTLD (27).

**Cytomegalovirus**

CMV is a ubiquitous human herpesvirus, with a seroprevalence rate of 30%–97% (28,29). The risk of CMV infection or disease after transplant is determined primarily by the donor and recipient CMV serostatus (from highest to lowest risk: D+/R–, D+/R+, D–/R+, D–/R–) (29). Use of lymphocyte-depleting agents, as induction or for allograft rejection, has been shown to significantly increase the risk of CMV disease (28,29). Of the newer immunosuppressive agents, belatacept has been associated with an increased risk of CMV primary infection and a prolonged course of viral replication in patients at high risk of CMV (30). In the absence of preventive measures, CMV infection and disease develop in 40%–100% and 67% in kidney transplant recipients, respectively. With the current preventive strategies, the incidence is about 17%–37%, with the highest risk in the first 100 days (28,29).

Immune monitoring of CMV-specific T cell responses is another strategy to assess post-transplant CMV risk. IFN-γ release assays (Quantiferon-CMV, ELISPOT) and intracellular cytokine staining for IFN-γ have been shown to predict both CMV viremia and disease (31). Emerging data suggest that detection of CMV-specific immunity is associated with a lower risk of infection and may be helpful in determining duration of prophylaxis and preemptive monitoring (28).

The key strategies for prevention of CMV are universal prophylaxis, preemptive therapy, and a hybrid approach known as “surveillance after prophylaxis” (29). There are data to support each strategy, and current guidelines suggest any approach is acceptable. Prophylaxis is easier in the outpatient setting, protects against HSV and varicella zoster virus, and is associated with rare instances of early CMV infection and lower rates of graft rejection. It is, however, associated with risk of late-onset CMV, resistance development, higher drug costs, and side effects. In a single-center study of 176 patients with CMV D+/R– serostatus, 29% of patients developed CMV disease at a median of 61 days after stopping antiviral prophylaxis (32). Preemptive therapy lacks some of the benefits listed above, but results in lower rates of late-onset CMV and less drug toxicity. Preemptive therapy has higher laboratory costs and has also been associated with resistance development.

Oral valganciclovir is the most commonly used prophylaxis medication, with a recommended dose of 900 mg daily, and dose reduction for kidney dysfunction (28,29). Most guidelines recommend 100 days of prophylaxis for intermediate-risk patients and 200 days of prophylaxis for high-risk patients (33). Letermovir, a novel viral terminase inhibitor, is being evaluated for prophylaxis in CMV D+/R– kidney recipients, but does not have HSV coverage. Patients with CMV D–/R– serostatus have a very low risk of CMV disease, and acyclovir prophylaxis can be used to prevent HSV (29).

CMV can present as asymptomatic DNAemia, CMV syndrome (viremia, constitutional symptoms, cytopenias without organ involvement), or tissue invasive disease. CMV disease can affect many organs; most commonly, the gastrointestinal tract, liver, pancreas, and lung. CMV also has a predilection to cause allograft nephritis. CMV has been described to have immunomodulatory effects and can increase risk of activation of other herpes viruses, EBV-
mediated PTLD, allograft rejection, and other opportunistic infections. CMV infection and disease have been associated with higher risk of mortality and graft loss (34).

All patients with a clinical suspicion for CMV infection or disease should be tested by PCR of blood or serum, which are less sensitive for certain organ-invasive diseases like gastrointestinal disease and retinitis (35). Histopathologic examination of tissue biopsy specimens may be needed to diagnose invasive CMV disease (36).

CMV management involves immunosuppression reduction and antiviral therapy. Antimetabolites may be stopped or reduced, depending upon the immunologic profile of the recipient. First-line therapy for CMV is valganciclovir or intravenous ganciclovir. Intravenous therapy is preferred in life-threatening illness, CMV pneumonitis, and colitis. Both agents require monitoring of blood counts and kidney function, with dose reduction for kidney dysfunction. Treatment is continued until there is clinical improvement and CMV viral loads are undetectable. Although secondary prophylaxis has been previously widely used, recent data suggest it may not be required for most patients (28,29). Genotypic assays for resistance should be performed if DNAemia persists despite 2 weeks of antiviral therapy (37). Second-line agents used for treatment of resistant CMV include foscarnet, high-dose ganciclovir, cidofovir, and CMV Ig. Letermovir is not approved for CMV treatment. Off-label use for ganciclovir-resistant CMV has been complicated by emergence of the letermovir-resistant virus (38). Adoptive transfer of CMV-specific T cells may be considered as adjunctive therapies for resistant CMV, in collaboration with transplant infectious disease experts (29).

**Polyomaviruses**

The BK polyomavirus is a human polyomavirus, first identified in the urine of a kidney transplant recipient with ureteral stenosis (39). Primary BK polyomavirus infection occurs during childhood, with 80%–90% adults being exposed (40). The virus remains latent in the kidney tubules and uroepithelium (41).

In immunocompromised hosts, the disease can progress from asymptomatic viruria to viremia and organ-invasive disease. It usually presents as BK polyomavirus-associated nephropathy in kidney transplant recipients (42). Asymptomatic viruria, detected on routine screening, is the earliest manifestation and is seen in 25%–40% of patients in the first year. Of those with persistent viruria and high urinary viral loads, 10%–20% develop viremia after a few weeks. BK polyomavirus-associated nephropathy occurs in patients with persistent high-titer viremia, typically >10,000 copies/ml, and is seen in 1%–10% of all kidney transplant recipients (40,43). It most commonly occurs in the first post-transplant year, when the degree of immunosuppression is the highest. The most significant risk is the degree of immunosuppression, but other factors are donor related (viruria, female sex, deceased donor), recipient related (male sex, highly sensitized status, AB0 incompatibility, HLA mismatch, low BK polyomavirus-specific neutralizing antibody or T cell activity), or transplant related (ureteric stent, treatment for acute rejection, tacrolimus exposure) (40,44).

Current guidelines recommend routine post-transplant screening for BK viremia monthly for 9 months, and then every 3 months until 2 years’ post-transplant. Screening is also recommended when evaluating for graft dysfunction and with a kidney allograft biopsy (40). Early detection of BK polyomavirus viremia combined with reduction in immunosuppression can prevent progression to BK polyomavirus-associated nephropathy and preserve graft function (45).

Viremia has a 50%–60% positive predictive value for diagnosis of BK polyomavirus-associated nephropathy, and patients with sustained viral loads of ≥10,000 copies/ml are presumed to have BK polyomavirus-associated nephropathy (40,43). Kidney biopsy is the gold standard for diagnosis and is helpful in assessing disease severity, chronicity, and concurrent rejection. Given the patchy involvement of the kidney, guidelines recommend two biopsy cores containing medulla and immunohistochemistry for SV40 T antigen (46).

The cornerstone of management of BK viremia and nephropathy is immunosuppression reduction (45). The various strategies for reduction have not been compared in randomized controlled trials, and center-specific, individualized protocols are used. Worsening kidney allograft function after reduction of immunosuppression should prompt evaluation for possible graft rejection with a biopsy (19). Acute rejection has been reported in 8%–12% after reduction of immunosuppression for BK viremia or nephropathy (45,47). In a retrospective cohort of patients with BK polyomavirus-associated nephropathy, 14% developed de novo donor-specific antibodies, which was a risk factor for subsequent antibody-mediated rejection and graft loss (48).

Other adjunctive treatments used with varying degree of success include intravenous Ig, leflunomide, and cidofovir (40). Data from randomized controlled trials do not demonstrate superiority of one or more of these therapies over immunosuppression reduction alone (49). Intravenous IG may be considered in patients with severe hypogammaglobulinemia, concomitant rejection, or those at high immunologic risk. Leflunomide has both immunosuppressive and antiviral activity and has been used to replace the antimetabolites in recipients with a higher risk of rejection. It is, however, associated with hematologic and hepatotoxicity, and therapeutic drug monitoring is difficult (50). Cidofovir is associated with a dose-dependent nephrotoxicity, and its use is not recommended in patients with significant kidney dysfunction or proteinuria. Quinolones are no longer recommended for treatment of BK polyomavirus-associated nephropathy (51). Adoptive T cell therapy is a novel therapeutic option in BK polyomavirus-associated nephropathy and has been shown to reduce viral load in the kidney tubules when used early in the course of the disease (52).

Unfortunately, graft loss occurs in 15%–50% of BK polyomavirus-associated nephropathy cases. Retransplantation in these patients has been successful, with 5-year death-censored graft survival of 90.6% (53). Undetectable levels of viremia at time of retransplantation were associated with absence of BK viremia at 1 year post-transplant. In patients with persistent viremia, a decline of at least 2 log10 copies/ml after reduction of immunosuppression indicates an antiviral immune response, and retransplant may be considered (54). The role of transplant nephrectomy before a second transplant is not well defined, but can be considered in those with persistent viremia (55).
Norovirus

Norovirus infections typically present as an acute infection characterized by severe nausea; vomiting; watery, nonbloody diarrhea; abdominal cramps; and, occasionally, low-grade fever, muscle aches, chills, and headache in immunocompetent hosts (56). Immunocompromised patients can develop chronic norovirus infections, associated with relapsing and remitting episodes of watery diarrhea that may last for months to years (57). Norovirus is the second most common documented cause of diarrhea, after C. difficile, among solid-organ transplant recipients (58). A total of 30% of patients with chronic norovirus have a ≥20% increase in creatinine within 1 year of the diagnosis, as a result of recurrent dehydration and supratherapeutic tacrolimus levels during periods of diarrhea (58). Given the high prevalence of norovirus, kidney transplant recipients with diarrhea, particularly chronic or relapsing diarrhea, should be screened for norovirus by PCR or antigen testing of stool (59).

The current mainstay of therapy for norovirus is supportive, with antimotility agents and hydration (57–59). Reduction of immunosuppression is commonly practiced, although there is no clear evidence that it is associated with viral clearance (57). Several agents, including oral and intravenous Igs and nitazoxanide, are used off-label, with variable evidence to support their use, and a clinical trial of nitazoxanide is ongoing (57).

Bacterial Infections

Clostridioides difficile

C. (formerly Clostridium) difficile, an anaerobic, spore-forming, Gram-positive bacterium, causes C. difficile infection, which is five times more likely in hospitalized solid-organ transplant recipients compared with the general population (60). C. difficile infection affects 3%–16% of kidney transplant recipients, often early post-transplant (60,61). Severe presentation with fulminant colitis (5.3%) and need for colectomy (2.7%) appear to be higher than in other patient populations, and C. difficile infection has been associated with graft loss in at least one study (61,62). Recurrences of C. difficile infection have been reported in nearly 20% of solid-organ transplant recipients, comparable with other hospitalized patients (62). Risk factors for C. difficile infection include those reported in nontransplant patients such as recent antibiotic exposure, age >65 years, acid suppression medications, and hospitalization (60). Additionally, transplant-specific risks include induction with antithymocyte globulin and hypogammaglobulinemia (60,63). Diagnosis relies on presence of three or more unformed stools in a 24-hour period, and the demonstration of C. difficile toxin or PCR testing of the stool. Unexplained abdominal pain with fever and leukocytosis in a patient with ileus should prompt C. difficile infection testing (60). Primary therapy with oral vancomycin or fidaxomicin is suggested for both severe and nonsevere events (60,64). High-dose oral vancomycin with intravenous metronidazole is recommended for fulminant cases, with consideration for surgical intervention (60,64). In addition, bezlotoxumab, a human mAb against toxin B, can be considered in solid-organ transplant recipients at higher risk for recurrence of C. difficile infection (60,65). For recurrences, treatment options include either fidaxomicin or prolonged, tapered, or pulsed oral vancomycin (64). Additionally, fecal microbiota transplantation should be considered with multiple recurrences and has been shown to be safe and potentially helpful in some, but not all, solid-organ transplant recipients (66).

Urinary Tract Infection

UTIs are the most common infections in kidney transplant recipients. They occur most commonly in the first year post-transplant, with a prevalence that ranges widely from 7%–80% (67). Similar to nontransplant patients, the incidence of UTIs is higher in female kidney transplant recipients because of anatomic predisposition (68). Gram-negative bacteria cause up to 90% of cases, and Escherichia coli was most commonly reported (69).

Perioperative and prophylactic antibiotics during the early post-transplant period are standard-of-care measures adopted to prevent UTIs. Trimethoprim-sulfamethoxazole is recommended for 6–12 months post-transplant to prevent P. jirovecii pneumonia, but it also serves as an effective UTI prophylaxis and lowers the risk of both UTI and bacteremia (12). Current guidelines recommend that patients who cannot take trimethoprim-sulfamethoxazole for prophylaxis receive an additional antibiotic for UTI prevention, at least until the ureteral stent is removed (70). Minimizing the stent duration is associated with the lowest risk of early post-transplant UTIs, but needs to be balanced against risk of urological complications (71).

Postkidney transplant UTIs can be categorized as asymptomatic bacteriuria, uncomplicated UTI/simple cystitis, complicated UTI/pyelonephritis, or recurrent UTI. Asymptomatic bacteriuria is diagnosed by a screening urine culture without concurrent symptoms. Although it was once thought to be associated with complications, recent data suggest that there is no benefit in treating asymptomatic bacteriuria, with treatment associated with risks of adverse events, including C. difficile infection (72). Current guidelines recommend against surveillance urine cultures or treating asymptomatic bacteriuria in most kidney transplant recipients. However, if two consecutive urine samples yield >10⁵ of the same uropathogen in the first 2 months post-transplant, antibiotic treatment for 5 days may be considered (70).

Uncomplicated UTIs are diagnosed in patients with lower urinary tract symptoms and a positive urine culture. Transplant recipients with clinical symptoms of cystitis can be treated with oral antibiotics based on the organism isolated for 5–7 days (70). Complicated UTIs present with systemic symptoms (fever, chills, malaise, nausea, vomiting) and/or allograft pain with a positive urine culture. Bacteremia may be present in approximately 10% of cases. Urine and blood cultures should be collected before initiation of therapy, and imaging of the urinary tract should be obtained. Management includes empirical broad-spectrum parenteral antibiotics, which can be narrowed to definitive treatment once the organism and susceptibilities are identified. Patients can be switched to oral antibiotics once the clinical condition improves, to complete a 7–14 day course (70).

Recurrent UTIs are defined as three or more episodes in 1 year, or two or more episodes in 6 months. Urinary tract obstruction owing to strictures or calculi, indwelling urinary stents, complex kidney cysts, vesico-ureteric reflux, and bladder dysfunction can result in recurrent UTIs.
Suppressive antibiotic prophylaxis has limited efficacy in kidney transplant recipients (73) and poses risk of emergence of drug-resistant organisms. Methylene hippurate has been shown to reduce frequency of UTIs, antibiotic use, and need for hospitalization in kidney transplant recipients (74,75). Although strong evidence is lacking, strategies such as behavioral education (perineal hygiene, postcoital voiding in women, frequent voiding), *Lactobacillus* probiotics, d-mannose, cranberry products, and vaginal estrogens and hyaluronic acid/chondroitin sulfate in post-menopausal women can also be tried (70).

UTIs caused by drug-resistant organisms, such as extended-spectrum *β*-lactamase-producing Gram-negative bacteria and carbapenem-resistant Enterobacteriaceae, are increasing in kidney transplant recipients. Intravenous antibiotics are frequently required, namely, carbapenems for extended-spectrum *β*-lactamase organisms and amikacin and colistin for carbapenem-resistant Enterobacteriaceae. Fosfomycin and nitrofurantoin are the oral agents that retain broad-spectrum antimicrobial activity, and can be used judiciously in patients with cystitis (67). Data regarding the effect of UTIs on patient and graft outcomes are conflicting. Although some studies have shown a higher risk of mortality and graft loss (up to 41% and 29% in the first year, respectively), others have not found an effect on long-term graft function and survival (76–78).

**Fungal Infections**

As time from transplant increases, the risk of fungal pathogens associated with early post-operative infections, such as the *Candida* species, can be supplanted by more indolent infections with endemic mycoses, such as histoplasmosis, blastomycosis, and coccidioidomycosis. *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Coccidioides posadasii* are all dimorphic fungi that exist as yeast in the human body and mycelial forms in the environment. Each pathogen has regional endemicity, which emphasizes the need for local residence and travel evaluation to assess risk. Histoplasmosis and blastomycosis infections are endemic to the upper Midwest of the United States, around the Great Lakes (*Histoplasma*) and the Ohio and Mississippi River valleys (*Histoplasma/Blastomyces*), whereas *Coccidioides* is predominant in the Southwest United States (79).

Among the endemic mycoses in solid-organ transplant recipients, histoplasmosis is most frequent, causing 5%–9% of post-transplant invasive fungal infections when early infections with *Aspergillus* and *Candida* are included (80,81). Histoplasmosis occurs in 0.1%–0.3% of kidney transplant recipients, at median of 2–5 years post-transplant (81–83). The most common presentation in kidney transplant includes pneumonia and disseminated disease, but rare presentations occur with cutaneous lesions and hemophagocytic lymphohistiocytosis (82–85). Risk factors included leukopenia, CMV, and a diagnosis of bacterial pneumonia (81). One series reported 21% graft failure and 7% (one of 14) mortality (82). Diagnosis focuses on direct visualization or culture from sputum, bronchoalveolar lavage (BAL), or tissue. Noninvasive measures include histoplasma antigen enzyme immunoassay (EIA) from both urine and serum in suspected cases, and serology is of limited assistance (79). Post-transplant prophylaxis is not recommended, and treatment most frequently includes amphotericin, itraconazole, and, more recently, voriconazole and posaconazole (79,83,86). Monitoring histoplasma antigen EIA, particularly in the blood, to assess recovery is suggested by some experts (79).

Blastomycosis is less common overall (80), occurring at a median of 2 years post-transplant (82). Pneumonia has been reported in 80% of kidney transplant with blastomycoses, and disseminated disease commonly includes cutaneous manifestations (82). Risk for blastomycosis in kidney transplant is difficult to assess outside of environmental exposure given the relatively infrequent events; one study from Wisconsin identified two of three cases developed in a minority population, the Hmong (87). Similar to histoplasmosis, diagnosis focuses on direct visualization or culture from sputum, BAL, or tissue. Blastomycosis antigen EIA from urine, serum, BAL, or cerebrospinal fluid is available but less sensitive (62%–83%), and suffers from cross-reactivity with other fungi. Again, serology is of limited assistance (79). Treatment with lipid-formulation amphotericin, with transition to azole therapy after initial recovery, is recommended for severe cases, whereas primary azole therapy can be used for mild cases (79).

Coccidioidomycosis caused by *C. immitis* and *C. posadasii* can be donor-derived, newly acquired post-transplant, or a reactivation from prior recipient disease. In endemic regions, 3% of kidney transplant recipients will develop coccidioidomycosis; screening and prophylaxis of high-risk patients reduces infection frequency (79,88,89). Presentation includes cutaneous, skeletal, pulmonary, meningitis, and disseminated disease (89,90). Culture is confirmatory; however, several available serologic assays can provide

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### Table 1. Post-transplant vaccination for kidney transplant recipients

<table>
<thead>
<tr>
<th>Routine Vaccination</th>
<th>Travel-Related Vaccination</th>
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<tbody>
<tr>
<td>Influenza</td>
<td>Influenza</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Hepatitis A</td>
</tr>
<tr>
<td>Tdap (diphtheria/tetanus/pertussis)</td>
<td>Tdap (diphtheria/tetanus/pertussis)</td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em> (conjugate)</td>
<td>Rabies</td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em> (polysaccharide)</td>
<td>Japanese encephalitis</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td><em>Salmonella typhi</em> (intramuscular, inactivated: typhoid VI polysaccharide vaccine)</td>
</tr>
<tr>
<td>Herpes zoster (variella, subunit: Shingrix)</td>
<td></td>
</tr>
</tbody>
</table>

Travel-related vaccines should be determined on the basis of anticipated destination, planned activities, prior evidence of seroprotection (hepatitis A virus/hepatitis B virus) and time since prior vaccination (Tdap).
Safer Living

Continued health after kidney transplant relies on the identification and mitigation of risk in everyday life. Routine adherence to general infection prevention principles, such as hand washing, is paramount (91). Metabolic care with food preparation, avoidance of undercooked meat, and strict avoidance of well water can lower food-borne pathogen risk. Employment, hobbies, and pet ownership should be discussed. Behaviors that increase risk for sexually transmitted infections should be discussed, and appropriate prevention education and vaccination, such as hepatitis B and age-appropriate human papillomavirus vaccination, should be provided (91–93). Additional focus on vaccine-preventable illness, especially in those increased with travel, should be provided (see Table 1), including annual influenza vaccination, routine adult shingles vacci-
nation, and boosters for tetanus and pertussis (92–94). As many kidney transplant recipients thrive in the post-
transplant period, travel for enjoyment may increase. Safety for travel requires evaluation of travel destination, risk assessment dependent on planned activities, and preparation of emergency medication supplies (92). Infection-related risk can be mitigated with pretravel vaccination (i.e., hepatitis A), avoidance of environmental risk (i.e., mosqui-
itos), and preparation for common travel-related diseases (i.e., diarrhea and respiratory infection) (92,93).

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Long-Term Care of the Pediatric Kidney Transplant Recipient

Hilda E. Fernandez and Bethany J. Foster

Abstract

Pediatric kidney transplant recipients are distinguished from adult recipients by the need for many decades of graft function, the potential effect of CKD on neurodevelopment, and the changing immune environment of a developing human. The entire life of an individual who receives a transplant as a child is colored by their status as a transplant recipient. Not only must these young recipients negotiate all of the usual challenges of emerging adulthood (transition from school to work, romantic relationships, achieving independence from parents), but they must learn to manage a life-threatening medical condition independently. Regardless of the age at transplantation, graft failure rates are higher during adolescence and young adulthood than at any other age. All pediatric transplant recipients must pass through this high-risk period. Factors contributing to the high graft failure rates in this period include poor adherence to treatment, potentially exacerbated by the transfer of care from pediatric- to adult-oriented care providers, and perhaps an increased potency of the immune response. We describe the characteristics of pediatric kidney transplant recipients, particularly those factors that may influence their care throughout their lives. We also discuss the risks associated with the transition from pediatric- to adult-oriented care and provide some suggestions to optimize the transition to adult-oriented transplant care and long-term outcomes.

Introduction

The goal of kidney transplantation in children is to provide a duration and quality of life similar to their healthy peers. The life expectancy benefit of transplantation over dialysis may be as much as 25–30 years (1). Pediatric transplant recipients show superior growth, improved neurocognitive development and academic performance, and better quality of life compared with children treated with dialysis (2). However, many challenges lie ahead when a child receives a transplant. The hope for every pediatric transplant is that it will last for the child’s whole life. But even for an adolescent or young adult, this means ≥50 years of graft function. The vast majority of pediatric patients will require more than one transplant (3). To maintain graft function, pediatric recipients must negotiate numerous challenges. Very small pediatric recipients often must successfully perfuse an adult donor kidney, and the transplanted kidney must accommodate large changes in body size. Viral infections such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and polyoma virus may have more severe consequences in infection-naïve pediatric recipients (4–8). Furthermore, not only must pediatric transplant recipients get through the high-risk interval in the early post-transplant period, but they must also traverse a second high-risk period of adolescence and young adulthood, during which immunologic risk may be heightened and medication adherence may be suboptimal (9–11).

In this review, we describe the characteristics of pediatric kidney transplant recipients, highlight the unique features that distinguish pediatric from adult recipients and may be relevant to their care throughout their lives, and discuss the risks associated with the transition from pediatric- to adult-oriented care. We also provide some suggestions to ensure a smooth transition to adult-oriented transplant care and optimize outcomes after transfer.

Characteristics of Pediatric Kidney Transplant Recipients

Children of all ages receive kidney transplants. Most transplant programs require infants to reach at least 10 kg before considering transplant, but some will transplant babies as small as 6 kg (12,13). The majority of pediatric transplant recipients are adolescents, but a substantial fraction are under 5 years old. Consistent with the male predominance of diseases leading to kidney failure, a greater proportion of pediatric transplant recipients are male than female. The primary kidney diseases leading to kidney failure in children are different from those in adults. In addition, a substantial minority of pediatric transplant recipients have some type of congenital syndrome associated with other conditions, in addition to kidney disease. Depending on the country, between 30% and >50% receive a living donor transplant (14–17).
Currently, almost 30% are transplanted preemptively, having no exposure to dialysis (14–17). Table 1 compares characteristics and outcomes of international cohorts of pediatric kidney transplant recipients (16–21).

### Unique Considerations for Pediatric Transplant Recipients

Many of the issues surrounding post-transplant care are similar regardless of the age of the recipient. Attention to cardiovascular health, bone health, obesity, and anemia are important at all ages, but particularly crucial in developing children (22–25). In addition, there are some issues unique to pediatric recipients that are highlighted below.

### Primary Diseases

The majority of pediatric transplant recipients have congenital anomalies of the kidneys and urinary tract as their underlying disease. A substantial subset of patients with congenital anomalies of the kidneys and urinary tract have developmental bladder abnormalities, resulting in lifelong bladder dysfunction and requiring ongoing urology care. Patients with bladder dysfunction often have poor bladder emptying, putting them at high risk for urinary tract infections and obstructive nephropathy. Many such patients have chronic hydropnephrosis of the graft, leading to interstitial fibrosis and tubular atrophy; a need for intermittent catheterization to maintain continence, ensure complete emptying, and prevent urinary tract infection is also common (26,27). Oxybutynin may be prescribed to improve spontaneous bladder emptying per urethra. Intermittent assessment of bladder function with uroflow or urodynamics testing may be necessary.

A substantial minority of pediatric transplant recipients have inborn errors of metabolism, with important extrarenal manifestations including cystinosis, primary hyperoxaluria, and methylmalonic acidemia. Cystinosis requires lifelong enzyme therapy (28). Both primary hyperoxaluria type 1 and methylmalonic acidemia with kidney failure are preferentially treated with combined liver-kidney transplant (29,30). Isolated kidney transplant is preferred for primary hyperoxaluria type 2 (29).

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**Table 1. Comparison of international pediatric kidney transplant recipient characteristics**

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<tr>
<td><strong>Recipient age, yr</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>510 (23)</td>
<td>983 (26)</td>
<td>177 (24)</td>
<td>640 (20)</td>
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<tr>
<td>6–10</td>
<td>427 (19)</td>
<td>1540 (41)</td>
<td>157 (21)</td>
<td>918 (28)</td>
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<tr>
<td>11–17</td>
<td>1298 (58)</td>
<td>1195 (32)</td>
<td>416 (55)</td>
<td>1678 (52)</td>
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<tr>
<td>Male</td>
<td>1310 (59)</td>
<td>2109 (60)</td>
<td>437 (58)</td>
<td>1935 (60)</td>
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<tr>
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<tr>
<td>White</td>
<td>1079 (48)</td>
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<td>597 (80)</td>
<td>2354 (73)</td>
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<td>Black</td>
<td>389 (17)</td>
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<td>a</td>
<td>86 (3)</td>
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<td>Asian</td>
<td>102 (5)</td>
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<td>153 (20)</td>
<td>447 (14)</td>
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<tr>
<td>Other</td>
<td>58 (3)</td>
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<td>349 (11)</td>
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<tr>
<td>Preemptive</td>
<td>759 (34)</td>
<td>1098 (30)</td>
<td>497 (66)</td>
<td>1155 (36)</td>
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<tr>
<td><strong>Recipient age, yr</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td>1310 (59)</td>
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<td>172 (23)</td>
<td>641 (20)</td>
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<td>330 (44)</td>
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<td>11–17</td>
<td>437 (58)</td>
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<td>525 (16)</td>
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<td><strong>Recipient age, yr</strong></td>
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<td>Renal dysplasia</td>
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<td>2354 (73)</td>
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<td>1594 (46)</td>
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<td>1155 (36)</td>
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<td>1195 (32)</td>
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<tr>
<td><strong>Race</strong></td>
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<td>2354 (73)</td>
<td></td>
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<td><strong>Recipient age, yr</strong></td>
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<tr>
<td>0–5</td>
<td>61%</td>
<td>77%</td>
<td>81%</td>
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<tr>
<td>6–10</td>
<td>62%</td>
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<td>11–17</td>
<td>75%</td>
<td>72%</td>
<td>75%</td>
<td>74%</td>
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<td><strong>Patient survival</strong></td>
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<td>Deceased donor</td>
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<td>5-yr</td>
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<td>96%</td>
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<td>Living donor</td>
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<td>5-yr</td>
<td>95%</td>
<td>a</td>
<td>95%</td>
<td>98%</td>
</tr>
<tr>
<td>10-yr</td>
<td>95%</td>
<td>a</td>
<td>95%</td>
<td>98%</td>
</tr>
<tr>
<td><strong>Data are shown as n (%). Data obtained from OPTN/SRTR, ESPN/ERA-EDTA, ANZDATA, and NHS/UKTR.</strong></td>
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**Care of the Pediatric Kidney Transplant Recipient, Fernandez and Foster**
FSGS, the cause of kidney failure in 10%–14% of pediatric recipients (31), has a high risk of recurrence in its idiopathic form; recurrence commonly leads to graft failure, with little hope for successful repeat transplant (32). Atypical hemolytic uremic syndrome also frequently recurs post-transplant, although ecuclizumab therapy has improved the outlook for these patients (33).

For children with multisystem disease, multidisciplinary care is necessary, and eventual transfer to additional subspecialists for adult-oriented care must be planned.

**Effect of Kidney Failure on Neurodevelopment**

Children who have experienced kidney failure are at high risk for abnormal neurodevelopment (34). The younger the child, the higher the risk of cognitive impairments, with those under 5 years of age at kidney failure onset at highest risk (35). The majority of pediatric kidney transplant recipients show average intelligence. However, compared with healthy children, a greater than expected proportion of pediatric transplant recipients are in the impaired, borderline, or low-average intelligence range, and academic performance is often poorer than in healthy peers (36,37). Memory deficits, disturbances of executive function, and attention problems are common, but may go unrecognized (37–39). Formal assessment of cognitive assessment may reveal deficits in executive functions (e.g., planning, organization, problem solving) that may impair ability to engage in self-care behaviors such as medication adherence, whereas assessment of academic function may guide academic expectations and ensure appropriate provision of academic support (37). Recognition of such deficits will allow appropriate support structures to be put into place before adherence problems result in adverse outcomes.

**Age-Related Differences in Immune Function and Viral Infection Risk**

Immune function is associated with age (40). Both young infants and the elderly have a less robust immune response than other age groups. The age-related trajectory of immune development and senescence mirrors the association between recipient age and graft failure risk (41,42). Kidney and heart transplant recipients aged 17–24 years exhibit the highest risk of graft failure of all age groups (41,42). Although poorer adherence to immunosuppressive medications likely contributes to the peak in graft failure risk seen in adolescence and young adulthood, age-related variation in the immune response may also play a role (43).

The relatively immature immune system of very young infants may permit greater tolerance of transplanted organs; however, it also puts them at higher risk of infection (44). In addition, young pediatric transplant recipients are less likely to have been exposed to important viral illnesses such as BK and JC polyomavirus, CMV, and EBV, and are therefore less likely to have immunity to these viruses. Polyoma virus nephropathy is an important cause of graft dysfunction in children (7). The risks of CMV and EBV viremia are highest in CMV- and EBV-naïve patients who receive transplants from CMV- and EBV-positive donors; about 20% of pediatric recipients fall into this high-risk category for CMV, and 40% for EBV (21). EBV viremia is of particular concern because of the associated risk of post-transplant lymphoproliferative disorder (16). Subclinical CMV and EBV viremia have also been associated with allograft dysfunction and loss in pediatric kidney transplant (45). Routine surveillance for BK polyomavirus and EBV viremia permits early detection and intervention with reduction of immunosuppression to decrease the risk of severe complications (46,47).

**Age-Related Behavioral Issues**

As pediatric recipients transition from childhood to adulthood, the tasks related to transplant care must shift from the parents to the young recipient. This includes scheduling and keeping clinic appointments and routine blood tests, and managing medications. Adolescents and young adults with a broad range of chronic conditions have poorer adherence to both medications and general care than other age groups (48,49). This deterioration in adherence is likely related to the increasing independence combined with incomplete brain maturity. It has been suggested that relatively rapid development of the limbic system (responsible for reward-seeking behavior and emotions), paired with slower maturation of the prefrontal cortex (responsible for planning, impulse control, and organization), may lead adolescents and young adults to choose actions that maximize short-term rewards over those favoring improved long-term outcomes (50). The prefrontal cortex continues to develop well into the mid-20s (51). As parents step back, lapses in adherence may occur.

**Transplant Timing within the Life Course**

The entire life of an individual who receives a transplant as a child is shaped by their status as a transplant recipient. Short stature is common among pediatric transplant recipients and may negatively influence self-esteem (52). Academic and employment prospects may be permanently altered by the illness preceding the transplant and/or complications thereafter. Social development and independence from parents are often delayed. Opportunities to socialize and form romantic relationships may be delayed or impeded by the need for medical care (53). Social isolation owing to illness and frequent medical visits, and uncertainty surrounding future health, may contribute to the high rates of depression and anxiety in this population (54–56). Post-traumatic stress is increasingly recognized (57). The effects of the patient’s illness on siblings and parents must also be considered. Not only must the mental health of family members be addressed, but it should also be recognized that overall family functioning may also affect graft and patient outcomes (58). A multidisciplinary approach, including psychology and social work, is particularly important for young people and their families. Referrals to mental health services are often needed. Adolescents with chronic illnesses require psychosocial support throughout the transition process, with mental health screenings and financial counseling (59). Health disparities in medical care for patients from socially disadvantaged backgrounds also increase a need for psychosocial resources for this at-risk group (60).

Many young transplant recipients have questions about sexual health and fertility. Young women should be counseled...
about the risks of medications such as angiotensin-converting enzyme inhibitors and myophenolate mofetil during pregnancy, and about the importance of contraception and sexually transmitted infection prevention. Women who may wish to become pregnant need information about how to safely plan a pregnancy and the associated risks. Discussions with young men should include information about fertility and the fertility-related risks associated with their underlying condition, surgical procedures, and immunosuppressive medications such as sirolimus.

Transfer from Pediatric- to Adult-Oriented Care

The transfer from pediatric- to adult-oriented care typically takes place at around 18–21 years of age, right in the middle of the period of peak graft failure risk (42, 62). It is not completely clear whether the transfer to adult-oriented care contributes to the heightened risk observed during this age period, or rather that other factors associated with adolescence and young adulthood (poorer medication adherence, enhanced immune potency) are responsible for the higher graft failure risk. A study of 413 Canadian kidney transplant recipients found significantly higher graft failure risks in the interval after transfer to adult care compared with before transfer (63). However, there was insufficient overlap of the ages represented in the pre- and post-transfer periods to allow complete adjustment for age. It is possible that the higher risks of graft failure observed after transfer simply reflect age-related risk, rather than any real effect of the care environment.

There is some evidence that the risk of graft failure after transfer depends on age at transfer. A study of 440 American transplant recipients found a 57% higher risk of graft failure among recipients transferred at <21 years of age compared with recipients of the same age transferred at ≥21 years of age (64). There was no significant association between time since transplant and failure risk. These findings were interpreted as reflecting a mismatch between the way care is delivered in adult-oriented settings and the needs of adolescents and young adults. The major concern is that the adult care setting may not adequately support adherence to immunosuppressive medications and health and graft monitoring protocols (65). Substantial differences exist between pediatric and adult-oriented care, which may influence patient behavior. Pediatric care tends to be more nurturing and family focused, whereas adult-oriented care tends to emphasize the autonomy of the patient (66). The pediatric care environment may be better resourced than that of adult care, frequently including a multidisciplinary team of health care professionals who may have more time to spend with each patient; these services are not always available after transfer to adult-oriented care, and adult care providers often have less time available (66–68). These differences between pediatric and adult care may result in young people perceiving their new adult care providers as unavailable and/or disinterested. Other factors unrelated to the care environment, such as loss of medical and prescription drug insurance coverage, may also present barriers to adherence in this age group.

The importance of an engaged and caring parent or other adult caregiver in supporting the young recipient through the transition from pediatric to adult care cannot be overemphasized. Gradual shift of responsibilities for management of medications and transplant care from parent to young person is recommended. But this handover may not be complete when the transfer occurs; continued support after transfer remains important. Many young adults do not master self-management until they are >20 years old (69). Involvement of a supportive parent may be the single most important factor in successful transition (70).

Adherence

A comprehensive discussion of adherence is beyond the scope of this review. The interested reader is referred to other reviews devoted to this topic (71–73). We provide only a brief overview here.

Adherence among children before adolescence depends almost entirely on their parents. Young children are not developmentally capable of maintaining strict adherence. Adolescents and young adults have a reputation for poor adherence. However, although numerous studies showed poorer medication adherence among adolescents than younger children, no well-designed, unbiased studies compared adherence among adolescents and young adults with that in older adults (74–77). Nevertheless, it is likely that adolescents and young adults are at somewhat higher risk for poor adherence than older adults; the magnitude of the difference, however, is unknown. Multiple barriers to adherence have been identified in young people, but the most common are forgetting (29%–56%) and organizational challenges (58%); most nonadherence is unintentional (75, 78).

It has been proposed that adherence is influenced not only by patient-level factors unique to the particular patient, but also by the patient’s interactions with those around them, care processes and structures, and health care systems factors, including care and medication cost coverage, and overall care environment (79). Social determinants, including family functioning, social supports, and financial resources, are strongly associated with adherence; health beliefs, self-efficacy, knowledge, symptoms, comorbidities, psychiatric conditions, treatment side effects, and regimen complexity are also associated (80, 81). Recognition of the many factors that may influence adherence, including those over which the patient has no direct control, may help clinicians identify ways to support better adherence.

Despite the fact that numerous risk factors for poor adherence have been identified, our ability to predict adherence on an individual level is poor. Therefore, it is important that adherence be assessed regularly in all patients. Options for adherence assessment include using self-report tools (82–84) such as the Basel Assessment of Adherence to Immunosuppressive Medications Scale (85), variability in trough levels of tacrolimus, and electronic monitoring. Each method has advantages and disadvantages. Although self-reporting is believed to overestimate adherence, it is highly feasible; accuracy can be improved by remaining neutral and nonjudgmental when questioning, and by limiting recall to a relatively short time period.

Asking about adherence at every visit may even function as an intervention; by devoting time to this issue, its
importance is emphasized. Questions about adherence also provide a springboard for discussions about reasons for poor adherence and opportunities to help patients find solutions to their adherence challenges. Some relatively simple interventions include reducing the complexity of medication regimens where possible, and using pill organizers and cell phone alarms, although the effectiveness of these interventions has not been well established (73). A randomized controlled trial in kidney transplant demonstrated that once-daily tacrolimus was not inferior in regard to adherence or allograft rejection rate, suggesting a role for simplifying immunosuppression regimen (86). For patients believed to be experiencing difficulty with adherence, more frequent visits and bloodwork may be helpful (87). Only one randomized trial tested an intervention to improve medication adherence in the adolescent and young adult population. The Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial showed significantly better adherence among participants randomized to the multicomponent, adherence-promoting intervention than among those randomized to an attention control (77). The intervention included a combination of electronic monitoring with feedback of adherence data, text message dose reminders, identification of personal barriers to adherence, problem solving, and action planning, in addition to social support. A similar approach was also effective in improving adherence in adult kidney and heart, liver, and lung transplant recipients (88).

Guidelines for Transition from Pediatric- to Adult-Oriented Care

Significant effort has been devoted to identifying approaches to improving the transition from pediatric- to adult-oriented care. A variety of care models exist, including specialized transition clinics, care in a regular adult transplant program, and care by a community nephrologist. Patient satisfaction appears highest with transition clinics (89). However, although it is not clear whether outcomes truly differ by setting, there is some evidence of the success of the transition clinic model. Three small, non-randomized studies compared the outcomes of patients cared for in a specialized transition clinic with outcomes of those who did not attend this clinic. Harden et al. observed no graft failures or late acute rejections after transfer among patients who attended a joint pediatric-adult transition clinic during preparation for transfer, followed by a young adult clinic that included a youth worker after transfer (66). This contrasted starkly with the period before advent of the transition and young adult clinics, during which 67% experienced graft failure and 33% had late acute rejection. Prestidge et al. described similarly superior outcomes after establishment of a transition clinic compared with before (90). Before inception of the transition clinic, 24% experienced graft failure or death within 2 years of transfer, but after inception of the transition clinic, there were no graft failures or deaths within 2 years of transfer. McQuillan et al. (91) showed lower rates of nonadherence among patients attending a transition clinic (12.5%) compared with a group who did not attend this clinic (42.8%), and a smaller change in eGFR during the first year after transfer (−0.9 ± 13.2 versus −12.2 ± 14.9 ml/min per 1.73 m²).

Several professional organizations have provided guidance on best transition practices (92). In 2011, an international consensus statement advocated initiation of transition preparation as early as 12 years of age, with regular assessment of preparedness for adult-oriented care by using age-appropriate assessment tools (93–95). Resources for both pediatric and adult centers are available from Got Transition and the American Society of Transplantation Pediatric Transition Portal (96,97). Use of transition-readiness instruments can assist in identifying specific areas that must be addressed before transfer of care. In 2018, the Organ Procurement and Transplantation Network provided guidance on critical milestones for patients to achieve before transfer to adult care (Table 2) (98). Responsibilities of the transferring pediatric team and the accepting adult team before, at the time of, and after transfer of care are also outlined. Templates for correspondence between pediatric and adult transplant centers are available through several organizations, referenced here (94,96,97,99,100).

Table 2. Critical milestones for adolescents/young adults before transfer to adult care

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe original cause of their organ failure/need for transplant</td>
</tr>
<tr>
<td>Long- and short-term implications of transplant condition on overall health</td>
</tr>
<tr>
<td>Effect of illness on sexuality and reproductive health</td>
</tr>
<tr>
<td>Sense of responsibility for their own health care</td>
</tr>
<tr>
<td>Capacity to provide most self-care independently</td>
</tr>
<tr>
<td>Expressed readiness to move into adulthood</td>
</tr>
<tr>
<td>Ownership of medical information in a portable accessible summary</td>
</tr>
</tbody>
</table>

This list of critical milestones may be used during the preparatory phase of transition to assess readiness for transfer to adult care. Adapted from refs. 98 and 105.

A multidisciplinary approach to transition is helpful, with input from social work, adolescent medicine, pharmacy, and financial counselors. Referral for psychologic counseling may be helpful for patients experiencing particular difficulties. For patients with significant cognitive impairments, who may be limited in their capacity to make medical decisions, assessment for guardianship should be addressed before the age of legal adulthood is reached (101). The assistance of a social worker and community legal resources is invaluable in guardianship applications.

Adequate preparation for the transfer to adult care and the transfer of transplant management from parents to the young person is key to long-term graft survival and patient well-being. However, pediatric care providers cannot assume sole responsibility for the transition of young transplant recipients to full independence. Transition to adulthood and independence continues after the transfer to adult care. The most successful transition programs include ongoing support for young people even after transfer, recognizing that this is an interval of high risk. Physicians providing care to transplant recipients are accustomed to providing more intensive follow-up during periods of higher risk. For example, in the early post-transplant period, follow-up visits and blood tests are done more frequently than later post-transplant, when the risk is lower. Figure 1
demonstrates the pediatric to adult transition and transfer of care process. This approach may be applied to young adults, who are also in a period of high risk.

Summary

Pediatric kidney transplant recipients are distinguished from adult recipients by a different distribution of primary kidney diseases, the potential for developmental sequelae of kidney failure, and the need for many decades of graft function. Perhaps most importantly, all pediatric recipients must pass through a period of high risk for graft failure: adolescence and young adulthood. Potential contributors to this high-risk period include enhanced immune activity, age-related reductions in adherence to treatment, and declines in adherence related to transfer from pediatric to adult care. Universal immunosuppressive medication coverage may be helpful in mitigating declines in adherence in young adulthood (102,103). Understanding of the challenges faced by pediatric recipients will aid both pediatric and adult care providers in supporting young recipients across the lifespan. Future research for improving long-term outcomes could focus on effective ways to partner with adult care providers.

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De Novo Malignancies after Kidney Transplantation

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Abstract
Cancer is an important outcome after kidney transplantation because it is the second leading cause of death in most Western countries. The excess risk of cancer after transplantation is approximately two to three times higher than the age- and sex-matched general population, driven largely by viral- and immune-related cancers. Once cancer develops, outcomes are generally poor, particularly for those with melanoma, renal cell carcinoma, and post-transplant lymphoproliferative disease. More importantly, effective screening and treatment strategies are limited in this high-risk population. In this review, we begin with a patient’s journey that maps the experience of living with a kidney transplant and understand the patient’s knowledge, education, and experience of cancer in the context of transplantation. The epidemiology and burden of cancer in recipients of kidney transplants, along with the up-to-date screening and treatment strategies, are discussed. We also focus on the current understanding of optimal care for recipients of kidney transplants who are living with cancer from the patients’ perspectives.

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Patient’s Voice
As someone living with a kidney transplant for >16 years, this article resonated with me. When my nephrologist identified me as a preemptive candidate for a kidney transplant, he educated me immediately on the cardiovascular risks post-transplant. In addition, he persuaded me to adopt routine exercise into my lifestyle as a proactive measure. That recommendation has served me well because I have maintained routine exercise post-kidney transplant.

I have a sense of control in mitigating my cardiovascular risk. Beyond routine exercise, I have ensured my BP is within the recommended range. I strive to maintain a heart-healthy diet, and my transplant nephrologist prescribed a cholesterol-lowering medication immediately after my transplant when my metabolic panel was out of range. Recently, I scheduled an appointment with a preventive cardiologist. That appointment resulted in the prescription of a sodium-glucose cotransporter-2 inhibitor to reduce the risk of prediabetes, and a follow-up appointment for a computed tomography scan.

In contrast, my experience with managing cancer risks has not been clear. Although the risks of skin cancer were communicated, I had to ensure the guidelines were followed closely. For example, from the very beginning, I scheduled quarterly surveillance appointments with my dermatologist. Initially, quarterly appointments were discouraged until skin biopsy specimens were positive. Mole mapping was initially discouraged until the dermatologists discovered irregular moles. Nonetheless, I feel confident now in managing the risk of skin cancers. For my other cancer risks, a proactive path remains elusive.

Because the United States is moving to 3-year outcomes for transplant metrics, this affords the US transplant community to assess the effectiveness of patient education. As a first step, I would like to see the American Society of Transplantation and the American Society of Nephrology survey recipients of kidney transplants regarding their awareness of their health risks, including cancer. Moreover, the survey could also gain insights into the recipients’ ability to self-manage their health risks. In turn, this information would guide the community in their patient education and activation efforts.

Introduction
Kidney transplantation is the best treatment option for acceptable candidates with kidney failure because it improves the quality (1) of life and overall survival for patients on maintenance dialysis (2). It is also the most cost-effective treatment strategy for those needing KRT (3). However, transplantation is not a cure. Patients require lifelong immunosuppression to maintain optimal allograft function. One of the most feared complications associated with immunosuppression after kidney transplantation is cancer (4). Cancer is also considered as one of the core clinical outcomes by clinicians, patients, and caregivers, and there is now consensus among key stakeholders suggesting cancer should be included as an outcome in all interventional trials of kidney transplantation (5).

After cardiovascular disease, cancer is the second leading cause of death among recipients of transplants in most Western countries (6). The higher risks and poorer cancer outcomes have prompted clinicians and policy makers to adopt preventive policies, such as human papillomavirus (HPV) vaccination (7) and cancer-screening strategies, to detect cancers at their
earliest possible stage before they progress into advanced-stage, incurable disease (8). It is also imperative to understand the mechanistic insights into cancer cell development under the influence of immunosuppression and devise innovative treatment strategies for recipients of transplants. This review focuses on the incidence, mechanisms, diagnosis, prevention, and treatment of cancer after kidney transplantation.

Incidence of All-Cause and Site-Specific Cancer after Transplantation

The cumulative incidence of solid organ cancer ranges between 10% and 15% (6,9–11) at around 15 years after transplantation. For skin cancers, the cumulative incidence reaches >60% in Europe, Australia, and New Zealand. The excess overall cancer risk in patients with kidney transplant exceeds that of the general population by approximately two- to three-fold after adjustment for age and sex. The magnitude of the higher risk is also dependent on cancer types, with the greatest risk in viral-related and immune-driven cancers such as post-transplant lymphoproliferative disease (PTLD), anogenital cancer, and Kaposi sarcoma (12,13). Interestingly, certain solid organ cancers such as breast and prostate cancers are not increased in recipients of transplants (Figure 1).

Cancer Mortality in Recipients of Kidney Transplants

Once cancers develop, the risk of death is high. Observational data in most Western countries have shown the standard mortality ratios for all cancer types are at least 1.8–4.4 times higher compared with the age- and sex-matched general population. The risk is greatest among those with melanoma, urogenital cancers, and non-Hodgkin lymphoma, with an overall risk of cancer-related death exceeding five to ten times that of those without kidney transplants (Figure 2) (14). The exact reasons for the higher risk of death are unclear, but may be due to potential differences in the cancer cell biology in recipients of transplants resulting from long-term immunosuppression, associated comorbidities, and low uptake of recommended prevention and screening strategies (15). Patients are primarily committed to and preoccupied with their kidney and graft health, and their present health needs. Cancer screening and prevention may impose multiple burdens on patients’ daily lives (16), hence, effective patient education and heightened awareness are key.

Risk Factors for Cancer Development

There are many reasons for the higher cancer risk after transplantation. Some of these factors, such as increasing age, male sex, smoking, and prolonged sun exposures, are shared by patients in the general population. Other risk factors, including immunosuppression use (T cell–depleting agents), acute rejection (17), sensitization status (18), and duration of dialysis before transplantation (19), are specific to those with kidney disease and transplant populations. Although long-term immunosuppression is a major contributor to cancer development after transplantation, there is now convincing observational evidence to suggest that having CKD (irrespective of the CKD stage) is associated with higher cancer risk and poor cancer outcomes (20,21). Many of these cancers, such as renal cell carcinoma and multiple myeloma, are over-represented in the CKD/kidney-failure populations. Cancer may also develop in recipients of kidney transplants because of impaired tumor surveillance and immunity to viral or other tumor antigens. The observed higher cancer risk is further compounded in patients who have had a previously treated pretransplant malignancy (22–24). Recent studies indicate a higher incidence of all-cause mortality in recipients of solid organ transplants who have a pretransplant malignancy than those without, but the cause of death may not necessarily be driven by cancer recurrence alone (24–26).

The specific types of cancer that develop after transplantation also vary by geographic areas. Observational and registry data from Europe, North America, Australia, and New Zealand indicate the most common cancer types are nonmelanoma skin cancers (NMSCs), PTLD, and lip cancer (10,27–29). In contrast, data from non-Western Asian and Middle Eastern transplant cohorts suggest higher incidences of urothelial transitional cell carcinoma, renal cell carcinoma, and gastrointestinal cancers in their populations (9). It is unclear why these regional variations exist, but it may be related to distinct regional dietary supplementations, such as aristolochic acid, which have been associated with urothelial carcinoma (30). A nationwide population study of 4716 recipients of kidney transplants in Taiwan reported an excess risk of liver cancer of approximately five-fold compared with the sex- and age-matched general population (31). Taiwan is an endemic area for chronic hepatitis B virus (HBV) infection in Far East Asia. The estimated prevalence rate of HBV antigenemia in recipients of kidney transplants is estimated to be 9%–24%. HBV is also a major risk factor of liver cancer. This finding supports the hypothesis of a loss of control of oncogenic viral replication and control in

Figure 1. | The standardized incidence ratios of different cancer types in recipients of kidney transplants indicate that the overall risk of cancer is higher for certain cancer types compared to the age- and sex-matched general population. The size of the circle represents the absolute risk of developing cancer compared with the age- and sex-matched general population.
Mechanisms of Cancer Development after Transplantation

Maintenance immunosuppression decreases acute and chronic rejection, and subsequent allograft loss. Although the precise mechanisms are unclear, the effects of immunosuppression on dampening the immune system may create a variety of pathways for cancer development. One potential mechanism is through poor immune control of known oncogenic viruses in patients on immunosuppression. For example, increases in viral-associated cancers, such as Kaposi sarcoma (human herpesvirus 8), PTLD (Epstein–Barr virus [EBV]), and lip and anal cancers (HPV) are common in patients with suppressed immune systems (32).

Another mechanism of immunosuppression-related cancer development is through accumulation of mutations that would otherwise be repaired or recognized by the immune system. This mechanism may be predominant in skin cancers, where immunosuppression impairs the cells’ ability to repair ultraviolet (UV) radiation–induced DNA damage. More specifically, immunosuppression can lead to a decrease of xeroderma pigmentosum complementation groups A and G, which are components of nucleotide excision repair (33).

Currently, there is no conclusive evidence to suggest one type of immunosuppression is more oncogenic than others (34). However, experimental studies in hepatocellular carcinoma, human lung adenocarcinoma cells, and renal cell carcinoma have shown that tacrolimus increases the level of TGF-β and thereby promotes tumor progression and metastasis. In addition, calcineurin inhibitors inhibit signal transduction via calcineurin and NF of activated T cells, which can activate p53, a hallmark of some NMSCs (35). Cyclosporine also has direct effects on tumor development and progression, through TGF-β or IL-6 overexpression pathways (36). Recent evidence has shown cyclosporine is capable of inhibiting DNA repair, thereby accumulating mutations, inducing apoptosis in activated T cells, and inhibiting apoptosis in other cells by opening the mitochondrial permeability transition pores (37). The potential oncogenic potential of azathioprine is well known and well recognized. Azathioprine sensitiizes the skin to UVA radiation and causes the accumulation of 6-thioguanine in the DNA, leading to a higher risk of NMSCs (38).

Mammalian target of rapamycin (mTOR) inhibitors, on the contrary, may have potential antitumor effects by inhibiting cancer growth through cell-cycle arrest and initiation of apoptosis. Growth inhibition of tumor cells has been demonstrated in vitro for cells from tumors, such as small cell lung cancer, sarcoma, neuroblastoma, glioblastoma, osteosarcoma, pancreatic cancer, breast cancer, prostate cancer, leukemia, and B-cell lymphomas (39). On a molecular level, several mechanisms have been identified for mTOR inhibitor–mediated tumor inhibition. Specifically, mTOR inhibitors can induce apoptosis in a cell type–specific fashion. It can also induce cell death in B-cell lymphoma lines, phagocytosis and tensin homolog-lacking human tumors, and dendritic cells, possibly through p53 activation and reduction in the cyclin and survivin levels (39).

Induction therapy with T cell–depleting agents (including polyclonal agents, such as anti-thymocyte globulin, and monoclonal agents, such as anti-CD52 and, historically, Ortho Kung T3 [muromonab-CD3]) increases the risks of cancers, such as PTLD and melanoma (40). In addition, T cell–depleting agents used in the treatment of acute rejection of the kidney allograft also heighten the risk of cancer development (17). The mechanisms behind the short-term use of these therapies and the development of cancer years later are uncertain. However, after T-cell depletion, there is often an incomplete T-cell recovery (41), which may have a long-term effect on immune homeostasis, leading to an impaired immune system (42,43) and subsequent cancer development.

Common Cancers after Transplantation

Although the risk of overall cancer development is high after transplantation, the risks of certain cancer types are much higher than others. Here, we discuss the three most common cancer types: renal cell carcinoma, skin cancer, and PTLD.

Renal Cell Carcinoma

Compared with the general population, recipients of kidney transplants have a higher risk (up to seven-fold) of
renal cell carcinoma (44–48). Due to increased abdominal imaging, the majority of kidney masses detected in patients post-transplantation are typically early, low-grade, small kidney masses (8,49); of which, 75%–80% are renal cell carcinoma, with the risk of metastasis at presentation being <2% (50). Ninety percent of renal cell carcinomas develop in the native kidneys as opposed to the allograft. Risk factors for development of renal cell carcinomas post-transplantation include male sex (female hazard ratio [HR], 0.56; 95% CI, 0.47 to 0.66), increasing age (60+ years; HR, 6.59; 95% CI, 4.29 to 10.15), African descent (HR, 1.50; 95% CI, 1.24 to 1.80), and longer time on dialysis (3+ years; HR, 2.23; 95% CI, 1.58 to 3.13) (46). With regard to disease etiology, patients transplanted for kidney failure secondary to glomerular diseases (HR, 1.24; 95% CI, 1.05 to 1.47), hypertensive nephrosclerosis (HR, 1.55; 95% CI, 1.29 to 1.86), and vascular disease (HR, 1.53; 95% CI, 1.15 to 2.03) appear to have the greatest associated risk; in contrast, patients with kidney failure secondary to diabetes (HR, 0.77; 95% CI, 0.62 to 0.94) or autosomal dominant polycystic kidney disease (HR, 0.81; 95% CI, 0.62 to 1.06) have a lower risk of renal cell carcinomas. De novo renal cell carcinomas should be definitively managed according to urologic guidelines on the basis of risk stratification and staging (51,52), in conjunction with patient factors (age, comorbidities, functional status) and kidney-mass characteristics (size, biopsy specimen findings, growth kinetics).

The outcome of renal cell carcinomas after radical treatment in the transplant population is comparable with that of the general population, with 5-year, disease-specific and overall patient survival rates of 68%–97% and 69%–88%, respectively (53–56). Negative prognostic factors include presence of symptoms at diagnosis, higher Fuhrman grade (>2), absence of transplantation, and advanced-stage disease (53–56). Renal cell carcinoma in the kidney allograft is rare, and multicenter data have demonstrated an incidence of 0.1%. Most are low-grade T1 lesions, clear cell carcinomas, or papillary renal cell carcinomas, and occur more commonly in males. The majority of tumors were treated by partial nephrectomy (67%), radical nephrectomy (19%), and percutaneous ablation (12%); surveillance was rarely used. This experience suggests that nephron-sparing surgery was safe and an appropriate option with good long-term functional and oncologic outcomes, evading return to dialysis (56,57). Overall duration and intensity of immunosuppression, rather than individual components of the drug regimen, influence risk of renal cell carcinoma. The management of these malignancies should be individualized and use a patient-centered approach to ensure optimal care (58).

Skin Cancer
Skin cancer is the most common cancer type in recipients of kidney transplants and is more aggressive than skin cancers occurring in the general population. The most commonly reported skin cancers in recipients of kidney transplants include cutaneous squamous cell carcinoma, basal cell carcinoma, Kaposi sarcoma, and malignant melanoma, with keratinocyte carcinomas comprising 90%–95% of these skin cancers (59,60). The pathogenesis of skin carcinoma involves a complex interaction of risk factors, including exposure to UV radiation, HPV, pretransplant skin cancer, older age, race, and sex (males at greater risk than females). Additionally, immunosuppressive medications augment the carcinogenic effects (mainly cyclosporine and azathioprine) (61,62). Kaposi sarcoma is also more commonly seen in certain ethnic groups, including patients from the Mediterranean, Africa, and Central Europe. Although Kaposi sarcoma is a rare cancer, the incidence of Kaposi sarcoma in recipients of transplants exceeds 100 times that of the general population.

Compared with the general population, recipients of transplants experience an excess risk of squamous cell carcinoma by approximately 250 times (59). In patients with actinic keratoses and squamous cell carcinoma in situ, management options with good outcomes include topical fluorouracil and imiquimod cream, photodynamic therapy, and surgical excision or electrodesiccation and curettage. For biopsy sample–proven cutaneous squamous cell carcinoma in recipients of transplants, Mohs micrographic surgery, with histologic confirmation of negative margins, offers the most definitive method of treatment, with cure rates of 95%–100% (59). In inoperable cases, primary radiation therapy may achieve local cure rates. Patients who develop multiple squamous cell carcinomas (more than five) every year, those who have aggressive squamous cell carcinomas, or those with early onset of squamous cell carcinomas can be considered for chemoprophylaxis. These may include retinoids (63) and nicotinamide (64). In patients with metastatic cutaneous squamous cell carcinoma, systemic chemotherapy and/or immunotherapy are recommended (59).

Patients treated with calcineurin inhibitors are at particularly high risk for Kaposi sarcoma. Decreasing the intensity of or switching immunosuppressive agents to an mTOR inhibitor is the cornerstone of treatment. Regression of Kaposi sarcoma has been reported after switching from calcineurin inhibitors to sirolimus by restoring effector and memory T-cell immune activity against human herpesvirus 8 (65). The risk of developing malignant melanoma is elevated by approximately five- to eight-fold in recipients of transplants, and these patients have much poorer outcomes than the general population (59). Among all skin cancer types, melanoma has the highest mortality (66). History of pretransplant melanoma is the strongest risk factor for post-transplant melanoma, followed by White race and older age (>50 years). Primary treatment is surgical with wide excision and adequate margins, based on Breslow thickness, as per the National Comprehensive Cancer Network guidelines (59). Adjustment of immunosuppression is individualized to each patient on the basis of the extent of melanoma and transplant function.

Post-Transplant Lymphoproliferative Disease
PTLD is a well-recognized complication after kidney transplantation. Although it is a rare disease, it is associated with poor outcomes. In most instances (approximately 90%), PTLD is associated with EBV. EBV is a common virus, and most people acquire the virus during childhood. Most present with mild or minimal symptoms, but the virus can infect the B cells and remain dormant in these cells during the latent phase. After transplantation, these
viruses can reactivate because of depressed T-cell function, with a lack of T-cell control over B-cell proliferation, and contributes to the development of PTLD. Most PTLDs are of B-cell types, with approximately 5% of patients having the T-cell type.

The cumulative incidence of PTLD in the first 10 years after kidney transplantation is around 1%–2% in adult recipients and approximately 3% in pediatric recipients of transplants (67). There is evidence to suggest that the incidence of PTLD has been decreasing in recent years. A recent analysis from the Australian and New Zealand Dialysis and Transplant Registry reported the incidence of PTLD was higher in the period of 1995–2000 compared with the current era, with an 8% reduction in the risk of developing PTLD from 2000 onward (67). There also appears to be a bimodal distribution in PTLD incidence, with the risk of PTLD being the highest in the 12 months post-transplant, and it then decreases until the fifth year after transplantation. Pretransplant EBV seronegativity and primary EBV infection are important risk factors for early EBV-positive PTLD, particularly in younger recipients of transplants, and may explain the higher risk of disease early post-transplant. In contrast, a significant proportion (approximately 40%–50%) of late B-cell PTLDs involves EBV-negative lesions (68).

Compared with adult recipients of transplants, the risk of developing lymphoproliferative disease in pediatric recipients of transplants is at least 30-times higher than the age- and sex-matched general population. Apart from younger age at transplantation, male sex, use of T cell–depleting agents, Ortho Kung T3 (murmonab-CD3), and high dose tacrolimus, negative recipient EBV serology (with positive donor EBV serology) incur a four-fold excess risk of PTLD, after accounting for potential confounding factors (67). The use of costimulatory blockade, such as belatacept, has also been found to be associated with a higher risk of PTLD, particularly cerebral PTLD in patients who are EBV negative, and when used in higher doses (69).

The treatment goal of PTLD is to cure the disease, and the mainstay of treatment is immunosuppression reduction. However, the response to immunosuppression reduction varies considerably between individuals. Prior work reported the use of rituximab and chemotherapy (doxorubicin, cyclophosphamide, vincristine, prednisone) have improved overall survival, with 5-year survival at around 60% (70). Rituximab is also generally well tolerated with minimal side effects, and factors that predicted response included positive EBV status and normal lactate dehydrogenase levels (70).

Once PTLD develops, the risk of death is high. Epidemiologic studies have shown that the risk of death among recipients of kidney transplants who have PTLD is >14-fold higher than recipients without PTLD. However, contemporary data have shown there is an improvement in overall survival in more recent times due to the use of chemotherapies, such as rituximab, and other novel therapies, such as immunotherapy. Registry analyses have indicated the overall survival after PTLD was around 62%–68% at 1 year and approximately 41%–48% at 10 years (71). The risk of death also appears to be dependent on site, with those having bone marrow/reticuloendothelial disease experiencing the greatest risk of death, followed by extranodal and nodal disease. The median time from diagnosis to death is 6 months. Apart from site, other predictive factors of death included male sex and increasing age of diagnosis.

Cancer Screening Strategies in Transplant Recipients

High-quality, randomized controlled trials have shown that cancer screening through early detection reduces cancer-specific mortality in the general population (72). In patients with kidney disease, some have questioned the benefits of routine screening (73). Although some cancers are more common in patients with kidney disease, the expected patient survival, particularly for those on dialysis, is shorter than the time to develop cancers, suggesting screening may not be as effective in terms of costs and survival benefits (74). Despite the lack of trial-based evidence to support routine screening in this high-risk group, routine population-based cancer screening for breast, colorectal, and cervical cancer is recommended and should be aligned to the guidelines as per the general population (75) (Table 1). Some guidelines also suggest routine skin checks by dermatologists in recipients of transplants who are at high risk, and abdominal ultrasounds and serum α-fetoprotein levels should be checked every 6 months for those with underlying liver disease and chronic HBV infections. For patients who are at risk of developing renal cell carcinoma (such as those with a history of acquired cystic disease, those with a family history, those who are heavy smokers, and those who use long-term analgesics), ultrasonographic screening (annually or biennially) of the native kidneys may be considered to detect occult malignancy (76).

Patients with kidney disease and kidney transplants undergo radical changes to their overall health and wellbeing, which could be overwhelming for the patients and their caregivers. Many patients are unprepared to undertake a multitude of tests on issues they may see as distant (83,84). From the patient’s perspective, decisions about cancer screening are becoming increasingly complex. Screening decisions must be made with clear considerations of patients’ preferences and values, incorporating the potential harms and benefits of the various options. A shared decision-making process, defined as an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options to achieve informed preferences, should be adopted to guide decision making (85,86).

Human Papillomavirus Vaccination in Recipients of Kidney Transplants

The incidence of HPV-related anogenital cancer is at least ten- to 15-fold higher in recipients of kidney transplants compared with the age- and sex-matched general population. Quadrivalent vaccines (against genotype 6, 11, 16, and 18) and, more recently, the HPV 9-valent vaccines (against five additional genotypes of 31, 33, 45, 52, and 58) are highly effective and have an overall efficacy of 99%–100% for the prevention of cervical intraepithelial neoplasia in...
randomized clinical trials. HPV vaccination is indicated in both males and females aged 9–25 years in the general population for the prevention of HPV-related malignancies. Some recent data have shown that it is also efficacious in women up to the age of 45 years. In the transplant population, HPV vaccines are generally safe. However, seropositivity was only detected in approximately 50%–60% of patients, depending on genotypes, and higher tacrolimus levels were also detected in nonresponders (87). Although HPV vaccination is recommended for women after transplantation, it may be more efficacious to vaccinate before transplantation.

Management of Recipients of Kidney Transplants Who Have Cancer

Immunosuppression Management and Treatment in Transplant Recipients with Cancer

Management of immunosuppression in recipients of transplants who are living with cancer is complex and challenging. A concerted approach between transplant professionals, oncologists, and allied health professionals is therefore needed to ensure optimal care for our patients. Meticulous understanding of the underlying immunologic risk and cancer severity is needed to optimize immunosuppression dose to prevent the risk of acute rejection, while balancing against the need to induce regression of the malignant lesion and prevent future progression. In the absence of quality evidence, judicious reduction in the overall immunosuppression load for patients with early- to moderate-stage malignancy may be a reasonable first step, and this should be conducted in consultation with the patients, where they are informed about the potential adverse effects, and all strategies should be tailored to the individual’s needs. For patients with squamous cell carcinoma, there is now trial-based evidence to suggest conversion to an mTOR inhibitor may reduce the risk of cancer in the longer term (88,89). However, mTOR-inhibitor use may also be associated with a higher risk of death (90,91). Therefore, there are insufficient data to consider mTOR inhibitors as protective against other cancer types apart from squamous cell carcinoma and Kaposi sarcoma (92).

Immunotherapy

The use of immune-checkpoint inhibitors targeting the programmed death-1/programmed death ligand-1 interaction and/or the CD28-CD80/86 axis with cytotoxic T lymphocyte-associated protein-4 Ig has revolutionized the treatment of a variety of malignancies through immune-system activation against the cancer (93–95). However, the use of checkpoint inhibitors is limited in recipients of transplants given the potential for rejection with nonspecific immune-system activation (96,97). Although checkpoint

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| Table 1. Recommendations for cancer screening in recipients of kidney transplants |
|---|---|---|
| Cancers | Recommendations | Evidence |
| Breast | For women aged 50–74 years, screening mammography once every 2 years. For women <50, the decision to start regular screening should be an individual one (77). | Extrapolation from general population |
| Prostate | For men aged 55–69 years, screening decisions should be individualized after a conversation with their clinician about the potential benefits and harms. For men ≥70 years, the potential benefits may not outweigh the expected harms, and these men should not be routinely screened for prostate cancer (78). | Extrapolation from general population |
| Cervical | Annual Pap testing or HPV testing every 3–5 years starting at the age of 25 years until 74 years (72). | In view of the higher risk of disease, some have suggested more frequent Pap testing. However, no evidence to suggest increased frequency of HPV testing. |
| Bowel | For adults aged 45–75 years, fecal immunochemical testing biannually, sigmoidoscopy every 5 years, or colonoscopy every 5–10 years (79). | Screening using fecal immunochemical testing is accurate in recipients of kidney transplants. However, it may be associated with higher risk of complications associated with diagnostic colonoscopies (80). |
| Lung | For adults aged 55–79 years, annual low-dose computed tomography scans for those who have smoked one pack per day for 30 years or equivalent (two packs per day for 15 years) (81). | Extrapolation from general population |
| Skin | Monthly self-skin examination and 6- to 12-monthly total body skin examination by expert physicians and dermatologists (82). | Expert opinions |
| Liver | Routine screening using US, with and without α-fetoprotein, every 6 months in patients with cirrhosis. | Extrapolation from general population |
| PTLD | Routine monitoring of patients at high risk (donor EBV seropositive/recipient seronegative) for EBV by NAT. Once in the first week after transplantation, monthly for the first 3–6 months, and every 3 months until the end of the first post-transplant year (82). | Expert opinions |

Pap, Papanicolaou; HPV, human papillomavirus; US, ultrasonography; PTLD, post-transplant lymphoproliferative disease; EBV, Epstein–Barr virus; NAT, nucleic acid amplification techniques.
inhibitors are effective in treating melanoma, non–small cell lung cancer, and renal cell carcinoma in the general population, their use in the kidney transplant population requires further investigation and cannot be recommended at this time, outside of a study protocol.

**Putting Patients’ Perspectives at the Heart of Cancer Management**

Patients with cancer and transplant may experience multiple symptoms, and the burden of self-management in the context of multiple morbidities is immense. Understanding patients’ personal experiences in their journey for the fight of cancer is crucial because this will provide important insights to guide clinicians and health care professionals to deliver relevant and appropriate care. The use of multimodal interventions to alleviate concurrent, multiple symptoms is an example of where a multidisciplinary team could deliver the suitable measures for patients transitioning between many disciplines of care. Patients living with kidney transplants are often frustrated with the lack of insights to guide clinicians and health care professionals to deliver relevant and appropriate care. Therefore, a personalized, rather than a one-size-fits-all, approach is most preferred. Ongoing dialogues between clinicians and patients, and close attention to the patients’ overall personal needs, limited not only to health issues, are crucial to ensure our patients’ voices are heard. For patients who have progressed to advanced-stage malignancy, complete immunosuppression withdrawal is a difficult decision for both patients and clinicians. Patients may experience signs and symptoms of acute rejection, and, to some, it may also represent a loss of hope and complete medical abandonment. Some clinicians may consider stopping either or both the calcineurin inhibitors and antiproliferative agents gradually and rotate to higher-dose corticosteroids to prevent the anticipated symptoms. Therefore, a multidisciplinary, integrated approach that involves the transplant and palliative care team is crucial. The team should consist of a palliative care physician to assist with the medical aspects of managing the high symptom burden, together with a social worker, dietitian, clinical psychologist, and other allied health workers to address the psychosocial, functional, and nutritional issues experienced by our patients.

**Conclusions**

Cancer is the leading cause of morbidity and mortality in patients with kidney transplants. Having cancer is a devastating event for patients and their families because the lifestyle changes and the complex feelings caused by the diagnoses are overwhelming. The priorities of optimizing allograft function with immunosuppression are often challenged and superseded by having a “cure” for the cancer, and may involve immunosuppression reduction or cessation to reduce the risk of cancer relapse and improve long-term cancer survival. Currently, the evidence to define the amount of immunosuppression by which a clinician could safely reduce is unknown. More importantly, evidence to support primary prevention and screening programs in recipients of transplants are largely extrapolated from the general population, and the findings may not necessarily be applicable to the transplant population. Collaborative efforts between health care professionals, policy makers, trialists, and patients are needed to ensure quality evidence—in the form of intervention trials, large-care observational studies, and qualitative and health service research—are generated to support the long-term care of our recipients of transplants.

**Disclosures**

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Managing Patients with Failing Kidney Allograft
Many Questions Remain

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Abstract
Patients who receive a kidney transplant commonly experience failure of their allograft. Transplant failure often comes with complex management decisions, such as when and how to wean immunosuppression and start the transition to a second transplant or to dialysis. These decisions are made in the context of important concerns about competing risks, including sensitization and infection. Unfortunately, the management of the failed allograft is, at present, guided by relatively poor-quality data and, as a result, practice patterns are variable and suboptimal given that patients with failed allografts experience excess morbidity and mortality compared with their transplant-naive counterparts. In this review, we summarize the management strategies through the often-precarious transition from transplant to dialysis, highlighting the paucity of data and the critical gaps in our knowledge that are necessary to inform the optimal care of the patient with a failing kidney transplant.

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Introduction
Much of the focus of kidney transplantation is invested into guiding patients through listing, waitlist management, and transplant, with the goal of preserving allograft function for as long as possible (1,2). Although kidney transplantation outcomes in the short term have shown significant gains over time, improvements in long-term outcomes have been less impressive, thus ensuring that many recipients of a transplant will experience a failed allograft and the attendant physical and emotional consequences (3). Currently, one in five patients will lose their kidney transplant within 5 years, and over half will experience allograft loss by 10 years (4). With graft failure often comes unique and challenging management considerations, including questions related to relisting, continued immunosuppression exposure, graft nephrectomy, and overseeing dialysis initiation. Such decisions often represent competing risks that are subsequently magnified by fragmented transitions of care among providers and health systems.

Allograft loss is associated with a high burden of psychologic and medical morbidity, with patients faring poorly across many traditional measures of quality of care, including anemia management and phosphate control (5,6). These patients experience a higher risk of hospitalization, including an associated 1.5-fold higher risk of infection-related hospitalizations and an association with lower quality-of-life scores, lower physical functioning, and higher burden of depression (6). Patients with failed allografts who return to dialysis are also noted to have notably excess mortality (7). This higher risk of mortality on dialysis with a failed allograft is, at present, guided by relatively poor-quality data and, as a result, practice patterns are variable and suboptimal given that patients with failed allografts experience excess morbidity and mortality compared with their transplant-naive counterparts. In this review, we summarize the management strategies through the often-precarious transition from transplant to dialysis, highlighting the paucity of data and the critical gaps in our knowledge that are necessary to inform the optimal care of the patient with a failing kidney transplant.

Relisting and Repeat Transplant
Over the past 2 decades, transplantation after a failed allograft has increased slowly in absolute terms and actually decreased overall in relative terms (Figure 1), which is somewhat surprising given the rising number of total transplants and the modest gains in long-term allograft outcomes. Preemptive waitlisting and transplantation is recognized as the transplantation strategy associated with the best outcomes for patients with kidney failure. Currently, in the United States, individuals are allowed to be waitlisted and start to accrue allocation time once their kidney function is <20 ml/min. This approach is perhaps underused and rife with disparities that are, at least in part, linked to inadequate provider knowledge/awareness (9–11). Individuals with failing allografts, despite having successfully navigated the system for their first transplant and having established relationships with a transplant center, are placed on the waitlist preemptively less frequently than expected—even with provider awareness not being a limiting factor (12). The rates of preemptive relisting and/or transplantation appear to be highly variable across transplant centers, declining over time, and sig-
significantly lower among racial minorities and socioeconomically disadvantaged populations (12). The marked variation in clinical practice underscores the absence of a clear focus on optimizing this transition, or consensus on the management of patients with failing allografts with respect to relisting and repeat transplantation (12). Perhaps more concerning is the fact that, although the total number of candidates being added to the waitlist has increased steadily, the number of candidates with a prior transplant has not kept up; instead, the absolute number of such candidates has remained relatively flat since 2007, resulting in a sharp decline as a proportion of the total number of candidates added to the waitlist (Figure 2). Although there are increasingly older patients receiving their first transplant, there is likely a fairly equal number of older patients receiving their second transplant, given the comparable outcomes between the two, and this cannot wholly account for the trend. This reduction in the proportion of patients retransplanted is seen despite the fact that there is increasing evidence demonstrating acceptable allograft and patient outcomes with a second and third transplant, and the exclusion of these individuals from punitive regulatory oversight in the United States in regard to patient survival metrics (3,13).

In the current allocation system and with variable rapidity of decline in failing allografts, only a minority of patients with failing allografts will receive preemptive transplants. The overwhelming majority of patients will instead need KRT, and these patients must be adequately prepared for this transition. Despite being under the care of nephrologists for extended periods, two thirds of patients with failed allografts initiate dialysis with a catheter—and >50% have no permanent access already in place—contrary to the goals of the Fistula-First Breakthrough Initiative (14,15). While these proportions are marginally better than the overall incident kidney failure population, these are likely to be underestimates of the failure of nephrologists, given that many patients potentially continue to have functioning accesses that were placed before their initial transplant. Rather, these numbers underscore the failure of transplant centers and nephrologists who are caring for patients with failing allografts to adequately prepare their patients for life without a functioning kidney transplant on multiple fronts, beyond vascular access (14).

Immunosuppression Management

Immunosuppression management is one of the most important and complicated aspects in caring for patients with failing and failed allograft, given the potential for affecting the probability of repeat transplant, protecting residual kidney function, and preventing the development of graft-intolerance syndrome, which can be both painful and precipitate the need for a graft nephrectomy.

Although reduced immunosuppression is commonly recommended in failing allografts, this approach may be counterintuitive in some individuals—such as those with ongoing, chronic, antibody-mediated rejection—and may contribute to more rapid loss of the allograft. One strategy to consider in such patients is the late conversion to belatacept-based regimens, which may allow for an improvement in kidney function and retard the rate of decline, primarily from the elimination of calcineurin inhibitors coupled with improvement in acidosis and other metabolic parameters (16,17). Although there is reason for cautious optimism in this approach for prolonging the life of a failing allograft, supporting data remain limited to small observational cohorts and more robust prospective data are needed (18). This strategy may have the additional benefit of lowering the possible development of de novo donor-specific antibodies, which, if confirmed, would have significant prognostic value for subsequent transplants and is now the subject of a prospective clinical trial (NCT01921218).

Upon allograft failure, the benefits of continued immunosuppression must be weighed against the risk of complications from their ongoing exposure, such as infection, malignancy, secondary adrenal insufficiency, and cost. The higher risk of morbidity and mortality immediately after dialysis initiation for individuals with failed allografts appears to be driven largely by infection, underscoring the
need for a better understanding of the appropriate immunosuppression strategy that would weigh the risks of infections with the benefit of avoiding sensitization, which would result from abrupt cessation of immunosuppression (Figure 3) (19). This risk/benefit calculation is not a one-size-fits-all approach, and it has to take into consideration the likely interval before a subsequent transplant and the current kidney allocation policy, which prioritizes the most sensitized of patients to help mitigate the effect of sensitization on access to a future transplant (20).

Unfortunately, most data on immunosuppression strategies are restricted to single-center, retrospective analyses that provide little guidance on when and how to reduce medications. Consequently, practices vary widely regarding who takes ownership for management decisions (transplant versus dialysis center) and protocols for how immunosuppression withdrawal is carried out, including the duration of taper and the sequence in which each medication is reduced (21,22). Fractured care that occurs across transitions of care, coupled with this profound knowledge gap, likely plays a role in the excess morbidity and mortality among this patient population, and highlights the urgent need for quality, focused clinical research to inform clinical practice (19).

Sensitization is a primary concern for patients who may be eligible for a repeat transplant. Prior studies have demonstrated that complete withdrawal of immunosuppression is associated with a higher risk for the formation of human leukocyte antigen antibodies, although the interval over which the immunosuppression was weaned appears to be influential (20,22,23). The immunosuppression taper may also need to be individualized on the basis of the degree to which the original donor and recipient were mismatched (23). Increasing data support eplet mismatch as more precise than whole-antigen mismatch to risk stratify patients for the development of donor-specific antibodies during transplant and may also prove to be a useful tool to guide immunosuppression management upon graft failure (24).

It has also been argued that continued immunosuppression in the failed allograft may preserve residual kidney function. However, a few early studies evaluated residual function in a small number of patients with failed allografts initiating peritoneal dialysis and demonstrated a much more rapid decline in function compared with patients with kidney failure without transplant, typically occurring over 6–12 months (25). Ultimately, the chance that immunosuppression can preserve some residual kidney function likely depends on whether the underlying etiology of graft failure was immunologic in nature, one of the most common causes of intermediate and late graft loss. Continuing the calcineurin inhibitor may be the best choice for the small subset of patients in which maintaining function is a priority over the ensuing 6–12 months on dialysis, particularly peritoneal dialysis (Figure 3). For the majority of patients, a more rapid taper is likely warranted because there are no published studies that adequately address whether continuing immunosuppression will affect the time course of kidney function decline, especially when taken in the context of the complications associated with these medications.

The benefits of continued immunosuppression exposure on dialysis come with substantial risk, the extent of which has yet to be clearly delineated. The higher mortality in this patient population is related to cardiovascular, malignancy, and infectious etiologies, all of which can be exacerbated by immunosuppressive therapies. Many of these drugs have important adverse effects that likely affect cardiovascular health after return to dialysis, including diabetes, dyslipidemia, hypertension, and accelerated atherosclerotic vascular disease. The higher risk of infection-related malignancy among patients who have received a transplant compared with those on dialysis is well documented, and this risk likely decreases with withdrawal of immunosuppression, although only a few studies on this topic have been performed (26,27). Several small, single-center, retrospective studies have evaluated infection in patients on dialysis who are on immunosuppression. Although the risk of

Figure 2. | Percentage of waitlist registrations for candidates with failed (or failing) allografts have decreased over time.
graft-intolerance syndrome is decreased, this often comes at the cost of more infectious complications, with the most common being venous catheter–related bloodstream infections and pyelonephritis, followed by pneumonia, cellulitis, and clostridium difficile colitis (28).

The paucity of data to guide immunosuppressant management in the failed allograft mandates an individualized and thoughtful approach, one that includes clear communication among transplant and dialysis centers. The critical first step is to determine eligibility and timing of repeat transplant. In patients without an imminent plan for repeat transplant, the rate and sequence of immunosuppression wean must be a personalized assessment of risk-benefit for each patient, with a few expert-opinion algorithms available to serve as guidance, and most centers weaning patients off immunosuppression by 1 year after starting dialysis (Figure 3) (29).

**Allograft Nephrectomy**

The role of graft nephrectomy remains controversial and clinical practice varies widely, largely dependent on regional preferences rather than compelling data. In the absence of urgent indications like infection or hemorrhage, the most salient reason for surgical removal is the treatment of graft-intolerance syndrome. Overt symptoms of rejection can include malaise, pain, fever, and hematuria, which may be refractory to pulse dose steroids. However, the more important question is whether nephrectomy is indicated as prophylaxis against this syndrome, including its more subtle manifestations. An often-cited study by Lopez-Gomez *et al.* (30), reported in 2004, compared 43 patients who initially kept their transplant in situ to 121 patients who underwent allograft nephrectomy. Patients who did not undergo surgical removal of the allograft had worse anemia, erythropoietin resistance, lower serum albumin, and higher inflammatory markers. Two thirds of patients had persistent symptoms that ultimately required nephrectomy, with subsequent improvement in many biochemical parameters compared with patients who were asymptomatic and retained their grafts. The timing of graft failure was not reported in this study, and the risk of graft-intolerance syndrome may be associated with the timing and nature of graft failure. As a result, some advocate for preemptive nephrectomy in patients with graft failure within 12 months of transplant, although robust data in support of this strategy are lacking.

The potential benefits of nephrectomy must be weighed against the risks of the procedure. There is evidence that removal of the allograft generates donor-specific antibodies, independent of immunosuppression withdrawal (31). In a recent systematic review of 12 studies, levels of panel reactive antibody ranged from 10% to 55% in patients without allograft nephrectomy, compared with 20%–72% in patients who underwent the procedure (32). A few hypotheses have been proposed to explain this phenomenon.

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*For example, mycophenolate, mammalian target of rapamycin (mTOR) inhibitors, or azathioprine*
beyond a notably higher risk of blood transfusions (32). For one, the kidney may behave like a “sponge” that absorbs formed donor-specific antibodies to their antigenic targets, preventing detection in the serum until the graft is removed (33). Alternatively, surgery may engender an inflammatory response that promotes antibody formation in the setting of mechanical manipulation, remnant allograft tissue, and increased exposure of antigens.

The surgical procedure may be technically challenging depending on the indication, existing inflammation, and early or late graft failure. Complication rates, in single-center studies and a recent meta-analysis, ranged from 5% to 48% and included bleeding, hematoma formation, and infection (32). Several studies have also evaluated the effect of allograft nephrectomy on complications related to repeat transplant. In another systematic review and meta-analysis by Lin et al. (34), patients who underwent allograft nephrectomy had a higher risk of delayed graft function, acute rejection, and allograft and patient survival. However, many of the included studies were affected by methodologic challenges and results were mixed, making it difficult to draw meaningful conclusions. Percutaneous allograft embolization has emerged as an intriguing alternative to nephrectomy and may be associated with lower morbidity, and even mortality, among a growing number of reported case series (35). Although the common postembolization inflammatory syndrome can usually be managed with analgesics, up to 20% of patients may still require surgical removal for persistent graft-intolerance syndrome (36).

**CKD Management and Dialysis Modality**

Although the initiation of dialysis is often determined by patient symptoms, estimates of glomerular filtration and rates of decline may provide additional information. There are several limitations in estimating GFR as a marker of CKD stage in the kidney allograft. Both the Modification of Diet in Renal Disease study and Chronic Kidney Disease Epidemiology Collaboration creatinine equations likely do not perform as well in patients who have received a transplant compared with those without transplants. Moreover, studies comparing the two have produced heterogeneous results that have made it difficult to advocate strongly for one equation over another. Analyses evaluating cystatin C-based equations were previously hindered by lack of a standardized assay, have not consistently demonstrated superiority, and are not widely used in clinical practice (37–39). For prognostication, all of these equations likely perform reasonably well when placed within the context of eGFR trend; other biochemical parameters, such as proteinuria and presence of donor-specific antibodies; and histologic data evaluating inflammation and fibrosis scores (40,41).

While the time course of kidney function deterioration may be slower or less predictable in failing allografts, the clinical response sometimes focuses too heavily on salvaging what is left (35,36). Regardless of the reason, patients who have received a transplant often receive suboptimal CKD management. Prior studies have noted worse BP control, anemia, lower bicarbonate levels, and higher phosphate levels in patients with failed transplants compared with those with native CKD (6,42). Reports also indicate these patients are less likely to undergo appropriate dialysis planning and more often initiate dialysis with a central venous catheter (14). This is particularly troubling given evidence that early referral for patients with native kidney disease is associated with significantly improved clinical care at the start of dialysis and improved longer-term outcomes—a trend that does not appear to extend to transplant nephrologists and their patients with failing allografts (43). Appropriate planning, including modality counseling and the use of peritoneal dialysis, has also been shown to be associated with improved early outcomes for individuals with a failed allograft (41). While this difference has not been consistent across analyses, it is difficult to know if differences in immunosuppression did not contribute to higher risk of infections and adverse outcomes in some of these analyses (41,44).

Recent studies that suggest the possibility of improved prognostication of outcomes after kidney transplant may help identify failing allografts sooner and encourage better planning of transitions of care (45). Moreover, innovative solutions to provide more comprehensive care for this high-risk cohort show early promise. Multidisciplinary clinics dedicated to patients with low-functioning kidney allografts may improve KRT planning, and even reduce emergency-department visits and hospital admissions, although more research is needed (46,47). In the absence of such clinics and clear guidelines to assist the nontransplant nephrologist, transplant providers should take some responsibility for patients during this time period. There should be clear coordination of care among the transplant center and nontransplant nephrologist, with the former focusing on allograft progression, immunosuppression weaning, and relisting, and the latter ensuring optimal CKD management and guiding the patient through dialysis planning. Transplant centers may improve this communication by ensuring that patients have a final transplant clinic visit around the time of graft failure, with a standardized, templated note serving as a checklist to make recommendations regarding these issues and establishing continued lines of communications, should the need for shared decision making arise.

The optimal timing of dialysis initiation in patients who have received a transplant has been evaluated by several observational studies, but conclusions are limited due to inherent biases and the lack of a specific threshold of function, with similar measures used in native kidney disease to guide care; however, some have raised concerns that early initiation of dialysis could have detrimental consequences on patient outcomes (44,48). Moreover, dialysis modality should be individualized to each patient because there are no compelling data to support one form of replacement therapy over another at this time (44).

**Palliative Care**

Palliative care has a much broader scope beyond end-of-life care and has been associated with an improvement in various outcomes in other noncancer, advanced-organ-failure models—including quality of life, illness understanding, hospitalizations, health care costs, and even lower risk of death (49). Allograft failure is often associated with significant symptom burden, greater utilization of health care resources, transitions between health care systems, and
high patient morbidity and mortality. Moreover, patient and provider decisions about repeat transplant and the ensuing perioperative and post-transplant risks are likely to be more complex compared with the first transplant because patients are older, may face extended waitlist time on dialysis, and often have a greater burden of comorbid disease. Finally, a common refrain among patients who have been newly transplanted is that they would rather die than go back to dialysis. Although not always ultimately true, such statements emphasize the significant emotional trauma that can accompany the failing allograft. Palliative care is uniquely equipped to address many of the needs of this patient population, yet routine integration of palliative care services has been slow and currently lacks supporting data. Helping patients understand the role of palliative care and offering referral may be important to include in their management plan, with particular consideration for patients who experience significant change in functional status, worsening disease symptoms, and increasing visits to the emergency department (49).

Large cohort- and population-level studies demonstrate an association with lower risk of death for all patients who receive a transplant compared with those who remain on dialysis—in part, because of the selection bias that exists for the patients who did get a transplant. However, given that transplant centers also decline patients for relisting, there is clearly a subset of individuals in which the benefits of a second transplant are potentially outweighed by the risks (50–52). Despite the focus on inadequate referrals for waitlisting and increased delisting of patients from the waitlist, there are currently no clear data available to provide a rigorous approach for who should, or should not, be a candidate for a subsequent transplant (50). Recognizing which individuals would not experience a substantial

<table>
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<th>Summary of clinical considerations for patients with a failed allograft</th>
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<td><strong>Immunosuppression considerations</strong></td>
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<tr>
<td>• Consider transition to belatacept to delay/slow decline in kidney function over time</td>
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<tr>
<td>• Optimal immunosuppression strategy in patients with failed allograft balancing the potential risks (e.g., infection) and benefits (e.g., avoiding sensitization)</td>
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<tr>
<td>• Personalization of immunosuppression taper informed by the anticipated time interval to a subsequent transplant</td>
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<tr>
<td>• Strategies to avoid an allograft nephrectomy</td>
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<td><strong>Retransplantation considerations</strong></td>
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<tr>
<td>• Initiate discussion about identification of a potential living donor</td>
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<tr>
<td>• Preemptive waitlisting on the deceased donor waitlist as soon as the GFR &lt;40mL/min</td>
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<tr>
<td>• Immunosuppression management for patients with donors</td>
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<tr>
<td>• Timing of preemptive retransplantation relative to GFR when a donor is available</td>
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<td>• Helping patients advocate for a living donor transplant</td>
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<td><strong>Transition considerations</strong></td>
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<tr>
<td>• CKD management including management of anemia of CKD and secondary hyperparathyroidism</td>
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<tr>
<td>• Evaluation and timely placement of vascular access or peritoneal dialysis catheter</td>
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<tr>
<td>• Educating about role of palliative care and consideration of early referral when appropriate, especially for patients who are not candidates for relisting</td>
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<tr>
<td>• Modality counseling including home-based therapies</td>
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Figure 4. | Summary of clinical considerations for patients with a failed allograft.

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<th>Table 1. Summary of key knowledge gaps in the optimal clinical management of patients with failing allografts</th>
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<tr>
<td>Potential benefit, timing, and strategy of introducing calcineurin inhibitor–avoidance protocols that would prolong the life of a failing allograft</td>
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<td>Determining when the potential benefit of a transplant nephrectomy outweighs the potential risks</td>
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<td>Timing of initiation of discussion for the transition to dialysis in the absence of a living donor</td>
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<td>Timing of modality counseling and appropriate access placement, especially for those patients who are not candidates for a subsequent transplant</td>
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<td>Optimal strategy to offer either preemptive listing while encouraging seeking a living donor</td>
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<tr>
<td>Timing of preemptive transplantation when available as an option</td>
</tr>
<tr>
<td>Transition of care from transplant clinic to CKD clinic</td>
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<tr>
<td>Consideration for, and timing of, palliative care referral for patients who are not candidates for a subsequent transplant</td>
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</tbody>
</table>

Table 1. Summary of key knowledge gaps in the optimal clinical management of patients with failing allografts

Key Knowledge Gaps
improvement in their quality of life and other patient-centered outcome measures is perhaps as important, so as to be able to facilitate appropriate transitions of care and manage patient expectations/outcomes.

Future Directions

Critical questions about the ideal strategy for managing patients with failing allografts persist on several fronts (Figure 4). We urgently need more data to address the gaps in our clinical understanding of how to manage patients with failing allografts (Table 1).

Conclusions

Many patients undergoing transplant ultimately experience loss of their allograft, and improving intermediate- and long-term graft survival continues to be a paramount goal for the transplant community. Until this goal is achieved, it is critical that the care of patients with kidney failure acknowledge and optimize the transition to dialysis and, potentially, back to transplant. In the current environment, patients with a failing allograft often receive suboptimal chronic disease management and dialysis planning and poor continuity of care, and important decisions, with high stakes, are guided by low-quality data. The lack of robust data on optimal clinical management of these patients has contributed to significant variations in clinical practice patterns, with suboptimal outcomes being commonplace for patients. Going forward, if we are to avoid failing our patients, it will be important for the transplant community to recognize these challenges and allocate resources to support the focused, higher-quality research that is required to improve long-term graft survival.

Disclosures

S. Mohan reports serving as a member of the American Society of Nephrology Quality Committee, on the Angion Pharma scientific advisory board, as deputy editor of Kidney International Reports (International Society of Nephrology), as member of the Scientific Registry of Transplant Recipients visiting committee, and as vice chair of the United Network for Organ Sharing data advisory committee; having consultancy agreements with Angion Biomedica; and receiving research funding from the National Institutes of Health (National Institute of Biomedical Imaging and Bioengineering, National Institute of Diabetes and Digestive and Kidney Diseases, and National Institute on Minority Health and Health Disparities). The remaining author has nothing to disclose.

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