Acute Kidney Injury in Transplant Setting: Differential Diagnosis and Impact on Health and Health Care

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Acute kidney injury (AKI) is common in kidney transplant recipients. In addition to the usual causes of AKI in native kidneys, certain features and risk factors are unique to kidney allografts. In this article, we will present an overview of the common transplant-specific AKI etiologies that include increased susceptibility to hemodynamic-mediated AKI, acute rejection, medication-induced AKI, recurrence of native kidney disease, infections, urinary tract obstruction, vascular thrombosis and post-transplant lymphoproliferative disorder. AKI is independently associated with allograft loss and patient mortality. It is, therefore, prudent for transplant centers to address it as a major quality measure.

Key Words: Transplantation, Calcineurin Inhibitors, Rejection, Quality Improvement

INTRODUCTION

Acute kidney injury (AKI) is common in kidney transplant recipients (KTR) and independently associated with allograft loss and patient mortality.[1] In addition to the usual causes of AKI in the general population, certain features and risk factors are unique to kidney allografts, perhaps the most important of which being the solitary kidney status. Causes of AKI in KTR include acute rejection, recurrence of primary native kidney disease, medication induced, infections, urinary tract obstruction, vascular thrombosis, and rarely, post-transplant lymphoproliferative disorder (PTLD) infiltrating the allograft (Table 1). In this review, we will focus on these transplant-specific AKI etiologies and their impact on outcomes. Delayed graft function occurs in the immediate post-transplant surgery period secondary to ischemia reperfusion injury, donor co-morbidities, and organ handling factors and will not be covered in this review.[2]

SUSCEPTIBILITY TO AKI

Several transplant-related risk factors for developing hemodynamic-mediated AKI and acute tubular necrosis exist in KTR. Immunosuppressive regimens often include calcineurin inhibitors that harbor significant risk of nephrotoxicity. Calcineurin inhibitor-mediated nephrotoxicity is mediated by several mechanisms including afferent arteriolar vasoconstriction, peripheral arteriolar hyalinosis, isometric vacuolization of tubular epithelial cells, striped interstitial fibrosis, and thrombotic microangiopathy.[3] Moreover, kidney allografts lack sympathetic innervation that is responsible for a significant portion of sodium and water retention in the proximal tubules. As a result, KTR are prone to develop hemodynamic-mediated AKI secondary to a decrease in their effective arterial circulating volume.[4] Kidney allografts hyperfiltrate, undergo hemodynamic stress, and eventually develop maladaptive structural changes. Despite maintaining near-normal glomerular filtration rates (GFR) by maximizing intrarenal compensatory mechanisms, allografts have reduced kidney reserve that predisposes to AKI.

The burden of cardiovascular disease leads to frequent coronary angiograms, and the immunosuppressed state is associated with malignancies and infections that often require iodine contrast-enhanced studies and nephrotoxic antibiotics for evaluation and treatment.[5]

ACUTE REJECTION

Despite the significant advancement in the efficacy of modern immunosuppressive regimens, acute rejection continues to occur at an incidence of up to 10% per year and is associated with poorer long-term allograft outcomes. The Banff classification divides rejection into either cell or antibody mediated. Acute cell-mediated rejection manifests histologically as tubulitis (grades IA/IB), intimal arteritis (grades IIA/IIB), or transmural arteritis (grade III). Tubulitis and arteritis are not mutually exclusive and could also coexist with acute antibody-mediated rejection (AMR)—what we refer to as mixed rejection—or other AKI causes. For a patient to have AMR, there should be histologic evidence of acute tissue injury, antibody interaction with the vascular endothelium in addition to identifying donor-specific antibodies (DSA). Acute tissue injury is seen by obtaining kidney allograft biopsy and manifests as microcirculatory inflammation (glomerulitis and/or peritubular capillaritis), arteritis, thrombotic microangiopathy, or acute tubular necrosis. Antibody interaction with the endothelium is supported by positive staining for C4d, a split product of C4b and a surrogate of complement activation, significant microcirculatory inflammation, or increased expression of endothelial cell injury-related gene transcripts when available. DSA could be against human leukocyte antigens or non-human leukocyte antigens and are detected by solid-phase assays.[6,7]

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Depending on its grade, acute cell-mediated rejection is treated with corticosteroids or anti-thymocyte globulin, a polyclonal lymphocyte-depleting agent. Different center-specific protocols exist for the treatment of AMR. They mostly consist of a combination of 2 or more of the following: plasmapheresis for removal of already existing DSA, intravenous immunoglobulins (IVIG) for its anti-idiotypic effect against circulating DSA, rituximab, a CD20-specific chimeric murine-human monoclonal antibody that depletes B-lymphocytes, and proteasome inhibitors targeting the plasma cells that produce the DSA.[8,9]

RECURRENCE OF PRIMARY NATIVE KIDNEY DISEASE

Most native kidney diseases may recur after transplantation albeit to different extents. Disease recurrence could manifest as AKI and is negatively associated with allograft survival. Complement-mediated diseases, such as C3-glomerulonephritis and atypical hemolytic uremic syndrome, have high rates of recurrence approaching 90%; however, primary focal segmental glomerulosclerosis (FSGS) remains to be the most notorious among the common glomerular pathologies. Primary FSGS often recurs very early post-transplantation and is associated with significant nephrotic-range proteinuria. Light microscopy is usually unremarkable, but electron microscopy shows diffuse foot process effacement consistent with significant podocyte injury. FSGS recurrence rate is 30% and is associated with allograft loss in 50% of cases. To date, we do not have a universally effective treatment regimen although several case series have demonstrated remission of disease by specifically targeting pathways implicated in primary FSGS.[10-13]

CLINICAL SUMMARY

- Acute kidney injury (AKI) is common in kidney transplant recipients and associated with allograft loss and patient mortalit.
- AKI etiologies unique to kidney transplant recipients include increased susceptibility to hemodynamic stress, acute rejection, medication-induced AKI, recurrence of native kidney disease, infections, urinary tract obstruction, vascular thrombosis and post-transplant lymphoproliferative disorder.
- Kidney transplant programs should address post-transplant AKI as a major quality measure.

IgA glomerulonephritis and membranous nephropathy have a recurrence rate of about 30% but usually run an indolent course, especially if patients are on renin-angiotensin-aldosterone system blockers with adequate blood pressure control. Anti-GBM disease, pauci-immune glomerulonephritis, and lupus nephritis tend to recur the least. This could be because of the immunosuppressive medications initiated at transplantation.[14,15]

Primary hyperoxalurias are a group of autosomal recessive enzymatic defects that lead to overproduction of oxalate by the liver. This leads to progressive kidney damage mediated by tubulointerstitial deposition of calcium oxalate crystals. Primary hyperoxaluria is rare but recurs in up to 100% of patients after kidney transplantation. Although maintaining a high urine output, alkalinizing the urine and supplementing with pyridoxine might be helpful, the only definitive treatment is liver transplantation.[16]

Recurrent disease is a common cause of AKI in KTR and the third most common cause of allograft loss after rejection and death with a functioning kidney. Therefore, the 2015 Banff meeting report recommended forming a dedicated work group to study recurrent disease.[7]

MEDICATION-INDUCED AKI

Calcineurin inhibitors used for primary prevention of rejection and IVIG used for the treatment of AMR are associated with an increased risk of AKI. Mechanisms of calcineurin inhibitor-induced AKI include afferent arteriolar vasoconstriction, isometric vacuolization/injury of tubular epithelial cells, and rarely thrombotic microangiopathy.[3] Calcineurin inhibitors exert direct and endothelin-1-mediated vasoconstriction, thereby decreasing renal blood flow and aggravating tubular and endothelial cell injury. Endothelial cell injury subsequently predisposes to thrombotic microangiopathy.[17] AKI usually resolves on holding or reducing the dose of calcineurin inhibitors. The use of calcium channel blockers has been suggested to ameliorate calcineurin inhibitor toxicity.[18] Currently, we have options to use calcineurin inhibitor-sparing immunosuppression regimens based on the T-cell co-stimulatory blocker, belatacept. These regimens have proved to be efficacious and even superior to calcineurin inhibitors with significantly better mean GFR, allograft, and patient survival in the belatacept arms at 7-year follow-up.[19]

IVIG preparations stabilized in sucrose cause osmotic tubular epithelial cell injury of the kidney. This is less common now with the newer sucrose-free preparations.

INFECTIONS

BK Nephropathy

AKI secondary to BK virus infection occurs in up to 10% of transplanted patients. BK nephropathy tends to occur early after transplantation (within the first year) and is because of sustained high-grade viral replication in setting of an immunosuppressed state. BK virus causes AKI by inducing tubulointerstitial nephritis and rarely obstruction by a ureteral stricture. In addition to the tubulointersitial inflammation, histologically, the diagnosis of BK nephropathy is suggested by tubular epithelial cell cytopathic changes, including hyperchromasia and intranuclear basophilic viral inclusions. Immunohistochemistry staining directed specifically against BK or SV40 large T-antigen will be positive in BK nephropathy.[20] Urine cytologic examination looking for tubular epithelial cells with large basophilic intranuclear inclusions (decoy cells) is also supportive of BK infection. BK viruria is seen in more than 50% of all KTRs and, therefore, is not specific for BK nephropathy. Plasma BK viral DNA detected by PCR, however, was associated with nephropathy, with sensitivity and specificity of 100% and 88%, respectively.[21] As a result, most transplant programs monitor preemptively for BK viremia as a surrogate for BK nephropathy.