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Review Article

Post renal transplant acute kidney injury

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ABSTRACT

AKI specific to the renal transplant includes ischemia-reperfusion injury, acute rejection, acute calcineurin inhibitor (CNI) toxicity, venous or arterial thrombosis, urinary tract obstruction, graft pyelonephritis and recurrent disease. The graft is more susceptible to hemodynamic insults as it is denervated and there is at least partial loss of its autoregulatory capacity. Some factors unrelated to the transplant like sepsis may also predispose AKI in post-transplant period. The article particularly highlights the issues of AKI other than acute rejections.

1. Introduction

Acute kidney injury (AKI) can occur at any time after renal transplant but occurs most commonly in the early post-transplant period. The causes of AKI specific to the renal transplant include ischemia-reperfusion injury, acute rejection, acute calcineurin inhibitor (CNI) toxicity, venous or arterial thrombosis, urinary tract obstruction, graft pyelonephritis and recurrent disease. In addition, the graft is more susceptible to hemodynamic insults as it denervated and has partially lost its autoregulatory capacity. Finally, causes unrelated to the transplant (such as nephrotoxins) and sepsis may also cause post-transplant AKI.

Acute rejection is the Achilles heel of kidney transplantation, and can vary in severity from clinically silent injury picked only on histology to acute oliguric kidney injury requiring renal replacement therapy. It is one of the most important causes of AKI, however the occurrence of acute rejection in the first year following transplant has diminished significantly over the decades to the present rates of 10–15%. The use of newer potent immunosuppressive agents both for induction as well as for maintenance therapy is responsible for this decline in the rejection rates. Majority of the rejection episodes occur in the first two weeks post transplant. The factors which predict the occurrence of acute rejection are donor and recipient age and HLA match, race, presence of donor specific antibodies (DSAs), prolonged cold ischemia time, delayed graft function and inadequate immunosuppression/non-compliance. Activation of the T-cell mediated and the humoral limb of immune system result in occurrence of cellular and antibody mediated rejections, respectively.[1]

The relative frequency of each of the above insults may vary according to the post transplant duration. Patients with underlying allograft dysfunction because of any etiology are at higher risk of AKI. As in the general population, post-transplant AKI is associated with higher incidence of chronic kidney disease (CKD). Renal transplant recipients with AKI are at increased risk of graft loss and death. In this article, we review the common causes of post-transplant AKI other than rejection, their management and impact on graft survival.

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2. Impact of post-transplant AKI

Nakamura et al,[2] analyzed 289 kidney transplant recipients during the maintenance phase (at least 3 months post-transplant) of immunosuppression and found that the overall incidence of AKI by RIFLE criteria was 20.4% and 28% by AKIN classification. Majority (61.0%) of the AKI in this study occurred within two years of transplant and the most common etiology (64%) was bacterial infections (consisting of UTIs, infectious colitis and bacterial pneumonia). It was seen that AKI of any severity predisposed recipients to poorer graft survival and the risk of graft failure increased progressively in proportion to the severity of AKI.

In another retrospective analysis of over twenty seven thousand adult kidney transplant recipients, Mehrotra[3] et al found that 11.3% of the patients with at least 6 months of post-transplant graft survival were admitted to the hospital with AKI. Of these, 14.8% required dialysis therapy. This study showed that AKI was associated with increased risk of post-transplant graft loss (HR = 2.74; CI = 2.56–2.92) and death with a functioning graft (HR = 2.36; CI = 2.14–2.6).

3. Common causes of post transplant AKI (excluding acute rejection)

3.1. *Ischemia reperfusion injury*

AKI due to Ischemia reperfusion injury is significantly more common in cadaver donor kidney transplant than in live donor kidney transplants. This is possibly due to brain death resulting in an "autonomic storm", which results in sympathetic nervous system activation, cytokine release and endothelial cell activation.[4] Ischemia reperfusion injury has been shown to be predictive of interstitial fibrosis and tubular atrophy (IF/TA) and poor graft survival.[5] Besides causing direct graft injury, ischemia reperfusion injury can predispose to immune mediated injury by activation of the antigen-presenting cells and Toll-like receptors and release of proinflammatory cytokines. Interventions that have been proposed to reduce the risk of ischemia perfusion injury are use of preservation solutions and optimal recipient fluid management.[6]

3.2. *CNI toxicity*

AKI due to CNI toxicity can result from hemodynamic alterations (vasoconstriction) that is usually reversible once the dose is reduced. It can occur without any morphological changes or can lead to acute tubular necrosis, isometric vacuolation of tubules and, less commonly, thrombotic microangiopathy. It occurs because of substantial impairment of endothelial cell function, leading to reduced production of vasodilators (prostaglandins and nitric oxide) and enhanced release of vasoconstrictors (endothelin and thromboxane). The nephrotoxicity of CNIs can get aggravated when used along with mTOR inhibitors. Cyclosporine induced renal vasoconstriction can cause delayed recovery from early ATN and primary nonfunction. These complications are most likely to occur with prolonged ischemia time and high cyclosporine doses. However, even patients with therapeutic levels may show signs of nephrotoxicity. Strategies to reduce CNI exposure/toxicity include using lower doses of CNIs, using vasodilators e.g. calcium channel blockers and using alternative immunosuppressive drugs.[7]

3.3. *Vascular thrombosis*

Transplant renal artery thrombosis, although rare (occurs in less than 1% of all transplants), is one of the most catastrophic events following kidney transplant and usually results in graft loss. It may occur during the transplant procedure or within a few weeks of the transplant. Technical errors, hyperacute rejection and procoagulant states may precipitate acute renal artery thrombosis. The usual presentation is with sudden anuria. The diagnosis requires a high index of suspicion, particularly in the immediate post-operative period. An urgent Doppler examination is essential to make a diagnosis. Treatment is by an emergency re-exploration of the graft. In practice, the outcome of acute arterial thrombosis is generally poor unless the thrombosis occurs intraoperatively. Acutely thrombosed grafts should generally be removed to prevent risk of infection in the necrotic graft.[8,9]

Although venous thrombosis is more common than arterial thrombosis, the cause is usually less apparent. It usually presents about 3–9 days post-transplant with sudden decrease in urine output, gross hematuria, graft pain and rarely graft rupture. If the thrombus progresses to involve the iliac veins there may be swelling of the lower limb on the side where the graft has been placed. Renal vein thrombosis should also be considered in the differential diagnosis of delayed graft function. As with arterial thrombosis, the diagnosis is usually made on Doppler examination and urgent graft re-exploration is needed to salvage the graft. Interventional radiographic techniques can be used alternatively.[10,11]

3.4. *Ureteral obstruction*

Ureteral obstruction should always be considered in the differential diagnosis of post-transplant AKI and can be readily ruled out by ultrasound examination. It can occur from faulty surgical technique, a blood clot at the lower end of ureter or because of ischemia of the lower end leading to fibrosis over a period of time. The management involves percutaneous nephrostomy followed by antegrade pyelography. Once the cause of obstruction is defined, therapeutic options include placement of a double-J stent or surgical re-exploration and revision of the faulty anastomosis. Besides ureteral stricture, other potential causes of ureteral obstruction which can cause AKI in the post-transplant setting are extrinsic compression by lymphoceles, urinomas, hematomas, or abscesses. The diagnosis can be established by aspiration, macroscopic examination and simultaneous biochemical analysis of the fluid and serum. Macroscopic examination may be sufficient to establish the presence of blood/pus in the collection. Urinomas have a high creatinine values while lymphoceles tend to have a biochemical picture similar to that of serum. Management of lymphoceles is by repeated ultrasound guided aspirations and/or external drainage. Urinary leaks may be initially managed by a double-J stent placement which may