Review Article

Acute kidney injury in kidney transplant patients

C Dudreuilh, R Aguiar & M Ostermann

Abstract

Managing kidney transplant patients in an acute medical unit can be challenging, as patients have a single functioning kidney, underlying chronic kidney disease, and are immunosuppressed. Transplant patients develop AKI for all usual reasons but the differential diagnosis is wider and includes specific problems, such as obstruction of a single functioning kidney, vascular thrombosis, rejection, drug toxicity and drug-induced thrombotic microangiopathy. Septic AKI is common but again, the differential diagnosis of sepsis is wider. Transplant patients are at higher risk of developing both community and opportunistic infections, especially in the first year after the transplant or after any increase in immunosuppressive medication. In addition, there is always a risk of rejection, especially in case of reduction of immunosuppressive medications. Therefore, any change in the immunosuppressive therapy should to be discussed with the transplant team to achieve an appropriate balance between avoiding rejection and preventing opportunistic infections.

Keywords

Kidney transplantation, acute kidney injury, immunosuppressive therapies, opportunistic infections

Case

A 75-year old man presents to the emergency department with a two-day history of rigors, and 24 hours of vomiting. His past medical history consists of end-stage renal disease secondary to diabetes. Four weeks earlier, he received a kidney transplant from a living donor and had induction treatment, including Basiliximab. His current medication includes prednisolone 10 mg/day, tacrolimus 10mg twice a day, mycophenolate mofetil 500 mg 4 times/day, bisoprolol 5 mg/day, ranitidine 150mg twice a day, nystatin mouth wash, and short and long-acting insulin. His baseline creatinine is 100 µmol/l.

On admission, his blood pressure is 100/70 mmHg, heart rate 50/min, oxygen saturation 92% on room air and temperature of 38.9°C. Clinical examination is unremarkable apart from pain over the allograft.

His blood results show haemoglobin 108 g/L, white cell count 15.8 x 10^9/L, neutrophils 12.38 x 10^9/L, serum creatinine 350 µmol/l, urea 14 mmol/L, CRP 100, K+ 5 mmol/l. One week earlier, his serum creatinine was 180 µmol/l.

Diagnosis and management of AKI

Identification of the possible aetiologies

Acute kidney injury (AKI) is a syndrome characterised by a rapid (hours to days) deterioration of kidney function. As per latest Kidney Disease Improving Global Outcome (KDIGO) classification, AKI is defined by an increase in serum creatinine by ≥0.3mg/dl (26.5µmol/l) in 48 hours or less, a rise to at least 1.5-fold from baseline within 7 days or a fall in urine output to <0.5ml/kg/h for 6 hours or more. In general, AKI has multiple potential aetiologies[1] but hypovolaemia, hypotension, sepsis and drug nephrotoxicity are the most common causes. In transplant recipients, the differential diagnosis is wider and includes acute rejection, surgical and urological complications, side effects from immunosuppressants and opportunistic infections. Recurrence of the primary renal disease should also always be considered although it is less frequent.

Depending on the time course after the transplant, some aetiologies are more common than others (Figure 1).

Diagnostic work-up of AKI in renal transplant patients

Determining the aetiology of AKI is essential to guide management and potentially target and influence the disease process. The specific diagnostic work-up in individual transplant patients with AKI depends on the clinical context and severity and duration of AKI but should always include a renal ultrasound, review of the serum concentration of immunosuppressants, a sepsis screen and consideration of potential rejection.

Role of renal transplant biopsy

In renal transplant patients with AKI, the threshold to perform a renal transplant biopsy is generally lower than in other patients with AKI,[2] especially if acute rejection is a strong possibility or the cause of AKI is not known. Guidance from the expert transplant team is recommended before ordering a renal transplant biopsy.

C Dudreuilh*
MD
Senior Clinical Fellow in Transplantation and Renal Medicine
Departments of Nephrology and Transplantation, Guy's and St Thomas' NHS Foundation Trust, London, UK

R Aguiar*
MD
Clinical Fellow in Transplantation and Renal Medicine
Department of Nephrology and Transplantation, Guy's and St Thomas' NHS Foundation Trust, London, UK

M Ostermann
PhD
Consultant in Critical Care & Nephrology
Guy's & St Thomas' Hospital London

*Joint first authors who contributed equally to this article

Correspondence
M Ostermann
Consultant in Critical Care & Nephrology
Guy's & St Thomas' Hospital London
Email: Marlies.Ostermann@gstt.nhs.uk

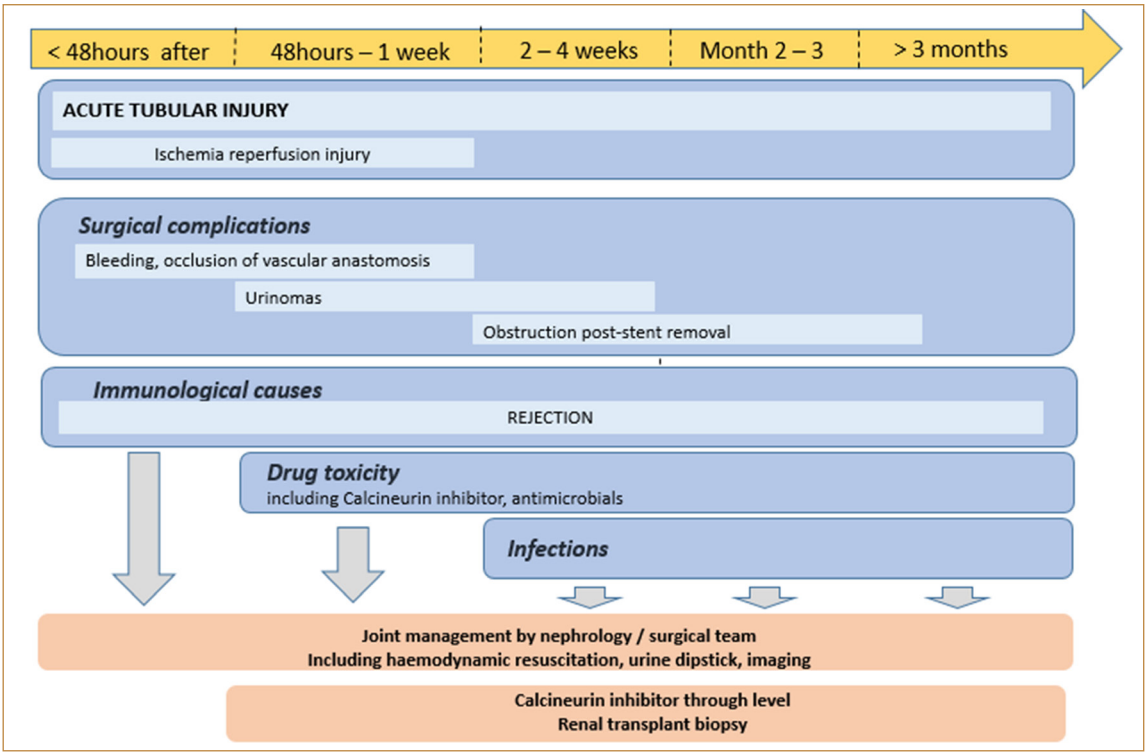

Figure 1. Frequent causes and management of AKI in a transplant patient according to time post-transplantation

Management of AKI

The specific management of AKI depends on the underlying aetiology but general measures include correction of hypovolaemia, haemodynamic resuscitation and early treatment of potential sepsis according to the sepsis care bundle. All nephrotoxic agents should be discontinued if possible, and hyperglycaemia should be avoided. Renally excreted drugs need to be dose adjusted.

Consideration of Renal Replacement Therapy (RRT)

The optimal time for initiation of RRT in AKI is not known and clinical practice is variable. However, life threatening scenarios such as refractory hyperkalemia with ECG changes, profound metabolic acidosis, and severe fluid overload resulting in pulmonary oedema and respiratory failure are complications of AKI that can be readily corrected with RRT. In such situations, the need to initiate RRT is unequivocal. However, in AKI without these complications, the optimal time for initiating RRT is unknown.

If RRT is needed and previous dialysis access is still in place, this should be used whenever possible. If new vascular access is required for haemodialysis or haemofiltration, subclavian catheters should be avoided as well as femoral catheters on the side of the transplant, if possible.

Progress of patient

The patient has an urgent ultrasound scan which is reported as normal. His tacrolimus is in therapeutic range. Clinically the patient is septic. Therefore, the most likely diagnosis is thought to be sepsis and hypovolaemia.

Most common causes of sepsis in transplant patients

Infection remains an important cause of morbidity and mortality in renal transplant patients and is often the cause for an acute admission to hospital.

Understanding the historical and current immunosuppression burden (use of depleting agents, treatment for rejection episode) and the time course of an infectious episode after transplantation is of utmost importance and can guide the clinician to choose the most appropriate antimicrobial therapy.[3]

In the first 6 months, common infections are usually related to postoperative complications and manipulation of the genitourinary tract or viral reactivations (Figure 2).

Common infections

Genitourinary infections

Genitourinary infections are the most frequent complication in renal transplant patients in both the early and late post-transplant period. The incidence varies widely between 20-70%.[4-6] The

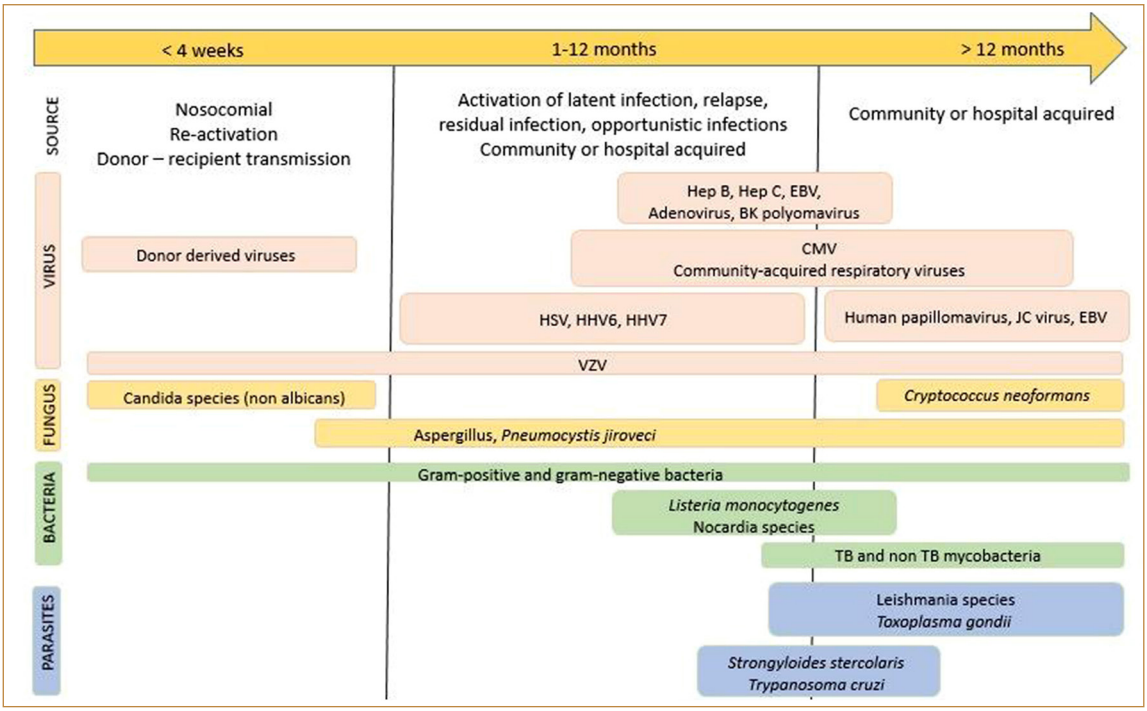

Figure 2. Most common post-transplantation infections. Hep : Hepatitis ; EBV : Epstein-Barr Virus ; CMV : Cytomegalovirus ; HSV : Herpes simplex virus ; HHV6 : Human Herpes Virus 6 ; HHV7 ; Human Herpes virus 7 ; PTLD : post-transplant lymphoproliferative disorder ; VZV : varicella-zoster virus ; TB :tuberculosis

presence of ureteral stents, an anastomotic leak or a wound hematoma are predisposing factors. Typical organisms include gram-negative organisms and fungi. Multi-resistant organisms are increasingly seen, including *Enterobacteriaceae*, *Pseudomonas* species and *Candida* species.[7] Co-infection with more than one pathogen should also be considered in patients who fail to improve.

Community acquired pneumonia

Usual respiratory pathogens are the most common organisms causing respiratory infections in transplant patients but opportunistic infections occur and should be considered, especially if patients fail to respond to conventional antibiotic treatment. Opportunistic organisms include *Legionella* species, *Nocardia* and *Pneumocystis jiroveci*. Nearly 10% of immunocompromised patients will have a normal chest x-ray with positive findings on CT scan.

Wound and abdominal infections

Wound infections, urinary tract infections, haematomas, urinomas or mycotic aneurysms are complications that typically occur within the first month after transplantation. *Diabetes mellitus* and obesity are known to be predisposing factors. Source control, including drainage or surgical evacuation and antimicrobial therapy are essential.

Diarrhoea is a frequent complaint of renal transplant patients. The differential diagnosis is wide but infectious causes should always be excluded.

Opportunistic infections

Transplant patients are at high risk of opportunistic infections. Typical organisms are viruses [ie. cytomegalovirus, herpes virus (CMV), Epstein Barr virus (EBV)] *Aspergillus, Pneumocystis jiroveci, Cryptococcus,Listeria monocytogenes, Nocardia, Legionella and Toxoplasma*. The prevalence depends on the time course after the transplant, the immunosuppression burden and co-existing medical problems and medications.

Mycobacterial and viral reactivations

Tuberculous and non-tuberculous mycobacteria

Renal transplant patients have an increased risk of developing infections by tuberculous and non-tuberculous mycobacteria compared to non-transplant patients. Atypical presentations (skin, central nervous system, visceral) are not infrequent and may delay diagnosis.

Viral reactivations

Viral reactivation occurs frequently in the first year after transplantation. CMV infection, BK virus infection and EBV-related lymphoproliferative disorder pose the major concerns.

Table 1. Common immunosuppressants after a renal transplant.

	Oral		IV		Sublingual		Monitoring
	Dose	Administration	Dose	Administration	Dose	Administration	
Ciclosporine	1	Twice a day, every 12 hours,	1/3 of oral dose	24 hours infusion	None	Twice a day, every 12 hours	Through level if oral No through level if IV
Tacrolimus	1	Twice a day, every 12 hours,	1/5 of oral dose	24 hours infusion	1/2	Twice a day, every 12 hours, same hours every day	Through level if oral No through level if IV
MMF	1	1 – 4x/day depending on tolerability	1	One hour infusion (same regimen as oral)	None		Area under the curve (T0, T30, T 120 min) only if taken twice a day
mTORi	1	Twice a day, every 12 hours	None	Discuss switch	None	Discuss switch	Trough level
Prednisolone	1	Once a day or alternate days	X4 of oral dose	Hydrocortisone	None		No

IV- intravenous; MMF- Mycophenolate mofetil ; mTORi- mTOR inhibitors (sirolimus, everolimus).

CMV infection is especially frequent in the first months after transplantation. In particular, kidney-pancreas transplant recipients are at substantially higher risk. Depending on the serological status of the donor and recipient, patients often receive antiviral prophylaxis.

The clinical presentation of CMV infection is broad and ranges from asymptomatic disease to CMV syndrome and CMV disease with organ involvement (gastrointestinal involvement, pneumonitis, retinitis, hepatitis, nephritis). CMV viral load should be requested to confirm or exclude the diagnosis and to monitor the response to antiviral therapy.

BK virus is ubiquitous. In renal transplant patients, BK virus infection can cause myriad of clinical syndromes, ranging from asymptomatic viremia, renal dysfunction with interstitial nephritis or BK nephropathy to ureteral stenosis and obstruction. BK infection is associated with both acute and chronic allograft injury. CMV infection is often accompanied by BK virus infection so BK viral load should be requested whenever CMV viraemia is present.

Post-transplantation lymphoproliferative disease (PTLD) is related to EBV infection and can present at any time after transplantation. The presentation is varied, from allograft dysfunction to typical lymphoma associated symptoms. Appropriate imaging and EBV viral load should be requested. Prompt reduction of the immunosuppression burden and referral to Haematology services are essential, as chemotherapy is often required.

Progress of patient

The patient's urine dipstick showed blood 2+, protein 2+, nitrites negative, leucocytes 1+. Clinically, the patient was diagnosed with sepsis due to transplant pyelonephritis and started on Co-omoxiclav and gentamicin. Subsequently, his blood culture grew candida albicans. His CMV viral load was undetectable. He was commenced on fluconazole and plans were made for his ureteric stent to be removed.

Management of immunosuppressants during episode of sepsis

There are many different combinations of immunosuppressants following a transplant, depending on the risk of rejection in the individual patient, time course following transplantation, previous adverse effects of immunosuppressants and local policy. (Table 1) The risk of rejection should always be balanced with the risk of life threatening complications. In most cases of severe sepsis, the benefits of reducing / discontinuing immunosuppressive drugs outweigh any benefits of continuing. However, long-term steroids should not be stopped but increased to compensate for potential adrenal insufficiency.

When deciding which immunosuppressant to reduce or stop, a discussion with the nephrology or transplant team is advisable. Similarly, the decision when to re-introduce immunosuppressive drugs depends on the progress of the patient, existing acute and chronic comorbidities and the patient's overall ability to tolerate immunosuppression. The decision is usually jointly made by the treating acute medical team and transplant team.

Potential drug interactions

Calcineurin inhibitors are known to interact with many different commonly used medications (Table 2) resulting in both, high and low serum levels. Therefore, whenever a new medication is started, it is essential to check for potential drug interactions and to adjust the dose accordingly.

Table 2.

Drugs that increase the blood concentrations of calcineurin inhibitors	Drugs that decrease the blood concentrations of calcineurin inhibitors
Diltiazem	Barbituric acid
Nicardipine	Carbamazepin
Fluconazole, Itraconazole, Ketoconazole	Cholestyramin
Metroclopramide	Phenytoin
Ritonavir	Rifabutin
Veramapil	Rifampicin
Erythromycine and all macrolides	Ticlopidin

Progress of patient

The patient was commenced on fluconazole and the dose of tacrolimus was reduced. Prednisolone was switched to an increased dose of Hydrocortisone. Mycophenolat mofetil was held until he had recovered from sepsis. At time of discharge from hospital, his serum creatinine was at baseline

Conclusion

The management of AKI in transplant patients includes adequate haemodynamic and fluid resuscitation, an ultrasound of the transplant kidney and search for the underlying aetiology of AKI. Patients are at higher risk of developing both community and opportunistic infections. The risk is particularly high in the first year post-transplant or after any increase in their immunosuppression. Immunosuppressive treatment is essential, drug levels have to be monitored if possible and oral medications may have to be converted to intravenous formulations. The risk of rejection is always present and the patient should be managed jointly between the acute medical team and the renal transplant experts.

Conflict of Interest

Nothing to declare.

References

1. Darmon M, Ostermann M, Cerda J, Dimopoulos MA, Forni L, Hoste E, et al. Diagnostic work-up and specific causes of acute kidney injury. *Intensive Care Med.* 2017;**43(6)**:829-40.
2. Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care.* 2016;**20(1)**:299.
3. Fishman JA. Introduction: infection in solid organ transplant recipients. *Am J Transplant.* 2009;**9 Suppl 4**:S3-6.
4. Parasuraman R, Julian K. Urinary tract infections in solid organ transplantation. *Am J Transplant.* 2013;**13 Suppl 4**:327-36.
5. Kotagiri P, Chembolli D, Ryan J, Hughes PD, Toussaint ND. Urinary Tract Infections in the First Year Post-Kidney Transplantation: Potential Benefits of Treating Asymptomatic Bacteriuria. *Transplant Proc.* 2017;**49(9)**:2070-5.
6. Britt NS, Hagopian JC, Brennan DC, Pottebaum AA, Santos CAQ, Gharabagi A, *et al.* Effects of recurrent urinary tract infections on graft and patient outcomes after kidney transplantation. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2017;**32(10)**:1758-66.
7. Rice JC, Safdar N. Urinary tract infections in solid organ transplant recipients. *Am J Transplant.* 2009;**9 Suppl 4**:S267-72.
8. Sawinski D, Trofe-Clark J, Leas B, Uhl S, Tuteja S, Kaczmarek JL, French B, Umscheid CA. Calcineurin Inhibitor Minimization, Conversion, Withdrawal, and Avoidance Strategies in Renal Transplantation: A Systematic Review and Meta-Analysis. *Am J Transplant.* 2016 Jul;**16(7)**:2117-38.
9. Shihab F, Christians U, Smith L, Wellen JR, Kaplan B. Focus on mTOR inhibitors and tacrolimus in renal transplantation: pharmacokinetics, exposure-response relationships, and clinical outcomes. *Transpl Immunol.* 2014 Jun;**31(1)**:22-32.
10. Venkataramanan R, Swaminathan A, Prasad T, Jain A, Zuckerman S, Warty V, McMichael J, Lever J, Burckart G, Starzl T. Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet.* 1995 Dec;**29(6)**:404-30.
11. Pennington CA, Park JM. Sublingual tacrolimus as an alternative to oral administration for solid organ transplant recipients. *Am J Health Syst Pharm.* 2015 Feb 15;**72(4)**:277-84
12. Lake KD, Canafax DM. Important interactions of drugs with immunosuppressive agents used in transplant recipients. *J Antimicrob Chemother.* 1995 Oct;**36 Suppl B**:11-22.
13. Seifeldin R. Drug interactions in transplantation. *Clin Ther.* 1995 Nov-Dec;**17(6)**:1043-61.
14. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet.* 1998 Jun;**34(6)**:429-55.
15. Mele TS, Halloran PF. The use of mycophenolate mofetil in transplant recipients. *Immunopharmacology.* 2000 May;**47(2-3)**:215-45.