Management of the kidney transplant recipient in the intensive care unit

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Purpose of review
Kidney transplantation is the ideal treatment for patients with chronic kidney disease and end stage renal disease. While centers are performing more transplants every year, the need for organ transplantation outpaces the supply of organ donors. Due to a growing population of patients with advanced kidney disease and a scarcity of kidneys from deceased donors, patients face extended wait times. By the time patients approach transplantation they have multiple comorbidities, in particular cardiovascular complications. Their risk of complications is further compounded by exposure to immunosuppression post kidney transplantation. Kidney transplant recipients (KTRs) are medically complex and may require acute management in the intensive care unit (ICU), as a result of cardiovascular complications, infections, and/or respiratory compromise from lung infections and/or acute pulmonary edema. Acute complication of immunosuppression, such as thrombotic microangiopathy and posterior reversible encephalopathy syndrome may also warrant ICU admission. This review will cover assessment of high-risk complications and management strategies following kidney transplantation.

Recent findings
For intensivists caring for KTRs, it is imperative to understand anatomical considerations of the transplanted kidney, unique infectious risks faced by this population, and appropriate modulation of immunosuppression.

Summary
Recognizing potential complications and implementing appropriate management strategies for KTRs admitted to the ICU will improve kidney allograft and patient survival outcomes.

Keywords
immunosuppression,, infectious complications, intensive care, kidney transplantation, vascular thrombosis

INTRODUCTION

Kidney transplantation is the optimal treatment for patients with end stage renal disease (ESRD), offering a survival benefit compared to dialysis [1]. As of 2021, in the United States, the number of patients living with a functioning kidney transplant exceeded 250,000, representing a decade long trend of growth [2]. Kidney transplant recipients (KTRs) are medically complex and 10% of recipients require intensive care unit (ICU) admission [3]. Due to extensive cardiovascular risk factors and high levels of immunosuppression, primary reasons for ICU admission are cardiovascular complications, respiratory compromise, and sepsis [4,5]. Acute postkidney transplant vascular and urinary complications may also require ICU care. Understanding common complications, infections, and management of immunosuppression are critical to optimize outcomes for KTRs.

KTRs admitted to the ICU have higher rates of acute kidney injury (AKI) due to additional potential risks such as ischemia-reperfusion injury, surgical complications, acute rejection, adverse effects from immunosuppression, graft pyelonephritis and sepsis [6]. Studies have shown that AKI, independent of etiology, is associated with higher risk of graft loss, death with a functional transplant and death-censored graft loss [7]. In a retrospective observational study amongst 200 KTRs admitted to the ICU, 40% required renal replacement therapy (RRT) in comparison to 20% of nontransplant patients with AKI. AKI progression to chronic kidney disease (CKD) in

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KEY POINTS

- The field of kidney transplantation is growing and an increasing number of kidney transplant recipients (KTRs) will require intensive care unit (ICU) care.
- Acute post transplant anatomical complications including urine leak, urinary obstruction and arterial and venous thrombosis require prompt diagnosis, typically with transplant ultrasound.
- Infections, frequently pneumonias, urinary tract infections and cytomegalovirus disease, are the most common causes of ICU mortality.
- Management of immunosuppression during sepsis requires careful reduction and understanding of drug-drug interactions to avoid toxicities and rejections.
- Knowledge of life-threatening complications of immunosuppression, such as thrombotic microangiopathy and posterior reversible encephalopathy syndrome, is critical in the ICU.

KTRs occurred in roughly half of ICU survivors at 6 months with hospital and 6-month mortality rates of 20% and 26.5%, respectively [8]. Independent of AKI, cardiovascular disease and development of donor-specific antibodies in the ICU may negatively impact graft survival [8,9]. De novo donor-specific antibody (DSA) can form after transfusions and reduction of immunosuppression.

IMMEDIATE POST-OPERATIVE COMPLICATIONS

Hypertensive urgency/emergency

Hypertension is common in the postoperative period, often driven by extrinsic factors including peri-transplant hypervolemia, induction immunosuppression, rebound hypertension, and inadequate pain control [10]. Donor allografts lack the ability to autoregulate blood flow, thus systemic hypertension can result in inflammation and injury to the allograft endothelium. Aggressive lowering of blood pressure can increase the risk of hypoperfusion, acute tubular necrosis, and delayed graft function. Currently there are insufficient randomized controlled trials to support goal blood pressure, and there are no guidelines in place for optimal pharmacologic therapy in the perioperative period. Beta-adrenergic agonists and clonidine should be continued in the postoperative period. Caution should be used with diltiazem due to potential drug-drug interactions. Acute management of hypertensive emergency can be safely managed by intravenous vasoactive drips [11].

Urine leak

Urine leaks are rare surgical complications that arise from obstruction or distal ureteric ischemia, especially when arterial blood flow to the lower renal pole is compromised. The use of a stent over the ureteric anastomosis to the bladder has decreased their incidence. Urine leaks present with AKI, decreased urine output, and allograft pain. Imaging, typically with transplant ultrasound, reveals a fluid collection and the diagnosis is made when the fluid creatinine is elevated compared to plasma creatinine. Cystogram, nuclear medicine scan, or antegrade nephrostogram can confirm the diagnosis. Urine leaks are often managed conservatively with prolonged bladder decompression and continuation of a perinephric drain, however persistent leaks require surgical intervention.

Urinary obstruction

Urinary obstruction most often occurs in the distal ureter from extrinsic compression from fluid collections, catheter blockages, kinking of a redundant ureter, stones, prostatic hyperplasia, or devascularization resulting in ureteral stricture. As the allograft is denervated, patients do not always develop symptoms. Recipients will present with AKI and decrease in urine output. Foley catheters should be flushed to assess for obstruction. Imaging should be obtained to assess for a perinephric collection, stone, and/or hydronephrosis. In those patients with ureteral obstruction, initial efforts should be directed towards decompressing the collecting system, either with stent or percutaneous nephrostomy tubes [12].

Arterial and venous thrombosis

Renal artery thrombosis often occurs within the first three days following kidney transplantation and most often occurs in those with thrombotic tendencies or in those donor allografts with multiple renal arteries. Patients can present with sudden anuria. Diagnosis is made when no blood flow is seen on transplant doppler ultrasound. If the diagnosis is made immediately, the allograft may be salvaged by emergent arteriotomy and thrombectomy, but most allografts with arterial thrombosis are lost [13–15]. Renal vein thrombosis is often due to kinking of the renal vein, hypotension, acute rejection, or a hypercoagulable state. With intraoperative venous thrombosis, the allograft will appear edematous and cyanotic. Delayed renal vein thrombosis is diagnosed by Doppler US, and while thrombolytic therapy may be helpful, an attempt should be made for emergent thrombectomy with revision of the anastomoses. Prolonged ischemia will otherwise result in graft failure.

Iatrogenic vascular compromise

During surgery, anastomoses are made between the donor renal vein and recipient external iliac vein and the donor renal artery and the recipient external iliac artery. When central venous access is required, cannulation of the ipsilateral femoral vein to the allograft should be avoided. Prolonged venous cannulation has been associated with stenosis of the iliac vein which can impair allograft blood flow [16]. Accidental formation of arterial-venous fistulas or large hematomas can also compromise allograft blood flow and result in vascular steal of the renal transplant.

INFECTIONS

Transplant related infections are a common cause of ICU admission, occurring in predictable patterns depending on the posttransplant period and associated with high mortality rates (Fig. 1) [5]. Depending on timing, the infections may be due to technical issues of the transplant, donor-derived infections or as a consequence of immunosuppression. The most common posttransplant infections in the ICU are pneumonias followed by urinary tract infections (UTIs) [17]. Infection in KTRs may be difficult to diagnose as immunosuppression impairs the inflammatory response [18]. As a result, more invasive procedures, such as bronchoscopy, biopsies or sampling fluid collections, to guide appropriate antimicrobial treatment may be required. Unique risk factors for infection post kidney transplant include increases in maintenance immunosuppression, recent treatment with antithymocyte globulin (ATG), plasmapheresis, neutropenia and immunomodulatory viral infections [18]. ATG's effect on the immune system is long lasting (months-years), severe, and associated with increased risk of opportunistic infections and latent viral infections.

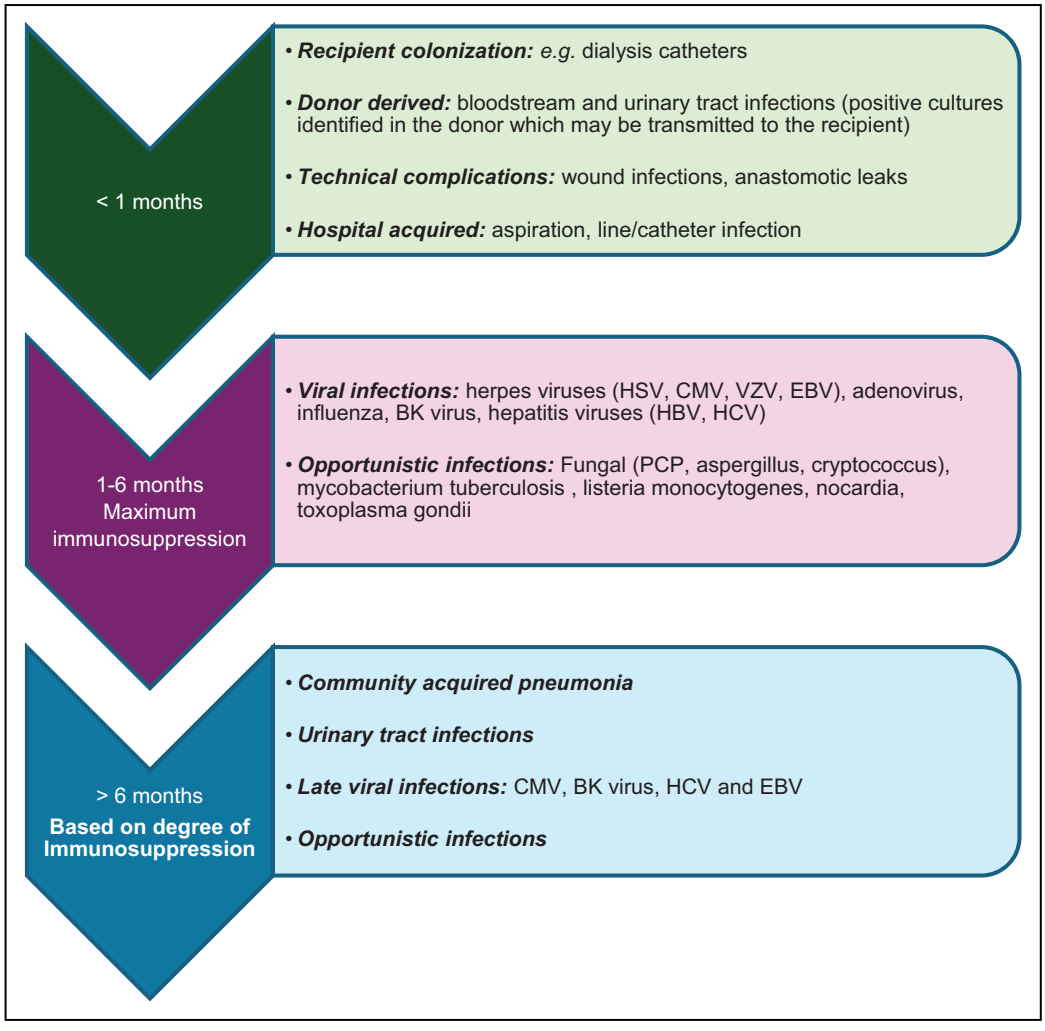

FIGURE 1. Timeline of infections post transplantation [18]. Common sources of infection according to posttransplant period. CMV, cytomegalovirus; EBV, epstein barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

Most transplant patients receive prophylaxis against cytomegalovirus (CMV) and pneumocystis pneumonia (PCP) for the first 3–6 months after transplant, during which time infection with these organisms is uncommon [18].

Urinary tract infections

Urinary tract infections (UTIs) and urosepsis are the most common infectious complication post kidney transplantation and represent nearly a quarter of infection-related ICU admissions [19▪]. Risk factors include the presence of ureteral stents and the anatomical positioning of the transplanted kidney, including shorter ureter, lack of antireflux properties and denervation that may result in delayed diagnosis [20▪]. Escherichia coli and *Klebsiella pneumonia* are the most common pathogens, however in recent years, increased incidence of multidrug resistant organisms (Enterobacteriaceae and pseudomonas species) and candida have been noted [21]. Acute graft pyelonephritis is an independent risk factor for persistent decline in renal function and graft loss [22]. Additional imaging to evaluate for abscess should be obtained in those nonresponsive to antimicrobial therapy.

Pneumonias

Lower respiratory infections are the leading cause of admission to the ICU in KTRs [30]. In a retrospective study in 200 KTRs admitted to the ICU for acute respiratory failure, bacterial pneumonia was the most common diagnosis, with Escherichia coli and *Streptococcus pneumoniae* being the most recovered pathogen on bronchoalveolar lavage and PCP being the most common opportunistic infection. Mechanical ventilation was required in 46.5% of patients, vasopressors in 41% and RRT in 52%. Both in-hospital and 90-day mortality rates were 22.5% [23]. A more recent retrospective study of 183 KTRs admitted to the ICU for acute respiratory failure found the need for vasopressor drugs [odds ratio (OR) 8.13, $P < 0.001$], mechanical ventilation (OR 3.87, $P = 0.016$) and a Simplified Acute Physiology Score (SAPS) 3 (OR 1.04, $P = 0.045$) were associated with mortality in the multivariate analysis [24].

Viral Infections

Cytomegalovirus

CMV is the most common viral infection affecting KTR with an incidence of 40–80% [25]. Transplantation from a seropositive donor, ATG therapy, advanced recipient age, lymphocytopenia and mycophenolate therapy are risk factors for the development of CMV. After CMV prophylaxis is completed, the risk of CMV infection increases, with peak incidence 6–12 months posttransplant. In patients with CMV disease, fever, leukopenia, myalgias and transaminitis are common. Patients may have gastrointestinal, pulmonary, ocular or renal involvement. Treatment includes intravenous ganciclovir or oral valganciclovir, in mild disease without gastrointestinal involvement. Refractory CMV viremia should prompt testing for mutations in the CMV genome. Second line treatments such as foscarnet and cidofovir may be used for UL 97 resistance mutations [26]. Alternative agents such as letermovir and marabavir are under evaluation for refractory disease [27▪▪,28].

COVID-19

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, significantly impacted solid organ transplantation, resulting in a substantial decrease in transplant activity and an increase in mortality due to infection in transplant recipients. KTRs are at higher risk of COVID-19 compared to nontransplant recipients (5% vs. 0.3%) and have worse outcomes [29]. A large prospective cohort study demonstrated that mortality amongst KTRs with severe COVID pneumonia (requiring intubation, death or ICU admission) was significantly higher (17.9 vs. 11.4%, $P = 0.038$) than nontransplant counterparts [30]. Systematic review of hospitalized COVID-19 KTRs showed similar mortality rates by region: USA (18%; 95% CI: 14–23%), Asia/Pacific [24%; 95% confidence interval (CI): 13–40%] and Europe (26%; 95 CI: 22–30%) [31]. A retrospective study of 3213 hospitalized COVID-19 patients found higher rates of mechanical ventilation (34% vs. 14%, $P < 0.010$), vasopressor use (41% vs. 16%, $P < 0.01$) and AKI (47% vs. 15%, $P < 0.01$) in KTRs vs. non transplanted patients [32]. Treatments for hospitalized COVID-19 patients include dexamethasone, remdesivir, tocilizumab and baricitinib. Dexamethasone should be used to treat COVID positive KTRs requiring oxygen therapy [33]. A retrospective single center cohort study of 165 KTRs hospitalized for COVID-19, demonstrated higher survival rates in patients treated with remdesivir compared to standard of care (39% vs. 83%, $P < 0.05$) without significant nephrotoxicity or AKI [34▪▪]. The role of tocilizumab in KTRs was evaluated in a multicenter cohort study which found that tocilizumab administration did not significantly affect mortality in multivariate analysis [35], however further randomized controlled are necessary. Baricitinib has not been studied in KTRs.

MAINTENANCE IMMUNOSUPPRESSION

Modification of maintenance immunosuppression in sepsis

Appropriate management of immunosuppression in sepsis and septic shock remains controversial with no consensus guidelines on which immunosuppression medication should be initially stopped or reduced and for what duration. The risk of life-threatening infection must be balanced against rejection. Current retrospective studies demonstrate a potential survival benefit without risk of rejection with immunosuppressive reduction in the setting of severe bacterial and PCP pneumonia [36,37]. However, which immunosuppressive drug, the degree of dose reduction and timing were not specified. In a small retrospective study ($n = 31$) of KTRs admitted to the ICU for severe sepsis (pneumonias, central nervous system infections and urosepsis) 74.2% were given steroids alone with a mean of 32 $\pm$ 23 mg/day and 25.8% were changed from triple to dual drug immunosuppressive regimens (mycophenolate mofetil (MMF) and corticosteroids or tacrolimus and corticosteroids). The mortality rate amongst these patients was 51.6%, similar to previously documented mortality rates amongst KTRs in the ICU, and 62.5% of these patients died with a functional graft. In the surviving patients with AKI, all graft functions returned to baseline without evidence of acute rejection [38].

In the setting of COVID-19 infection, evidence is lacking for immunosuppression modification and it is largely individualized. While immunosuppression may play a protective role via antiviral or anti-inflammatory properties, a common approach is reduction of immunosuppression to restore the host immune response. In a retrospective study of hospitalized KTRs with COVID-19, a majority (32/51, 62.7%) had their antimetabolite drug (AD: mycophenolate mofetil, mycophenolic acid and azathioprine) or mammalian target of rapamycin inhibitor (MTORi) suspended and calcineurin inhibitor (CNI) and steroids were maintained at reduced doses. In the 19 patients admitted to the ICU 89.5% (17/19), AD and CNIs were completely stopped, while steroids were continued [39]. At our institution, our approach includes cessation of the antimetabolite, typically mycophenolate, in early sepsis, according to the sepsis-3 consensus definition [40], and if progressive, we simultaneously lower calcineurin inhibitor CNI trough targets. In patients with septic shock, all agents, except for intravenous corticosteroids, are discontinued. Of note, certain infections such as PCP and streptococcus pneumoniae meningitis may require adjuvant steroids [41].

Role of corticosteroids for septic shock

The use of intravenous corticosteroids for the treatment of septic shock has been recommended for decades, largely studied in immunocompetent patients [42]. However, studies evaluating the safety and efficacy of intravenous corticosteroids in the immunocompromised population are limited and remain controversial[43]. An observational cohort study of 866 immunocompromised patients admitted to the ICU with septic shock, of whom176 were solid organ recipients, demonstrated no significant difference in 30-day mortality between those patients who received intravenous corticosteroids compared to those who did not (34.7 vs. 32.1%, $P = 0.37$). However, worse hemodynamic outcomes were observed in the intravenous corticosteroid group, including vasopressor weaning within 6 h (3.8% vs. 11.5%, $P \leq 0.001$). Similarly, patients in the corticosteroid group had longer time to weaning from vasopressors ($P < 0.001$) and significantly less vasopressor-free days than those who did not receive corticosteroids ($P = 0.001$). The authors hypothesize that unlike immunocompetent patients with a hyperinflammatory response in the setting of septic shock, immunocompromised patients have sustained immunosuppression where corticosteroids may deteriorate shock [44]. The findings suggest corticosteroid usage for septic shock is associated with adverse outcomes for immunocompromised patients. Future randomized clinical trials are required to corroborate these findings in KTRs.

Route of immunosuppression administration

In patients who are unable to tolerate oral medications, intravenous or sublingual formulations can be administered. MMF and corticosteroids can safely be administered intravenously with reliable dose conversions from their oral equivalents. Tacrolimus can also be given intravenously or sublingually with a 3 : 1 and 2 : 1 dose conversion from the oral formulation respectively. Sublingual formations may have erratic absorption and less predictable drug-drug interactions; however, they can be used as a safe alternative in transplant recipients. Cyclosporine can be given intravenously with a 3 : 1 dose conversation from the oral formation. Intravenous (IV) formulations of tacrolimus and cyclosporine should be used with caution given risk for overdosing and subsequent nephro- and neuro toxicities [45].

Drug-drug Interactions

CNIs and MTORis (sirolimus or everolimus) are metabolized by the cytochrome P450 system,

Table 1. Common drug–drug interactions [46–49]

Drug	Interacting drug	Interaction	Suggested management
Antimicrobials			
Macrolide			
Erythromycin	CSA, TAC, SRL, EVR	Severe, increase in IS levels	CSA/TAC reduce by 35–50%, SRL reduce by 50% and EVR by 25%
Clarithromycin	CSA, TAC, SRL, EVR	Severe, increase in IS levels	SRL reduce by 50%
Azithromycin	CSA, TAC, SRL, EVR	Unknown, increase in IS levels	Monitor
Azoles			
Ketoconazole	CSA, TAC, SRL, EVR	Severe, increase in IS levels	CSA/TAC reduce by 50%. Avoid SRL/EVR, reduce by 50–75% if necessary
Voriconazole	CSA, TAC, SRL, EVR	Severe, increase in IS levels	CSA reduce by 50%, TAC reduce by 66%. Avoid SRL/EVR, reduce by 75% if necessary
Itraconazole	CSA, TAC, SRL, EVR	Severe, increase in IS levels	Avoid SRL, reduce by 50–75% if necessary
Posaconazole	CSA, TAC, SRL, EVR	Severe, increase in IS levels	CSA reduce by 25%, TAC reduce by 66%. Avoid SRL/EVR, SRL reduce by 75%, EVR reduce by 50–66%, if necessary
Fluconazole	CSA, TAC, SRL, EVR	Moderate, increase in IS levels	Dose dependent, reduce by 50% for fluconazole 200mg/day or more
Clotrimazole (troche)	CSA, TAC, SRL, EVR	Moderate, increase in IS levels	50% reduction in CSA/TAC
Isavuconazole	CSA, TAC, SRL, EVR	Moderate, increase in IS levels	Monitor
Rifamycins			
Rifabutin	CSA, TAC, SRL, EVR	Moderate, decrease IS levels	Monitor
Rifapentine	CSA, TAC, SRL, EVR	Moderate, decrease IS levels	Monitor
Rifampin	CSA, TAC, SRL, EVR	Severe, decrease in IS levels	Avoid CSA/TAC. CSA increase dose 1–2 mg/kg/day with TID dosing if necessary. Monitor TAC. Avoid SRL/EVR.
Cardiovascular agents			
Statins			
Atorvastatin	CSA	Severe, increase in statin exposure	Avoid, maximum 10 mg/day if necessary
Simvastatin	CSA	Severe, increase in statin exposure	Contraindicated
Lovastatin	CSA	Severe, increase in statin exposure	Avoid
Rosuvastatin	CSA	Moderate, increase in statin exposure	Maximum 5 mg/day
Pravastatin	CSA	Moderate, increase in statin exposure	Maximum 20 mg/day
Pitavastatin	CSA	Severe, increase in statin exposure	Contraindicated
Fluvastatin	CSA	Moderate, increase in statin exposure	Maximum 20–40 mg per day
Antiarrhythmics			
Amiodarone	TAC, CSA, SRL, EVR	Moderate, increase in IS level	Monitor CSA/TAC/EVR. SRL may require dose reduction
Non-DHP Calcium Channel Blockers			
Diltiazem	TAC, CSA, SRL, EVR	Moderate, increase in IS level	Monitor CSA/TAC/EVR. SRL may require dose reduction
Verapamil	TAC, CSA, SRL, EVR	Moderate, increase in IS level	Monitor CSA/TAC/EVR. SRL may require dose reduction

CSA, cyclosporin; EVR, everolimus; IS, immunosuppression; SRL, sirolimus; TAC, tacroliumus.

in particular the cytochrome P450-3A (CYP3A) isoenzyme. Drug–drug interactions are largely explained by drugs which inhibit or induce the CYP3A isoenzyme or the enterocyte P-glycoprotein membrane transporter leading to increases or decreases, respectively, in immunosuppression drug levels. Given risk of toxicities with supratherapeutic levels or rejection with subtherapeutic levels, familiarity with interacting drugs is necessary in the ICU. Due to its inhibitory effects on the organic anion transporting polypeptides, cyclosporine (CSA) can increase the risk of myopathy and rhabdomyolysis when combined with some statins. (Table 1, [46–49]). CNI/MTORi trough levels should be monitored at a minimum of 3 times per week and daily after dose adjustments or initiation of interacting drugs in consultation with a transplant nephrologist and pharmacist.

ACUTE ADVERSE EFFECTS OF IMMUNOSUPPRESSIVE THERAPY

Thrombotic microangiopathy

De-novo thrombotic microangiopathy (TMA) is a rare and destructive complication following kidney transplantation that has been associated with both CNIs and MTORis [50,51▪▪]. Clinically, TMA may present with thrombocytopenia, microangiopathic hemolytic anemia, acute kidney injury, and neurologic involvement. In some cases, systemic signs may be absent, and kidney biopsy is required to establish the diagnosis. Withdrawal of the offending drug and transition to a t-cell co-stimulatory blocker (e.g. belatacept or abatacept) may be an effective alternate immunosuppressive strategy [52].

Posterior reversible encephalopathy syndrome

In solid-organ transplantation, posterior reversible encephalopathy syndrome (PRES) has a reported incidence rate between 0.4% and 6% and is associated with the introduction of CNIs. PRES presents with altered mentation, seizures, headache, visual loss along with radiologic findings of symmetric vasogenic edema. While the exact pathophysiology of PRES is not known, it is often accompanied by hypertension and endothelial injury [53▪]. While serum levels of immunosuppressive drugs do not correlate with incidence, drug toxicity is thought to be through dysregulation of the blood-brain barrier and impaired vasoconstriction in the cerebral vasculature. If suspected, the causative agent should be reduced or discontinued.

Mammalian target of rapamycin associated pneumonitis

The MTORis everolimus and sirolimus, have been shown to cause pneumonitis, fibrosing alveolitis and pulmonary hemorrhages. Patients present with fever, cough and dyspnea. CT chest will demonstrate bilateral infiltrates and ground-glass opacities. Bronchoalveolar lavage cytology will demonstrate lymphocytic alveolitis. Treatment involves discontinuation of the offending drug.

CONCLUSION

The care of the KTR is complex due to the unique anatomy of the transplanted kidney, immunosuppression and cardiovascular comorbidities. Understanding of the common complications post kidney transplant is integral. Successful management of KTRs in the ICU requires an interdisciplinary approach with partnership between transplant nephrologists and surgeons, infectious disease specialists and intensivists. A collaborative approach will lead to prevention of iatrogenic complications, prompt recognition of anatomical compromise and appropriate management of immunosuppression with the goal of improved kidney allograft and patient outcomes in the ICU.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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