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EDITORIAL

Ten tips to manage renal transplant recipients

Michael Darmon[1,2,3*], Emmanuel Canet[4,5] and Marlies Ostermann[6]

Renal transplantation has brought improved survival and quality of life to patients with end-stage renal disease (ESRD). In 2015, nearly 85,000 renal transplantation were performed worldwide (http://www.transplant-observatory.org/download/newsletter-2017/. Accessed 7 Nov 2018). Renal transplant recipients are immunocompromised, have residual renal dysfunction along with cardiovascular comorbidities, and are at high risk of acute illnesses requiring ICU admission (Fig. 1). Here, we highlight ten important principles when caring for transplant patients in ICU, outside the immediate post-transplant period.

1. Search for bacterial infection and treat promptly

Sepsis remains the main reason for ICU admission. Acute bacterial graft pyelonephritis is the most frequent type of sepsis and should be considered in every patient. Urinary catheters and ureteral stents are common risk factors and their removal or replacement needs to be discussed to avoid recurrence. Renal imaging is recommended to rule out urinary tract obstruction, renal abscess, or urine leakage. Bacterial pneumonia is the second most common source of sepsis [1].

2. Rule out viral and fungal infections

Cytomegalovirus (CMV) can cause life-threatening organ dysfunction and CMV viremia should always be excluded. Rates of severe CMV disease have decreased owing to post-transplant prophylaxis and pre-emptive treatment strategies. Several other respiratory viruses (influenza respiratory syncytial virus, or adenovirus) may, however, cause severe viral pneumonia [2]. BK polyomavirus may reactivate in immunocompromised patients and lead to nephritis, ureteral stenosis, and less frequently haemorrhagic cystitis. Polymerase chain reaction (PCR) quantification of BK viremia and urinary PCR may indicate reactivation [3]. Epstein–Barr virus (EBV) reactivation increases the risk of developing opportunistic infections and post-transplant lymphoproliferative disorder and can also be detected by quantitative PCR [4]. Pneumocystis pneumonia is the most common fungal infection in patients without prophylaxis and after prophylaxis discontinuation. High dose co-trimoxazole remains the cornerstone of treatment and, in contrast to their use in HIV patients, adjunctive steroids remain controversial. Other fungal infections, such as invasive pulmonary aspergillosis, are uncommon in the late post-transplant period but carry a grim prognosis [5]. In the early post-transplant period, mycotic aneurysm of the vascular anastomosis is a very rare but potentially life-threatening complication, mostly caused by *Candida* or *Aspergillus* [6].

3. Challenges in managing anti-rejection drugs during critical illness

The management of immunosuppressive drugs in the ICU setting is based on expert opinion and takes into account the time from transplantation (longer delay being associated with lower risk of acute rejection), baseline graft function, immunological risks, and reason for ICU admission. Discontinuation is considered in patients with drug toxicity [neutropenia, sirolimus-associated pneumonitis, posterior reversible encephalopathy syndrome (PRESS), and thrombotic microangiopathy (TMA)]. In extreme situations, steroids can be used as sole anti-rejection agent. During sepsis, decreasing doses/stopping drugs which might induce neutropenia (antimetabolites and mTOR inhibitors) is advocated by some authors. However, this strategy might lead to a poorly evaluated increase in risk of rejection, even in the context of drug

*Correspondence: michael.darmon@aphp.fr
[1] Medical ICU, Saint-Louis University Hospital, AP-HP, 1 Avenue Claude Vellefaux, 75010 Paris, France
Full author information is available at the end of the article

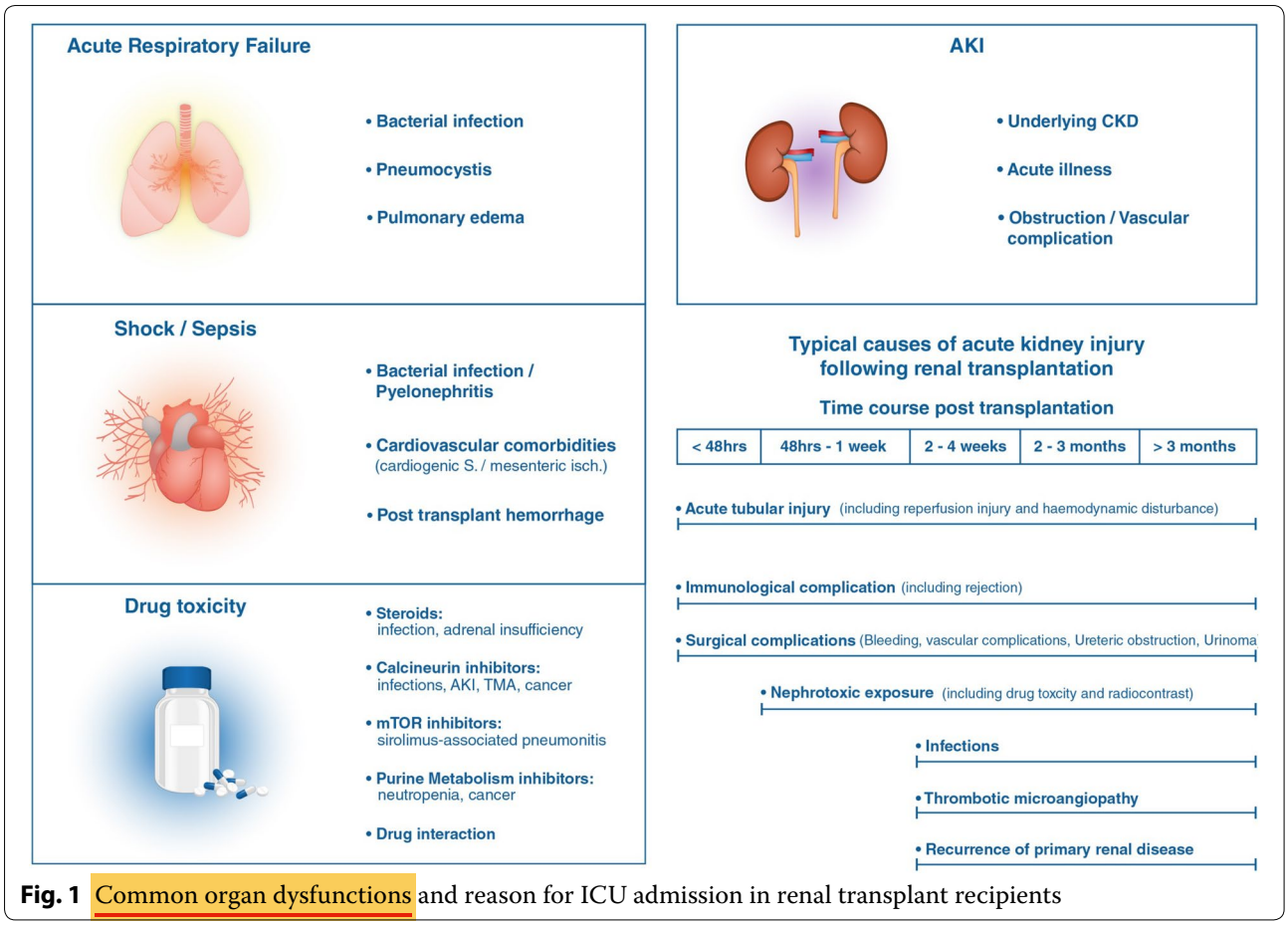

Fig. 1 Common organ dysfunctions and reason for ICU admission in renal transplant recipients

toxicity [7]. Careful attention should be paid to numerous drug interactions (including azole antifungals and macrolide antibiotics), and therapeutic drug monitoring is usually required in ICU patients [8].

4. Preserve vascular access

Vascular access is one of the most important clinical problems in patients with ESRD and arteriovenous fistula (AVF) is considered as the best vascular access for chronic haemodialysis. AVFs have been associated with haemodynamic complications including arterial steal and high-output cardiac failure in which case ligation may have to be discussed with the transplant team. On the other hand, closure or thrombosis of a functioning AVF may accelerate the decline of transplant function and compromise vascular access for potential future long-term dialysis [9]. Post-transplant, vascular access may be challenging because of previous vein thromboses and collateralization whilst at the same time vascular access should be preserved, especially in patients at risk of transplant failure. This includes the avoidance of subclavian lines if possible and the preservation of existing AVFs [10].Femoral venous access on the side of the graft should be avoided whenever possible.

5. Beware of residual long-term complications of chronic kidney disease (CKD)

The long-term complications of CKD including cardiovascular disease and renal bone disease persist following renal transplantation, even if the graft is working well [11, 12]. In fact, cardiovascular disease is the leading cause of mortality accounting for 40–50% of deaths after the first year following renal transplant [12]. The cardiovascular burden of renal transplant patients represents an amalgamation of traditional risk factors, risk factors related to chronic kidney disease (CKD), and factors unique to the transplant population. Post-transplant erythrocytosis is seen in 10–20% of transplant recipients and has been associated with thromboembolic events, too [11].

Most patients with CKD develop hyperparathyroidism and renal bone disease by the time they initiate long-term dialysis [12]. Both persist after transplantation and may exaggerate the risk of osteoporosis during critical illness. Residual renal bone disease also represents a risk factor

for cardiovascular disease especially in patients with a failing renal transplant.

6. Rule out uncommon causes of AKI

Transplant recipients are susceptible to all causes of acute kidney injury (AKI) but the differential diagnosis is wider and includes acute rejection, surgical and urological complications, side effects from immunosuppressive agents, and opportunistic infections [13]. AKI occurs more frequently in patients with lower levels of transplant function and is independently associated with increased risk of transplant failure [13].

Depending on the time course after the transplant, different aetiologies are more common than others (Fig. 1). Drug toxicity is particularly common, either due to inappropriate dosing or drug interactions with calcineurin inhibitors resulting in both high and low serum levels. Recurrence of the underlying primary renal disease may also have to be considered although it is less frequent.

TMA is a serious complication of transplantation. Upshaw–Schulman syndrome or atypical haemolytic uremic syndrome may lead to recurrences in the allografts. De Novo TMA related to calcineurin inhibitors, or less frequently sporadic, represents the overwhelming majority of cases of post-transplant TMA.

7. Be in touch with patient's renal transplant team

The impact of systematic rounds with the transplant team has never been assessed. Care of renal transplant recipients is, however, a specific field; specific complications may occur and practices evolve rapidly. Regular consultation with the transplant team is to be encouraged and may be as beneficial as in other fields of highly specialized management [14].

8. Renal transplantation = limited renal reserve: adjust management accordingly

Renal transplant recipients should be considered as patients with decreased renal reserve. This explains the high susceptibility to AKI and dynamic nature of kidney function [13]. A careful approach including assessment of risks and benefits of potentially nephrotoxic agents is required as in most high risk patients.

9. Consider complications of immunosuppression

A high degree of suspicion should be kept toward common and uncommon complications of anti-rejection drugs. Adrenal insufficiency resulting from steroids calcineurin inhibitor-induced TMA and PRESS, sirolimus-associated pneumonitis, serum sickness or infusion reaction resulting from anti-thymoglobulin or monoclonal antibodies, or neutropenia associated with purine metabolism inhibitors are usual complications if not common ones [15].

10. The best is still to come

Despite the high numbers of renal transplantation worldwide and the frequent need for ICU admission, most of the tips mentioned above are poorly supported by evidence.

There is an urgent need for data in this field ranging from epidemiological data/prognostic assessment studies to high-degree evidence trials. Research validating optimal anti-rejection drug strategies, delineating rate and severity of specific complications and safety profile of anti-rejection drugs in ICU, and studies assessing long-term renal outcome of transplant recipients after ICU are required.

Author details
[1] Medical ICU, Saint-Louis University Hospital, AP-HP, 1 Avenue Claude Vellefaux, 75010 Paris, France. [2] Faculté de Médecine, Université Paris-Diderot, Sorbonne-Paris-Cité, Paris, France. [3] ECSTRA Team, Biostatistics and Clinical Epidemiology, UMR 1153 (Center of Epidemiology and Biostatistics Sorbonne Paris Cité, CRESS), INSERM, Paris, France. [4] Medical Intensive Care Unit, Nantes University Hospital, Nantes, France. [5] University of Nantes, Nantes, France. [6] King's College London, Guy's & St. Thomas' Hospital, London, UK.

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