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Perioperative Care for Kidney Transplant Recipients

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Abstract

Transplantation carries significant mortality benefit compared to dialysis in end-stage kidney disease. Increased perioperative risk, however, results in a higher mortality in the first 3 months post-transplantation compared to remaining on haemodialysis. Consequently, optimal perioperative management is essential. Patients presenting for kidney transplantation require rapid assessment and preparation for theatre to minimise ischaemic times and improve mortality and graft outcomes. This task is often complicated by the presence of multiple medical comorbidities. Furthermore, early complications of hypotension, delayed graft function, renovascular and ureteric surgical complications and rejection render the perioperative phase of transplant challenging for the recipient and for the transplant team. In this chapter, we outline current practices in the assessment and management of kidney transplant recipients during the perioperative period, particularly focusing on their clinical application and the evidence underpinning them.

Keywords: comorbidity, kidney transplantation, perioperative care, risk assessment, treatment outcome

1. Introduction

Non-communicable diseases now account for 75% of deaths globally, with chronic kidney disease (CKD) rapidly rising up the ranks as a cause of death, reaching eleventh on the list in 2016 [1]. The estimated global crude prevalence of CKD in 2016 was 275.9 million cases associated with a crude mortality of 1.2 million [2].

As CKD patients' renal function declines, mortality rises to an estimated lifespan of 8 years for patients on dialysis of 40–44 years of age and 4.5 years to patients 60–64 years of age. Improvements in dialysis therapy have been accompanied by a decline in mortality rate [3]. Despite this, the long-term mortality on dialysis remains significantly inferior to that following kidney transplantation.

A systematic review in 2011 identified 110 studies including nearly 2 million patients with transplantation conferring a mortality advantage over dialysis. Only studies with follow-up periods <3 months favoured dialysis, attributed largely to perioperative complications and higher immunosuppression post-transplantation [4]. Accordingly, transplant and dialysis registry studies have confirmed increased mortality in transplanted patients compared to dialysis at 3 months (HR 2.0, 1.5–2.7, $p < 0.001$) with reversal at 6 months (HR 0.27, 0.16–0.47, $p < 0.001$) with 80% reduction in mortality following transplantation compared to dialysis at 12 months [5].

The increase in mortality associated with kidney transplantation highlights the need for optimal perioperative management to minimise the risks and maximise the benefits associated with transplantation. This chapter focuses on the principles and evidence of perioperative management of transplant patients.

2. Pre-operative transplant management

2.1 Initial clinical assessment pre-transplant

Patients on the kidney transplant waiting list have usually undergone a thorough medical and surgical assessment prior to listing to identify significant comorbidities that would preclude transplantation. Optimisation of cardiovascular comorbidities, including diabetes mellitus (DM) and hypertension, is important not only for prevention of cardiovascular disease but also for avoidance of hypertensive and diabetic damage to the transplanted graft. Nevertheless, at the point that an intended recipient is admitted to hospital for transplantation, a thorough reassessment is important to identify any new medical issues, as well as to ensure that the recipient is sufficiently medically stable for a general anaesthetic and surgery.

On arrival at the transplanting hospital, bloods are collected with a request for the laboratory to process these urgently (**Table 1**). In addition, a chest radiograph and ECG are performed.

While these investigations are being processed, a medical history and examination should be undertaken with the patient with the aim of documenting:

- Any new medical comorbidities, in particular symptoms suggesting the development of vascular disease (angina, claudication, peripheral ulceration), malignancy (unexpected weight loss, new mass or lymphadenopathy) or active infection (fever, constitutional symptoms).
- Signs or symptoms of fluid overload, with assessment of the patient's weight in relation to their recent clinic weights (or current target weight if on dialysis).
- The patient's usual daily urine volume.

The presence of potential new medical comorbidities should prompt review of suitability for, and safety of proceeding with transplantation. The development of ischaemic heart disease, vascular disease, malignancy or active infection would preclude proceeding with transplantation.

Blood tests:
Renal and liver chemistry including phosphate, calcium, and LDH
Full blood count
Coagulation profile
Blood group + hold
Serum for tissue typing investigations
Serology for CMV, EBV, VZV, toxoplasma hepatitis B, hepatitis C, HIV
Pregnancy test as appropriate
Urine culture unless anuric
Chest radiograph
Electrocardiogram

Table 1.
Usual investigations for a patient presenting for kidney transplant.

A key decision during the assessment is whether a patient requires dialysis prior to transplantation. Similarly, donor factors associated with a high probability of delayed graft function (e.g., donation after circulatory death [DCD] kidney, prolonged anticipated cold ischaemic time) require a lower threshold for dialysis. Significant hyperkalaemia (a typical threshold may be a serum potassium concentration > 5.5 mmol/L) or fluid overload should prompt urgent dialysis prior to transplantation. In general, it is better to control fluid and electrolyte abnormalities effectively with dialysis pre-operatively rather than to attempt dialysis in a less stable patient post-surgery. Due to tissue damage and intraoperative bleeding, hyperkalaemia may worsen post-operatively. If haemodialysis is required prior to transplantation, patients are usually slightly above their target weight with the aim of avoiding intraoperative hypotension. Minimal or no heparin should be administered during dialysis to minimise the risk of perioperative haemorrhage.

2.2 Management of pre-existing medication

Patients with advanced kidney disease are often on multiple medications, many of which can be safely discontinued at the time of transplantation, including most antihypertensive medication, phosphate binders, cinacalcet, and erythropoiesis-stimulating agents. However, some medications should usually be continued as follows:

- Active vitamin D compounds in patients post-parathyroidectomy are usually continued. Calcium levels post-transplant follow a biphasic pattern with early decline in the post-operative week without supplementation. The protective effect of raised PTH is absent in patients post-parathyroidectomy, thereby risking precipitating severe hypocalcaemia if such patients are not supplemented with active vitamin D compounds (calcitriol and alfacalcidol) [6].
- Beta blockers are usually not stopped abruptly in the perioperative period due to concerns that this may lead to rebound tachycardia and increase the risk of mortality [7]. However, it may be reasonable to reduce the dose and/or convert patients to a beta blocker with a shorter duration of action (e.g., metoprolol) to reduce the risk of hypotension in the post-operative period.
- Statins, although generally safe, can predispose to rhabdomyolysis if used in conjunction with CYP450-3A4 inhibitors [8]. We suggest ceasing statins until outside the perioperative period.
- Antiplatelet therapy with aspirin is usually continued perioperatively, and many transplant centres routinely prescribe aspirin to recipients who are not already receiving this agent to reduce the risk of transplant vessel thrombosis, although this has a poor evidence base [9]. Dual antiplatelet therapy with aspirin plus agents, such as platelet P2Y₁₂ receptor inhibitors (e.g., clopidogrel and ticagrelor), would usually be considered a contraindication to transplantation, both because of the increased risk of bleeding and the frequent association of significant vascular disease in patients requiring this combination.
- Erythropoiesis stimulating agents (ESA) may be continued on the basis of some studies identifying anaemia as an independent predictor of mortality in the intermediate post-transplant period [10]. There are, however, no studies showing benefits of continued ESA therapy or defining optimal haemoglobin

targets [11]. European Best Practices Guidelines for anaemia management recommend that ESA not be ceased in patients undergoing surgery, but no specific recommendations are made regarding transplantation [12].

Potential transplant recipients who are anti-coagulated with warfarin require urgent reversal of anticoagulation prior to surgery. There are often local protocols for warfarin reversal, but a typical approach would be 1–2 mg oral vitamin K administered as soon as the patient presents to hospital, followed by infusion of either fresh frozen plasma or a prothrombin complex concentrate, such as prothrombinex-VF, depending on the INR [13]. Whether intravenous heparin is required post-operatively will depend on the strength of the indication for anti-coagulation, the degree of post-operative haemorrhage, and a decision regarding this should be made in consultation with the transplant surgeons. Where the risk of thrombosis is not excessively high, it is preferable to defer recommencing warfarin until at least 4 weeks post-transplant due to the frequent requirement for a transplant biopsy during this period.

Although non-vitamin K oral anticoagulants (NOACs) are currently not used routinely in end-stage kidney disease (ESKD) patients, indications for their use have been expanding into patients with more severe renal dysfunction. Nonetheless, NOACs should be avoided in ESKD patients on the active transplant list.

2.3 Pre-operative management of diabetes and hyperglycaemia

In Australia, over 23% of patients who are listed for a deceased donor transplant have diabetes [ANZDATA 2016]. The presence of autonomic neuropathy should be noted, as this may help predict haemodynamic instability and risk for graft hypoperfusion post-operatively. Similarly, gastroparesis may have important implications for immunosuppressive drug absorption if severe and retinopathy may complicate post-operative medication management if visual acuity is substantially reduced.

After admission for kidney transplantation, patients with type 2 diabetes should omit hypoglycaemic medication during the period of preoperative fasting, with regular capillary glucose monitoring performed every 1–2 h. Hypoglycaemia is managed with intravenous dextrose. If significant hyperglycaemia develops, an intravenous insulin infusion is the safest method to control glucose levels until the recipient is able to eat post-operatively. Patients with type 1 diabetes should commence an intravenous insulin infusion after admission to hospital to prevent the development of ketoacidosis.

2.4 Immunosuppression

After the decision has been made to proceed with a transplant, an immunosuppression regimen is selected. This regimen is usually initiated before the recipient goes to theatre so that immune function is attenuated prior to donor antigen exposure after reperfusion of the allograft. The choice of immunosuppressive regimen is individualised depending on the circumstances of the recipient and, in particular, the perception of immunological risk (**Table 2**).

Most patients undergoing kidney transplantation will receive induction immunosuppression, typically consisting of intravenous methylprednisolone combined with either a monoclonal antibody targeting CD25 (the high affinity α -chain of the IL-2 receptor) [14], such as basiliximab, or a lymphocyte-depleting antibody (such as thymoglobulin [15] or alemtuzumab [16–18]). Induction therapy is combined with ongoing maintenance immunosuppressive therapy, typically consisting of

Very low risk	Identical twin donor
Low risk	HLA-identical sibling donor, no DSA
Average risk	HLA-mismatched donor, no DSA
High risk	HLA-mismatched donor, detectable DSA, negative cross-match or ABO-incompatible donor following desensitisation
Very high risk	HLA-mismatched donor, detectable DSA, positive cross-match

DSA, donor-specific antibody.

Table 2.
Immunological risk assessment for kidney transplantation.

three immunosuppressive agents [19]. The most commonly prescribed combination in Australia and the USA currently is tacrolimus, mycophenolate and prednisolone [20, 21]. ABO-incompatible transplants as well transplants where there is a pre-transplant DSA requiring plasma-exchange prior to transplantation are outside the scope of this chapter. Similarly, special circumstances including steroid-free immunosuppression are not discussed here.

2.5 Prophylactic medications

The administration of immunosuppression needs to be balanced against the increased risk of infection. With ESKD patients being routinely subjected to hospital environments, additional consideration should be given for prophylaxis in patients colonised with multi-resistant organisms. Patients with prior known serious or recurrent infections should be evaluated carefully and assessed for recurrence and presence of occult infection prior to proceeding with transplantation. In addition, gastro-protection, infection and VTE prophylaxis is charted (**Table 3**).

Despite some controversy for the use of surgical antibiotic prophylaxis, routine prescribing is common, generally following local practices and guidelines [22]. No consensus currently exists for optimal antibacterial prophylaxis, but the general approach is to minimise dose and duration of administration to prevent emergence of antibiotic resistance [23]. A Cochrane systematic review is currently being undertaken to evaluate the evidence for antibiotic prophylaxis in preventing postsurgical site infections in solid organ transplant recipients [24]. Where there are risk factors that may predispose the recipient to bacterial transmission from the donor, such as treated bacteraemia or urine infection, the duration of antibiotic prophylaxis is adapted to cover the appropriate organisms.

Prior to introduction of prophylaxis, PJP was an important cause of severe pneumonia, associated with an estimated 29–50% mortality [25]. Since the widespread use of co-trimoxazole prophylaxis, the incidence of PJP has declined to an estimated incidence of 0.8 case per 1000 person at 1-year post-transplant [26]. Co-trimoxazole prophylaxis is routinely prescribed in most transplant centres for 6–12 months post-transplant and many centres now advocate for continued prophylaxis following PJP outbreaks [27]. If co-trimoxazole is contraindicated, alternative agents are inhaled pentamidine isethionate or oral dapsone.

Prophylaxis against urinary tract infections (UTIs) is usually provided by the co-trimoxazole therapy administered for PJP prophylaxis. On the basis of limited evidence, perioperative UTI prophylaxis is recommended and in the case of co-trimoxazole intolerance, another agent could be chosen [11].

Systemic anti-fungal prophylaxis is not routinely administered to kidney transplant recipients [28]. However, oral nystatin or amphotericin is frequently

Gastro-protection	Ranitidine (or PPI) therapy while on high dose steroids
Bacterial prophylaxis	Perioperative antibiotic therapy prescribed based on local guidelines and adapted for recipient multi-resistant organism colonization or potential donor infection
PJP prophylaxis	6–12 months co-trimoxazole. Consider lifelong therapy
UTI prophylaxis	6 months co-trimoxazole
Oropharyngeal candidiasis prophylaxis	Oral nystatin or amphotericin for duration of admission. Optimal duration uncertain
Systemic fungal prophylaxis	Not generally prescribed due to low incidence of invasive fungal infection
CMV prophylaxis	Oral valganciclovir. Duration depending on donor and recipient serostatus—see Table 4
VTE prophylaxis	Unfractionated heparin and mechanical calf compressors unless contraindicated until patient mobile

Table 3.
Perioperative prophylaxis.

prescribed in the early post-operative period to reduce the risk of oropharyngeal candida infection [11]. The optimal duration of therapy is unknown, largely due to low event rates, but a typical approach would be therapy for the first month post-transplant [29].

Previous cytomegalovirus (CMV) infection is common, with a seroprevalence of up to 75% in transplant recipients [30]. The risk of developing CMV viraemia post-transplant depends on the serostatus of both donor and recipient as well as the induction immunosuppression agent (**Table 4**). The highest risk CMV infection is seen in seronegative recipients of a transplant from a seropositive donor, and is increased in patients treated with T cell depleting agents [31].

Several antiviral agents have been shown to reduce the risk of CMV infection (with the added benefit of also providing prophylaxis against herpes simplex and herpes zoster reactivation) in transplant recipients, including intravenous ganciclovir and oral acyclovir and valganciclovir, irrespective of donor status and induction immunosuppressive regimen [32]. Unfortunately, viral prophylaxis has shown little benefit in reducing the incidence of EBV-related PTLD [33]. Sustained prophylaxis benefit is observed with longer duration therapy (>3 months) with the main adverse effects being leukopenia with longer therapy duration [32]. Due to the observed benefit in reducing the incidence of CMV disease and cost effectiveness, 6 months antiviral prophylaxis is generally prescribed in high-risk CMV D+R– pairs [34]. An accepted alternative approach to universal prophylaxis is to monitor for CMV viraemia regularly post-transplant and initiate pre-emptive therapy should significant viraemia develop [32, 35].

Due to the gastro-erosive effects of prednisolone, ranitidine 150 mg twice daily for gastro-protection is usually recommended, noting the potential risk of interstitial nephritis and chronic kidney disease with proton-pump inhibitors (PPIs) [36, 37]. If ranitidine is contraindicated or ineffective, use of low dose PPIs as second line is recommended.

Deep venous thrombosis (DVT) has not been extensively evaluated in the literature. Kidney transplantation is categorised as a moderate risk group of patients for development of thromboprophylaxis conferring an estimated risk of DVT of 6% [38]. Limited studies have suggested the incidence to be lower with mechanical thromboprophylaxis alone [39]. Despite the lack of evidence, thromboprophylaxis

CMV D–R–	Usually no prophylaxis
CMV D+R+ or D–R+	Valganciclovir for 3 months
CMV D+R–	Valganciclovir for 6 months

D, donor serostatus; R, recipient serostatus.

Table 4.
Prophylaxis for cytomegalovirus.

is generally initiated immediately post-operatively in the absence of contraindications or concerns of active haemorrhage. A combination of unfractionated heparin prophylaxis and mechanical calf compression is used, following local guidelines.

3. Intra-operative and immediate post-operative considerations

Although surgical and anaesthetic approaches and considerations are outside the scope of this chapter, intra-operative events have significant impacts on patient and graft outcomes. Review and documentation of intra-operative and immediate post-operative factors can help predict and guide subsequent clinical course (**Table 5**).

Any surgical complications or anatomical challenges (notably presence of multiple renal arteries, difficult bench surgery and renal capsule tear) should be communicated by the transplant surgeons as these can help predict perioperative complications. If available, intraoperative Doppler assessments should be documented to confirm adequate post-perfusion flow parameters in the transplanted kidney. Where there is perioperative concern regarding allograft perfusion, or early unexpected oligoanuria, an early duplex ultrasound may be requested to confirm flow in the transplant vessels.

Significant blood loss, requirement of inotropic support and intra-operative haemodynamic instability indicate suboptimal organ perfusion and are risk factors for delayed graft function (Section 5.4). Central venous line is placed at the time of surgery, and central venous pressure (CVP) is still used intra-operatively and in the immediate post-operative period. It is important to acknowledge controversies in absolute CVP targets, with studies advocating improved outcomes with high CVP (10–15 mmHg) targets at reperfusion [40, 41] and others observing increased kidney dysfunction with CVP >11 mmHg [42]. In general, intra-operative CVP trends can inform fluid management, but should not form the basis of a fluid management strategy due to inconsistent correlation with intravascular volumes [43].

Despite preoperative optimization, hyperkalaemia is common post-operatively due to tissue trauma and resorption of intra-abdominal blood. The presence of

Donor graft	Graft anatomy, backbench surgery, renal capsule tear
Graft perfusion	Appearance on cross-clamp release. Intraoperative Dopplers
Haemodynamics	Blood pressure profile, CVP, need for inotropic support, blood loss volume
Fluid balance	Volume of intravenous fluid administration during procedure, urine output
Biochemistry	Intraoperative insulin dextrose. Post-operative renal chemistry panel including urea, creatinine and potassium

Assessment of listed factors helps guide and predict perioperative management

Table 5.
Post-operative documentation.

hyperkalaemia >6 mmol/L in the immediate post-operative period should prompt consideration of dialysis depending on the urine output. If graft urine output (with native residual renal function deducted) is >100 mL/h, it may be reasonable to manage the patient medically with insulin-dextrose infusion and loop diuretics. It should also be noted that intraoperative use of insulin-dextrose often results in rebound hyperkalaemia postoperatively.

4. Perioperative fluid management

Optimal fluid management strategy is contentious, although there is good evidence that fluid loading to maintain cardiac output and optimise renal perfusion, improves outcomes [44]. Intra-operative blood losses and fluid balance can be estimated through discussion with the transplant surgeon and anaesthetist and review of anaesthetic chart (Section 3). Currently, no studies on fluid management in the perioperative phase of renal transplantation exist to guide practice. A recent randomised trial demonstrated non-inferiority of a non-restrictive perioperative intravenous fluid strategy in high-risk abdominal surgery in terms of disability-free survival. Furthermore, the restrictive fluid strategy was associated with increased rates of acute kidney injury (8.6 vs. 5.0%, $p < 0.001$) [45]. Although generalizability to renal transplantation is uncertain, a restrictive fluid strategy should be avoided.

A common strategy for managing post-operative fluid replacement in the hours after kidney transplantation is to replace the urine output from the previous hour plus 30 mL to account for insensible losses. A loop diuretic and/or mannitol is sometimes administered during the transplant surgery to precipitate a diuresis, decreasing requirement for dialysis, but has not been shown to improve graft outcomes [46].

Frequent clinical assessment of the recipient's fluid status, including the jugular venous pressure, heart rate, blood pressure and urine output, is important to ensure adequate fluid replacement and to avoid volume overload. Traditional parameters and clinical assessment of fluid status, however, may be unreliable due to compromised homeostatic mechanisms in ESKD and the post-ischaemic transplanted kidney [47]. As soon as it is feasible post-transplant, recipients should be weighed with comparison to their preoperative weight as an objective guide to fluid status.

There is currently no evidence supporting one type of intravenous fluid therapy over another, although a pragmatic, registry-based, multi-centre, double-blind, randomised controlled trial comparing balanced crystalloid solution (PlasmaLyte) with 0.9% saline on the incidence of delayed graft function in 800 adults and children with end-stage kidney disease (ESKD) receiving a deceased donor kidney transplant in Australia and New Zealand is currently underway (ACTRN12617000358347).

A good urine output in the early post-transplant period is a helpful indicator of early graft function, although it may not be possible to differentiate allograft urine output from native urine output in recipients who have significant residual renal function. Oligoanuria may be an indicator of delayed graft function or a harbinger of an early complication, especially if the urine output was good initially (Section 5.4). An urgent ultrasound is a useful investigation to assess perfusion of the allograft at the bedside and to check for evidence of ureteric or vascular complications. The presence of hypoechoic fluid collections may indicate haemorrhage or urinary anastomotic leak (Section 5).

Blood tests to monitor serum creatinine and electrolytes are collected immediately post-transplant and then 6–12 h to monitor renal function and exclude

hyperkalaemia. Some recipients may develop a significant diuresis, passing over a litre of urine per hour, and in this situation, frequent monitoring of blood tests 4–6 h is recommended to avoid over or under replacement of electrolytes.

5. Early complications

Complications in the perioperative phase are diverse, reflecting pre-existing transplant recipient comorbidities as well as individual surgical challenges. With the potential for there to be few symptoms from the denervated graft, most centres follow a protocol of investigations for early identification of post-transplant complications (Table 6).

Generally, an early renal transplant duplex ultrasound can identify vascular or anastomotic complications including renal vessel thrombosis or compression. The resistive index (RI) (measured peak systolic velocity—end diastolic velocity/peak systolic velocity), normally, between 0.60 and 0.80, with levels >0.8 suggesting abnormal perfusion of the allograft, is a widely reported measure of allograft perfusion for duplex scans but does not seem to correlate well with renal histology [48]. A positive correlation has been reported between RI and recipient mortality, and the strongest predictor of an elevated RI was recipient age, suggesting that RI may be an indicator of recipient vascular disease [48]. Consequently, although the RI is commonly reported, clinicians need to be aware of its limitations.

Similarly, nuclear medicine imaging, such as a mercaptoacetyltriglycine (MAG3) or diethylenetriamine pentaacetic acid (DTPA) renogram, can assist in the assessment of allograft perfusion and early graft function as well as identify a ureteric anastomotic leak. Radionuclide scanning may give an indication of the likely duration of delayed graft function [49, 50].

5.1 Haematological, biochemical and metabolic derangement

Electrolyte abnormalities are a frequent occurrence in the early post-transplant period. Perioperative hyperkalaemia is often followed by hypokalaemia due to diuretics and polyuria combined with large volume IV fluid replacement. Hypomagnesaemia is exacerbated by the tubular effects of CNI therapy and is associated with an increased risk of post-transplant diabetes [51, 52]. Hypophosphatemia is almost universal as a consequence of elevated FGF23 and PTH levels [53, 54]. To reduce the chance of arrhythmias, intravenous electrolyte replacement should target potassium levels in the normal range (3.5–5 mmol/L) and a serum magnesium >0.4 mmol/L. Hypophosphatemia is not usually associated with adverse clinical sequelae, but if severe (<0.4 mmol/L) can also be managed with intravenous replacement. Many transplant recipients require ongoing oral replacement of potassium, magnesium and occasionally phosphate in the first few weeks post-transplant, although this may be limited by gastrointestinal adverse effects.

Blood tests:

Twice daily full blood count and serum biochemistry

Alternate day CNI levels

Daily capillary glucose levels—if abnormal, manage as diabetes mellitus

Post-operative chest radiograph

Duplex ultrasound imaging, usually at days 2–4 post-transplant

MAG3/DTPA renogram as indicated by clinical progress

Table 6.
Common post-operative surveillance investigations.

Myelosuppression is commonly observed in post-transplant patients receiving immunosuppressive therapy. Myeloid, lymphoid and erythroid lineages can separately be affected in combination. Investigations focus on identification of the underlying cause for the haematological abnormality, and blood films are often helpful.

Post-operative anaemia is observed in around 40% of kidney transplant recipients due to erythropoietin deficiency, pre-transplant anaemia and intra-operative blood loss [55]. Initial management should focus ruling out haemorrhage as discussed in Section 5.2. The administration of an erythropoiesis-stimulating agent may be appropriate in recipients with poor initial graft function [11].

Lymphopenia and neutropenia are also common after transplantation, typically as a consequence of the medication-related bone marrow suppression associated with anti-proliferative agents (mycophenolate and azathioprine), mTOR inhibitors (sirolimus and everolimus) and antiviral agents such as valganciclovir for CMV prophylaxis [56–58]. G-CSF is typically administered if the absolute neutrophil count falls below $1000/\mu\text{L}$ ($1.0 \times 10^9/\text{L}$) to try to avoid a severe neutropenia (neutrophil count $<500/\mu\text{L}$, or $< 0.5 \times 10^9/\text{L}$), which is associated with a significant risk of severe infections and requires reverse barrier nursing [59]. Alternative causes of neutropenia should also be considered including parvovirus B12 and CMV infection [60].

Thrombocytopenia is comparatively less common, often occurring in conjunction with leukopenia due to bone marrow suppression as previously discussed. More severe thrombocytopenia is a risk factor for bleeding, and platelet transfusion may be necessary if invasive procedures, such as a renal biopsy, are required and the platelet count is $<50 \times 10^9/\text{L}$ [61]. An important consideration, if thrombocytopenia is observed post-transplant, is to look for any other evidence of thrombotic microangiopathy (TMA, **Table 7**) [62]. TMA occurring after transplant may be due to recurrence of primary haemolytic uraemic syndrome, or a de novo problem. Many triggers for de novo TMA post-transplant have been reported, including medication (CNI therapy, particularly in combination with mTOR inhibitors; valganciclovir), and infections (CMV, parvovirus B19) have all been associated with TMA with the potential for graft damage and kidney injury [63–65].

The post-operative stress response, combined with induction corticosteroid and cyclosporine or tacrolimus therapy, can result in significant perioperative hyperglycaemia even in patients who do not have pre-existing diabetes, with a reported incidence as high as 80–90% in some studies [67, 68] with post-transplant diabetes persisting in 10–45% depending on the definition used [69–73]. Hyperglycaemia is also associated with rejection in the perioperative period and in the long term carries adverse metabolic outcomes [74]. It is, therefore, important to monitor capillary glucose levels in all patients after kidney transplantation. Due to the contributions of immunosuppressive medications, and depending on other metabolic risk factors (pre-existing impaired glucose tolerance or diabetes, ethnicity, age and obesity)

-
- Thrombocytopenia—platelet count $<150 \times 10^9/\text{L}$
 - Microangiopathic haemolytic anaemia (MAHA)—haemoglobin <10 g/dL with evidence of red cell fragments on blood film (schistocytes)
 - Elevated lactate dehydrogenase
 - Elevated reticulocyte count
 - Elevated bilirubin
 - Reduced haptoglobin
-

Table 7.
Features of thrombotic microangiopathy on laboratory tests [66].

and immune risk, immunotherapy should be individualised [11]. A detailed discussion of the management of post-transplant hyperglycaemia and diabetes is beyond the scope of this chapter.

5.2 Hypotension: haemorrhage, sepsis and cardiac dysfunction

Perioperative hypotension is common and may reflect inadequate intravascular volume, vasoplegia induced by anaesthetic or analgaesic agents or cardiac dysfunction. Management involves perioperative fluid status optimization with judicious administration of fluid boluses while excluding alternative causes of hypotension including haemorrhage, sepsis and cardiac dysfunction. Recipients with persistent hypotension, despite what appears to be adequate fluid replacement, may require temporary inotropic support. Hypovolaemia, even in the absence of hypotension, increases the risk of delayed graft function resulting in worse graft outcomes [75, 76]. As coronary artery disease is common in patients with ESKD, ruling out ischaemic myocardial damage with ECG review and cardiac enzyme assay measurements is essential (Section 5.3).

Haemorrhage is common in the early period of kidney transplantation, frequently occurring within 48 h of surgery with a reported incidence of 15% [77]. Apart from hypotension, bleeding may manifest clinically with increasing surgical drain output, pain or swelling at the site of the transplant or a falling haemoglobin on serial blood tests. Risk factors for perioperative bleeding include difficult bench surgery, uraemic platelet dysfunction and administration of antiplatelet agents or heparin (either as thromboprophylaxis or during haemodialysis). In a retrospective analysis, difficult bench surgery was identified as the most significant risk factor for post-operative haemorrhage with a 4-fold increased risk. The use of antiplatelet drugs pre-transplant conferred a 2-fold increased risk. Additionally, dialysis vintage was also a risk factor, and each year on dialysis was associated with a 2% increased bleeding risk [77].

In the early post-operative phase, clinical features suggestive of haemorrhage should prompt urgent review of haematology profile, and consideration of imaging in liaison with the transplant surgeon. Peri-nephric hematomas may be identified on ultrasound, but deep or retroperitoneal haemorrhage may be difficult to identify requiring computed tomography. The development of a peri-nephric haematoma may lead to allograft compression, which if significant, may impair graft perfusion with increased diastolic pressures despite normal, or near normal, arcuate artery blood flow indices.

Management of perioperative bleeding requires administration of crystalloid fluids together with judicious transfusion of packed red cells to maintain adequate haemodynamic and haemoglobin targets. Transfusions should be minimised as much as possible, as perioperative blood transfusion leads to recipient sensitization and can increase the likelihood of de novo DSA formation [78]. The decision to proceed to surgical drainage should be individualised, following discussion with the transplant surgeon. The presence of a large haematoma, ongoing haemodynamic instability or features suggesting compression of the allograft, would usually lead to surgical re-exploration.

Sepsis should also be considered in the setting of unexplained hypotension. A high index of suspicion for infection should be maintained at all times since transplant recipients may not develop a fever, leukocytosis or raised inflammatory markers because of their immunosuppressed state (Section 5.7).

5.3 Cardiovascular complications

Due to the significant cardiovascular disease burden and risk associated with chronic kidney disease, cardiovascular complications post-renal transplantation are

common. In a retrospective cohort study, the most common perioperative cardiovascular complication was arrhythmia (53%), followed by myocardial infarction (26.4%) with congestive heart failure being relatively rare (1%) [79, 80].

Hypertension, although often overlooked as a perioperative complication, is common, occurring in 50–70% of recipients. It is likely driven by multiple factors including pre-existing hypertension associated with ESKD, cessation of previous antihypertensive therapy at the time of transplantation, iatrogenic fluid administration to optimise allograft perfusion, calcineurin inhibitor therapy (CNI) and corticosteroid-related fluid retention [81]. Modification of fluid status, diuretic therapy and administration of dihydropyridine calcium channel blockers are common initial strategies used to control BP in the early post-transplant period. The non-dihydropyridine agents (diltiazem and verapamil) may be used, but have significant interactions with CNI (cyclosporine > tacrolimus) increasing CNI exposure. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are usually avoided in the perioperative period to due to their potential to increase creatinine levels but can be introduced once allograft function has stabilised with appropriate monitoring of creatinine and potassium levels.

Despite pre-transplant screening for ischaemic heart disease, acute coronary syndromes (ACS) are still seen in the peri-transplant period, an indication of the limited sensitivity of non-invasive cardiac testing to detect clinically significant coronary disease in the ESKD population [82, 83]. ACS are a difficult complication to manage in the perioperative setting due to competing clinical priorities, and the potential benefits of antiplatelet and anticoagulant therapy need to be balanced against the risk of bleeding. Evaluation of the impact of the infarct on ventricular function can be assessed by echocardiography. Decisions on the optimal management including the potential need for angiography should be discussed with the local cardiology team.

Pre-existing congestive cardiac failure should be identified pre-transplantation and optimised through high-quality dialysis to control uraemia and volume overload as well as medical therapy. Large fluctuations in blood pressure and inter-dialytic weight gain will adversely affect myocardial function through cardiomyopathic remodelling and vasoactive humoral-mediated increases in vascular tone and damage. It is important to acknowledge controversies surrounding optimal blood pressure targets in dialysis patients and to individualise both blood pressure target and pharmacological hypertensive therapy [84, 85].

5.4 Delayed graft function

Delayed graft function (DGF) is a form of acute kidney injury and is usually defined as the need for dialysis post-transplant. DGF is associated with a higher incidence of acute rejection as well as poorer allograft survival, with a reported 40% greater risk of allograft loss and higher mean serum creatinine concentration [86, 87]. The reported frequency varies significantly (from 2 to 50%) due to heterogeneity of recipient and donor factors and definition of the event [75]. In Australia and New Zealand, nephrologist reported DGF is present in 19.5% of cadaveric renal transplants [ANZDATA 1997–2014].

Post-operative oliguria, failure of improvement of serum creatinine or the need for dialysis should prompt investigations to identify reversible causes of acute kidney injury, including assessment of risk factors for ATN, recipient hypotension or hypovolaemia, presence of post-surgical vascular or urological complications and rejection. In addition to a review of fluid status, haemodynamic parameters and the timing of a decrease in urine output, the following testing should be considered:

- Repeat serum biochemistry and haematology profile to rule out pre-renal kidney injury from anaemia and sepsis, taking account of haemoglobin and haematocrit fluctuations with fluid status dilution and unpredictable inflammatory response in the context of immunosuppression.
- Repeat CNI trough levels and review of CNI dosing and trends. These are nephrotoxic and may necessitate adjustment depending on the immune risk of the transplanted patient.
- Ultrasound duplex scan to rule out renovascular pathology. This also allows exclusion of peri-nephric collections and obstructive uropathy.
- Functional nuclear medical imaging, such as a MAG3, scan will allow assessment of perfusion, graft tracer uptake, and excretion.
- A renal biopsy is usually undertaken if DGF persists at day 5 post-transplant to rule out rejection, and is repeated weekly until there are signs of improving allograft function.

It is also helpful to consider risk factors associated with DGF in order to risk stratify and anticipate the clinical course of the transplanted patient (**Table 8**) [75].

In the setting of DGF, ongoing dialysis is often required. In haemodialysis patients, every effort should be made to preserve haemodialysis access. If haemodialysis is delivered through a central vascular catheter, this access should be preserved for this purpose alone and additional central access obtained as needed. If the peritoneum is breached in a peritoneal dialysis patient, alternative access for dialysis needs to be considered as peritoneal dialysis is less likely to be successful.

Depending on the immunological risk of the patient, in the presence of DGF, a reduction in target tacrolimus levels can be contemplated. Many transplant centres target a tacrolimus level 8–10 µg/L in the peri-transplantation period. Provided the patient is not considered high immunological risk, reduction of the target range could be considered. The use of thymoglobulin in the setting of DGF is controversial in the absence of immunological risk factors advocating its use as an induction agent [15].

Risk factor	Relative impact
Donation after circulatory death	2× higher rate of ATN. No difference in outcome at 1 year
Donor on inotropes	Early function 58% (vs. 83%). 1-year survival 73% (vs. 91%)
Cold ischemia time	23% increase risk of DGF for every 6 h
Donor age > 55y	2× higher rate of DGF
Other donor factors	Poor reperfusion, death from stroke, presence of AKI associated with increased risk
Higher PRA%	Associated higher risk of requiring dialysis post-transplant
Recipient hypovolaemia	Lower pre-operative DBP, intra-operative albumin requirement and pre-operative haemodialysis with UF
Dialysis modality	Higher rate of DGF in haemodialysis vs. peritoneal dialysis
Special circumstances	Thrombophilia, previous transplant

Adapted from Perico et al. [75].

Table 8.
 Risk factors for delayed graft function.

5.5 Renal vascular complication

In transplant recipients who have established a good urine output post-operatively, the sudden development of oliguria or anuria should prompt a review of urinary catheter patency as well as raise the possibility of transplant vessel pathology. Early vascular pathology may be caused by structural or anatomical factors such as vessel kinking, anatomically disadvantageous configurations putting traction on the recipient vessels or thrombosis. Distinguishing between the various pathologies can be challenging clinically, with reliance on duplex ultrasound imaging and knowledge of donor vascular pathology through collaboration with transplant surgeons.

Renal transplant artery or vein thrombosis is a serious, although fortunately uncommon peri-transplant complication, with an incidence of 2–3%, classically occurring in the first week post-transplant [77]. Clinical features of transplant artery thrombosis are typically limited to the sudden onset of oligoanuria, while transplant vein thrombosis may cause allograft swelling, pain and frank haematuria in addition. Predisposing risk factors are decreased perfusion pressures and hypotension as well as donor factors—difficult bench surgery, multiple vessels, prolonged cold ischaemia time and vessel atherosclerosis [77, 88]. Rarer recipient risk factors, when present, can dramatically increase the risk of thrombosis, including in the transplant vessels. Recipients with thrombophilia, notably factor V Leiden mutation or anti-phospholipid antibodies, have been associated with higher risk (2.87 increased risk in one study) of adverse graft outcomes [89, 90]. Diagnosis of transplant vessel pathology may be obtained by urgent renal duplex ultrasonography; however, the abrupt onset of anuria in the early post-operative period is an indication for urgent surgical review and consideration of surgical re-exploration, due to the very short window after transplant arterial thrombosis before irretrievable graft loss occurs.

Renal transplant artery stenosis tends to be a later complication but can occasionally manifest in the perioperative period. The classical clinical features associated with stenosis of the transplant artery are hypertension, allograft dysfunction and fluid overload due to salt and water retention. Risk factors for early transplant artery stenosis tend to be donor related with atherosclerotic vessels or difficult bench surgery [77]. An association with acute rejection has also been described [91]. Diagnosis is by duplex scan showing increased velocity across the anastomotic sites and a flow differential between the aorta and transplant artery.

Intermittent vessel kinking caused by allograft nephroptosis can be diagnostically challenging due to the positional nature of the pathology [92]. Duplex scans may be non-diagnostic, and performing imaging in a non-prone position may assist in the diagnosis of positional vessel compression or kinking, and CT angiography may provide additional diagnostic information in this situation.

5.6 Renal ureteric complications

Ureteric pathology is more common than vascular pathology, but rarely affects graft survival [93]. The most common early urological complication is a urine leak with an estimated incidence of 8%, followed by ureteric stenoses with a similar incidence occurring later in the transplant course [77, 94]. Other complications of vesicoureteric reflux and urolithiasis are uncommon [95].

Ureteric leaks, like vascular pathology, typically occur in first few weeks post-transplant and may present with localised pain or swelling at the site of the allograft, increased surgical drain output or a peri-transplant collection seen on

imaging [95]. Non-technical risk factors include recipient agent, pre-transplant urological pathology, immunosuppressive regimen and donor factors [94].

When there is a clinical suspicion for a urine leak due to increased surgical drain output, or if a peri-transplant collection is drained, the fluid should be sent for creatinine concentration analysis to differentiate serous or lymphatic fluid (which will have a similar creatinine concentration to the blood) from urine. Following drain removal, recipients with a urine leak may complain of pain due to fluid accumulation or if there is a significant urine leak, graft function will appear to deteriorate due to reabsorption of urinary creatinine and urea.

The management of urine leaks can be complex and often requires liaison with a transplant urologist. It may be possible to manage minor urine leaks conservatively via bladder decompression with an indwelling catheter in addition to ureteric stenting to allow the distal anastomosis to heal. Larger leaks may require further investigation in contrast to enhanced computer tomography, insertion of a percutaneous nephrostomy or surgical repair [95]. A more detailed discussion of this topic is beyond the scope of this chapter.

5.7 Infection

As a consequence of induction immunosuppression, transplant patients are particularly prone to infection in the perioperative phase. However, sepsis can be challenging to diagnose during this period because immunocompromised patients may not manifest the typical features of a systemic inflammatory response. Due to steroid therapy, most patients will exhibit a peripheral neutrophilia. In general, any change in physiological parameters, clinical deterioration or a temperature $> 37.5^{\circ}\text{C}$ should prompt consideration of sepsis, and a sepsis screen should be requested including [96]:

- haematology panel
- C-reactive protein
- blood culture and venous lactate
- urinalysis and urine culture
- chest X-ray
- additional testing as appropriate—respiratory virus screen, lumbar puncture, opportunistic infection screen
- empiric antibiotic therapy within 1 h of suspected sepsis diagnosis

Although transplant recipients are susceptible to opportunistic pathogens such as CMV, EBV, mycobacteria, *Pneumocystis jiroveci* and fungi, these are unusual in the early post-transplant period. Infections occurring soon after transplantation are frequently nosocomial, associated with hospitalisation, intravenous and urinary catheters and intubation during surgery. In some instances, infection may be donor derived [97].

5.7.1 Bacterial infection

Urinary tract infections (UTI) are the most common cause of bacterial infection requiring hospitalisation in transplant patients, followed by pneumonia,

surgical site infections and septicaemia [98]. Retrospective database studies have estimated a cumulative incidence of 17% in the first 6 months post-transplant, which rises to 60% for women and 47% for men at 3 years [99]. The presentation for UTI is similar to that of the general population and management identical to complicated UTIs with 7–14 days of antibiotic therapy, although the optimal duration has not been well established [98]. Management of post-transplant candiduria is controversial, without definite improvement in clinical outcomes following therapy [100]. Other bacterial pathologies are treated in the same way as in the general population with anticipated more frequent and longer duration antibiotic use due to physician concern over immunosuppressed state and propensity for more severe infection.

5.8 Rejection

In the early era of transplantation, hyperacute rejection due to the presence of preformed donor-specific antibodies (DSAs) occurring in the first minutes or hours after perfusion of the transplant was a significant risk. However, with the introduction of the complement-dependent cytotoxic cross-match, as described by Patel and Terasaki [101], and more recently solid phase assays that are able to detect DSAs with high sensitivity, hyperacute rejection is now extremely rare [102]. Nevertheless, early acute rejection remains a common occurrence, with a reported incidence of 7–25% depending on the level of immunological risk and choice of induction immunosuppression [21, 103–106]. Contemporary rejection rates in Australia and New Zealand are shown in **Table 9**.

In the perioperative period, DGF persisting beyond 4–5 days, decreasing urine output or an unexplained rise in creatinine by >15–20%, should prompt consideration of rejection as the underlying cause (Section 5.4). Unless there is a contraindication such as active bleeding or an unavoidable requirement for anticoagulation, the diagnosis requires a renal biopsy, both to exclude alternative causes of graft dysfunction and to characterise the histological pattern and severity of rejection. Rejection is classified histologically using the Banff criteria into borderline rejection, cell-mediated rejection, antibody-mediated rejection and mixed rejection [107, 108]. Treatment of cellular rejection would usually involve pulsed methylprednisolone 0.25–1.0 g daily for 3 days as first-line treatment, combined with a T-cell depleting therapy such as thymoglobulin/ATG if the rejection is histologically severe rejection (Banff class 2 or greater), or if there is a suboptimal response to methylprednisolone [109]. The optimal therapy for acute antibody-mediated rejection remains unclear, but would typically include pulsed methylprednisolone, plasma exchange (often combined with intravenous immunoglobulin at a dose of 0.1 g/kg following each exchange) outcomes [110–112]. Some centres also advocate the use of a B cell depleting antibody such as rituximab or the proteasome inhibitor bortezomib, although currently there is no strong evidence that these agents improve clinical outcomes [111, 113–115].

	First allograft (%)	Second or subsequent allograft (%)
Living donor	17.4	16.7
Deceased donor	15.2	18.6

Data from ANZDATA Registry. 41st Report, Chapter 7: Kidney Transplantation. Australia and New Zealand Dialysis and Transplant Registry, Adelaide, Australia. 2018. <http://www.anzdata.org.au>.

Table 9.
Acute rejection rates in the first six months post-transplant.

6. Conclusions

Kidney transplantation has evolved from a highly experimental therapy to become recognised as the gold standard treatment for many patients with ESKD [116]. This progress has occurred through the many iterative developments in the surgical and medical management of transplant recipients, not the least of which being the introduction of highly effective immunosuppressive agents. Delivering high standards of clinical care during the perioperative period is a crucial step in achieving excellent allograft outcomes. This chapter provides an overview of the approach to assessing potential recipients admitted for transplantation, and guidance on typical perioperative medication and fluid prescriptions, as well as post-operative monitoring and early complications.

Conflict of interest

David Johnson has previously received consultancy fees, research grants, speaker's honoraria and travel sponsorships from Baxter Healthcare and Fresenius Medical Care. He has also received consultancy fees from Astra Zeneca and travel sponsorships from Amgen. He is a current recipient of an Australian National Health and Medical Research Council Practitioner Fellowship. Carmel Hawley has received a research grant from Baxter Healthcare. Ross Francis has received honoraria and travel sponsorships from Novartis, Astellas and Amgen. The other authors have no conflict of interest to declare.

Notes/thanks/other declarations

Nil.

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