# Transplantation

# 19

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**Abstract**

Renal transplantation is the best modality of renal replacement therapy available for most patients with end-stage renal disease and is one of the breakthroughs in medical science in recent decades. Our knowledge of HLA typing, cross-match testing, recipient preparation, donor management, and postoperative care have advanced and brought widespread benefits, and these are crucial for clinicians to formulate an appropriate treatment regimen. Great effects should be paid to selection and preparation of kidney transplant recipients because of the risks from immunosuppressive therapy. Reducing acute rejection episodes and minimizing ischemic damage is the main goal of immunosuppressive therapy. The general concepts that most clinicians agree useful include induction therapy and maintenance treatment. Delayed graft function after kidney transplantation is usually defined as the need for dialysis during the first postoperative week, anuria, or failure of prompt azotemia resolution, and most studies suggest that patients with DGF have worse long-term outcomes than patients with immediate function. Although the outcomes of renal transplant patients have improved over the years, this population continues to show significant morbidity and mortality due to infection. Transplantation team should attempt to achieve a balance between preventing allograft rejection and maintaining immune system integrity.

## 19.1 Introduction

End-stage renal disease (ESRD) represents a growing global public health epidemic, and the prevalence of ESRD may rise sharply over the next few decades. Renal replacement therapy is available as three different modalities, i.e., hemodialysis, peritoneal dialysis, and a kidney transplant. Renal transplantation is one of the pioneering advances in medicine. It not only improves quality of life of patients with ESRD but also has been proven to prolong life [1]. Renal transplantation is a relatively young field of medicine, with the successful induction of immunological tolerance in rats by Peter Medawar and his colleagues at University College London in 1953 and the first successful kidney transplantation by Joseph Murray and his colleagues at Harvard in 1954.

Our knowledge of HLA typing and cross-match testing, immunosuppression, recipient preparation, donor management, and postoperative care has advanced and brought widespread

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benefits. The acute immune response to the transplanted tissue can now be controlled such that short-term graft survival has improved impressively. Nonetheless, this progress has not been accompanied with the improvement of long-term graft survival, and antibody-mediated rejection (AMR) has adverse long-term effects on the graft. Managing transplant recipients is challenging even for the most experienced transplant physicians, who need to understand not only the relevant basic research but also clinical transplant medicine.

With the invention of novel immunosuppressive drugs, kidney transplantation has made great progress in recent years. Unfortunately, the shortage of donated organs remains a major limiting factor, and the issues associated with organ donation, retrieval, and preservation are still challenging. Furthermore, the immune system poses many problems that have yet to be resolved, and donor-specific tolerance, which is the ultimate goal of transplantation, has still a long way to go. Clinical xenotransplantation—a procedure holding promise to solve the shortage of human donor organs—and engineered allografts are unlikely to be realized in the near future.

## 19.2 Histocompatibility Testing

The recipient's lymphocytes recognize the cell surface proteins of the transplanted tissue that are different from those of the recipient and trigger inflammatory events that cause allograft injury. Once the patient is determined to be a suitable transplant candidate, HLA typing and antibody screening tests are performed by the methods described in the following sections.

The histocompatibility test should be considered a risk assessment before transplantation. Therefore, a complete risk assessment of any donor–recipient pair must take into account HLA typing and possibly involve multiantibody detection methods. In addition, antibody analysis is increasingly being carried out posttransplant as a noninvasive predictor of acute and chronic alloimmune complications. Understanding the complexity and interactivity of these histocompatibility methods and their interpretation parameters is crucial for clinicians to formulate appropriate treatment interventions.

### 19.2.1 ABO Incompatibility

The ABO blood group antigen system is the most important immune barrier for successful transplantation. At the time of transplantation, ABO-incompatible kidneys can be rejected immediately. Nevertheless, in some cases, a transplant with a different ABO blood type is possible. Several research groups have already developed protocols for transplanting kidneys across major ABO barriers. These programs are based on various techniques and drugs to reduce the amounts of anti-A or anti-B antibodies. These antibody reduction methods help to expand the number of patients who may receive a kidney from a living donor [2].

### 19.2.2 HLA Typing

HLA typing quantifies the number of HLA antigen mismatches between donor and recipient, and it is one of the most important risk assessment tools for predicting non-self-HLA recognition. Serological tests have been performed in small plastic trays with a grid of small flat-bottomed wells containing antibodies. If lymphocytes from an individual have antigens on their surface that the antibodies can bind, then complement is activated and vital dyes are absorbed into those cells on which the membrane attack complex forms. Serological typing can yield rapid results, which are important for deceased donor typing. Nonetheless, small amino acid differences in HLA proteins may have strong immunological consequences and are not easily detectable by serological methods. In addition, the number of HLA alleles increases annually, and it is difficult to find high-quality serum samples with sufficient antibody to identify.

It is now more common to type individuals by DNA-based rather than serological methods. Advantages of molecular typing include greater

accuracy and reproducibility of the reagents. Aside from lymphocytes, typing can be performed on tissues containing other nucleated cells. Today's next-generation sequencing (NGS) has become an everyday research tool to address HLA-typing tasks. NGS offers more powerful higher-throughput sequencing, and the protocol is getting simpler for clinical laboratories. The ultimate goal of accurate high-resolution typing is to improve transplant outcomes.

- Past: RFLP (restriction fragment length polymorphism)
- Present: SSOP (sequence-specific oligonucleotide probes), reverse SSOP, real-time PCR, NGS
- Future: NGS

### 19.2.3 HLA Antibody Screening

Sensitization to HLA antigens occurs during pregnancy or in patients who had received blood transfusion or a previous transplant. Patients with circulating anti-HLA antibodies are at a high risk of rejection. Therefore, sensitive and specific detection of anti-HLA antibodies is necessary for the identification of the sensitized recipients. By considering all relevant antibodies and avoiding false-positive cross-matching of antibodies that are not clinically relevant, the anti-HLA antibody screening process must ensure a true negative cross-match with the intended donor. Over the past 40 years, various methods for detecting and characterizing anti-HLA antibodies have been developed:

- NIH-CDC
- AMOS modified
- Antiglobulin-augmented AHG-CC
- ELISA
- Flow cytometry
- Luminex

The complement-dependent lymphocyte toxicity (CDC) assay is the most popular method for anti-HLA antibody screening. B cells and T cells which have variable HLA types incubated with patient's serum, complement will be activated if the serum contains antibodies that bind to the cell surface at sufficient density, and the absorption of vital dyes allows for easy identification of dead cells. For example, in a 50-cell group, the positive reaction to 30 cells represents 60% of PRA. The CDC PRA assay has serious limitations. For example, the percentage of PRA may vary according to the cell group employed in the screening. In addition, substantial false-positive results and false-negative results may be obtained. Finally, it is almost impossible to compile an accurate and complete antibody-specific list in this way.

Due to the limitations of the CDC assay, there is an urgent need for more sensitive analytical methods. Solid-phase analysis by means of affinity-purified HLA antigens is now available for a variety of platforms. These methods involve only soluble or recombinant HLA molecules that are applied to solid-phase media platforms (ELISA) or beads; therefore, the solid phase will bind HLA antibodies only when recipient serum is added. Neither viable lymphocytes nor complement fixation is required, and target HLA specificity can be determined next by using a panel of HLA antigens from individual donors or by means of a single HLA antigen. The outputs of the solid-phase analysis can show substantial interlaboratory differences because there is considerable controversy as to what thresholds should be considered a cutoff for positive results. To determine whether the recipient has a donor antibody, the solid-phase antibody screening data should be analyzed in conjunction with cross-matching results [3].

### 19.2.4 Cross-Matching

The cross-match test is the final pretransplantation immunological screening step. Cross-matching determines whether the recipient has antibodies against donor. Just as cytotoxic PRA, cytotoxic cross-matching may miss low-titer antibodies, resulting in false negatives or detection of false-positive antibodies. To address this issue, serum samples from patients with IgM autoantibodies should be heated or treated with dithioth-

reitol to eliminate IgM prior to final cross-pairing. Flow-cytometric cross-match (FCXM) assays are more sensitive to complement-binding antibodies than standard complement-dependent cytotoxicity assays. Nonetheless, the thresholds of positivity may differ between laboratories. Therefore, there is considerable interlaboratory variability in the routine methods of FCXM. The status of FCXM remains controversial, and its role in the assessment of patients' immune risk has not been confirmed. Furthermore, these tests may not be available in all laboratories.

### 19.2.5 Non-HLA Antibodies

In some cases, antibody-mediated results are histopathologically or clinically suspicious while circulating anti-HLA antibodies have not been detected. Those immunity-associated, non-HLA antibodies may contribute to these cases, and detection of these non-HLA antibodies is still being studied.

## 19.3 Selection and Preparation of the Living Kidney Donor

Renal transplant is the best treatment for patients with ESRD; however, it cannot be performed without kidney donors. Both living and deceased donors contribute critically to the success of the transplantation endeavor on the individual, national, and international levels. Nevertheless, the shortage of cadaveric kidney transplants has caused patients to wait for longer periods to reap the benefits of transplantation. In comparison with deceased donor transplantation, live donor transplantation has the following advantages:

- Better long-term outcomes
- The procedure can be performed preemptively, thereby helping to avoid dialysis
- This procedure is elective and allows for optimization of the recipient
- Low rates of delayed graft function (DGF)

Even when corrected for ischemic times and DGF, live donor source is one of the strongest factors associated with good graft survival. The use of live kidney donors varies widely, and agreements to evaluate potential donors may vary widely among medical centers. On the other hand, many published expert recommendations can serve as the basis for most living donor experiments, including the United States guidelines and the Amsterdam living kidney donor guidelines.

### 19.3.1 Informed Consent

An important part of living kidney donation involves informed consent. According to the consensus conference, living donors should be willing to donate, be under no coercion, be suitable according to medical and social psychology, and must fully understand the risks, benefits, and alternative treatments available to the recipient. Donor advocates should ensure that potential donors fully and undeniably understand the immediate and long-term team risks and benefits of organ donation, so that donors can independently decide whether to perform a donation assessment.

### 19.3.2 Risks to Donors

Laparoscopic technique is associated with decreased discomfort and postsurgical pain and most transplant centers perform this technique. Two studies in the United States have estimated perioperative mortality at ~0.02–0.03%. The most common causes of death are a pulmonary embolus and cardiac events. In addition, there has been concern about the possibility that patients with a single kidney may develop glomerular hyperfiltration, hypertension, proteinuria, and renal insufficiency long-term. Living kidney donors are at a small but significantly increased risk of ESRD as compared with nondonors [4].

### 19.3.3 Evaluation of Living Kidney Donor

Living-donor evaluation includes a complete medical history taking, past medical history tak-

ing, physical examination, laboratory tests, serological screening for infectious diseases, renal scintigraphy, radiological imaging, and appropriate cancer screening. Furthermore, people being considered for the donation should be healthy or have only mild diseases that do not cause functional limitations.

### 19.3.4 Renal Function Evaluation

Serum creatinine and creatinine clearance testing is employed to estimate glomerular filtration rate (GFR) in most centers, whereas practice varies widely around the world. In the UK, GFR should be measured by an isotopic method, most often involving $^{51}$Cr-EDTA, and normalized to body surface area (mL/min/1.73 m$^2$). In the USA and many European countries, GFR is often estimated from creatinine clearance calculated via 24-h urine collection. Renal echography and sequential scintigraphy are helpful for assessing morphological and function characteristics of the two kidneys. Imaging of arterial and venous anatomy includes

- Intra-arterial angiography
- Spiral computed tomography (CT) angiography
- Magnetic resonance (MR) angiography (less accurate than CT)

Spiral CT angiography has largely replaced intra-arterial angiography because this technique helps to avoid the complications of arterial puncture and provides accurate arterial and venous phase images. Furthermore, 3D reconstruction of spiral CT is helpful for planning laparoscopic nephrectomy.

### 19.3.5 Summary

Comprehensive assessment and education of living kidney donors is a complex and time-consuming process requiring a thoughtful approach and extensive detailed communication among all members of the transplant team. There is an urgent need for new studies on donor and recipient outcomes after transplantation in contemporary cohorts [5].

## 19.4 Selection and Preparation of the Recipient

Kidney transplantation is the treatment of choice for patients with ESRD, and there are few conditions that are absolute contraindications for kidney transplantation. Proper selection and preparation of kidney transplant recipients are important goals of the transplant team due to the risks associated with immunosuppressive therapy. The goal of pretransplantation assessment is to obtain maximal benefits from transplantation which in turn leads to an increase in quality of life and life expectancy of the patients.

### 19.4.1 Timing of Referral and Contraindications of Transplantation

In ideal circumstances, preparation for transplantation begins as soon as progressive CKD is recognized. Increased cardiovascular risk, which is a major determinant of posttransplantation morbidity and mortality, can be recognized as soon as the serum creatinine level is elevated. It is well known that preemptive renal transplantation leads to improved patients' and allograft outcomes. Compared with patients who have been on dialysis for more than 2 years, patients who have not undergone dialysis (or have been on dialysis for less than 6 months) have longer graft survival time.

Contraindications to transplantation are listed below:

- Active or metastatic cancer
- Untreated current infection
- Severe irreversible extrarenal disease
- Uncontrolled psychiatric illness impairing compliance or consent
- Active substance or alcohol abuse
- Recalcitrant treatment noncompliance
- Aggressive recurrent native kidney disease
- Limited, irreversible rehabilitative potential
- Primary oxalosis

### 19.4.2 Complete Medical History and Physical Exam

A complete medical history of the transplant candidate is crucial. The history may be useful to ascertain whether the renal disease has a hereditary or familial origin, and a general screening examination should be conducted when a full medical history is obtained.

### 19.4.3 Evaluation of Renal Disease

The history of kidney disease should be reviewed with a focus on the nature and duration of primary kidney disease. All forms of glomerulonephritis may recur after transplantation and may lead to graft failure, but the risks of disease recurrence and its consequences differ among the various subtypes of glomerulonephritis.

### 19.4.4 Screening for Cardiovascular Disease

Cardiovascular disease occurs early after transplantation, and these events are the most common cause of death after renal transplantation. Almost half of the deaths of patients who have functional grafts within 30 days after transplantation are due to a cardiovascular event, mainly acute myocardial infarction. Careful study of the cardiovascular system and proper treatment of aberrations before placement of candidates on an active waiting list are necessary because cardiovascular disease is the main cause of late graft loss and long-term mortality.

### 19.4.5 Screening for Infectious Diseases

Infection may worsen with immunosuppressive drug application which is the second most common cause of death among patients with ESRD. Kidney transplant candidates must be screened to determine the presence of infection, and pretransplantation screenings are designed to eliminate any infections that may reactivate during the posttransplant period.

### 19.4.6 Screening for Cancers

Nine to 12% of deaths among kidney transplant recipients are caused by cancer. At baseline, patients with ESRD are at a higher risk of cancer than is the age-matched control population. Therefore, detecting cancer and reducing risk factors of cancer are important components of pretransplant evaluation. In addition, immunosuppressive drug application increases the risk of cancer, and existing cancer may turn more aggressive.

## 19.5 Immunosuppressive Medication and Protocols for Kidney Transplantation

Management of renal transplant recipients to achieve long-term survival is the main goal of transplant physicians. An immunosuppressant treatment that reduces acute rejection reactions and minimizes ischemic damage is the cornerstone of successful management of these delicate organs. Prevention of rejection while favoring the development of an immunological adaptation is the main goal of immunosuppressive therapy. More potent and specific immunosuppressive agents have enabled a significant reduction in the incidence and severity of rejection.

### 19.5.1 History of Immunosuppression and Transplant

The ability of the immune system, particularly T lymphocytes, to mediate acute rejection of organs transplanted between genetically nonidentical individuals was well known before the first successful renal transplant, in 1954. In the absence of any means of suppressing the immune system, this first transplant was performed between identical twins.

Whole-body irradiation was used for the first attempt at immunosuppression; azathioprine was introduced in the early 1960s and was soon followed by prednisone. Polyclonal antilymphocyte globulin and antithymocyte globulin came onto the scene in the 1970s. The introduction of cyclosporine in the 1980s was a seminal milestone, which reduced the acute rejection rate significantly and transformed the kidney transplantation scenario, with improvement in 1-year graft survival to more than 80%. In 1985, the first monoclonal antibody OKT3 was introduced into clinical practice because of the ability to treat the first acute rejection. Tacrolimus and mycophenolate mofetil (MMF), which are two other major developments, then followed. In 1999, sirolimus was introduced, and later, everolimus was approved in 2007. Due to the constant research into the immune system, tremendous progress has been made in kidney transplantation. The short-term survival and mid-term survival of kidney transplants are now satisfactory.

### 19.5.2 Induction Immunosuppression

Induction therapy is a boost of immunosuppression for approximately several days immediately after the surgical operation (although it usually starts immediately before the operation) in order to "shut down" the immune system after transplantation to reduce the possibility of accelerated rejection and acute rejection. There are several important reasons for the use of induction therapy. First, induction agents can significantly reduce the rate of acute rejection and improve 1-year graft survival. Second, induction therapy is important for preventing early calcineurin inhibitor (CNI)-induced nephrotoxicity. In addition, these drugs are also considered for high-risk patients such as those with multiple HLA mismatches, with organ transplant history, or with preformed antibodies.

Induction therapeutic agents are pharmacologically classified as monoclonal or polyclonal antibodies. Nevertheless, it is more accurate to classify them as depleting or nondepleting proteins. The use of specialized induction agents has increased over time, with 87% of patients undergoing kidney transplantation in the Unites States in 2012 receiving such medication according to Organ Procurement and Transplantation Network data. Two T-cell-depleting agents—rabbit antithymocyte (rabbit ATG, thymoglobulin) and alemtuzumab (Campath)—and one nondepleting agent, basiliximab (Simulect), are used for induction therapy in most cases. The advantages and disadvantages of depleting-antibody induction are outlined in Table 19.1.

**Table 19.1** Potential advantages and disadvantages of depleting-antibody induction

| *Potential advantages* |
|---|
| • Improved graft survival for high-risk patients |
| • Onset of first rejection is delayed |
| • Period of delayed graft function may be foreshortened |
| • May allow for less aggressive maintenance regimen |
| *Potential disadvantages* |
| • Risk of first-dose reactions |
| • May prolong hospital stay and increase cost |
| • Higher incidence of cytomegalovirus infection |
| • May increase mortality |

### 19.5.3 Maintenance Immunosuppression

Maintaining immunosuppression is intended to prevent acute and chronic immune system-mediated graft injury. Continuous development of immunosuppressive drugs has led to several new options that can further prevent rejection and improve outcomes in the long run. Immunosuppressive drug application requires careful selection and dose titration to balance the risks of rejection and toxicity. Table 19.2 lists maintenance agents used in clinical practice.

The immunosuppressive treatment regimens for transplant centers vary, and the 2009 KDIGO guidelines on maintenance immunosuppression suggest the use of a CNI, antimetabolite, and corticosteroid in combination. This drug selection method also helps to minimize drug-related adverse events [6]. Selecting a suitable immuno-

**Table 19.2** Maintenance agents in renal transplantation [7]

| |
|---|
| *Calcineurin inhibitors* |
| • Cyclosporine<br>• Tacrolimus |
| *Antimetabolites* |
| • Mycophenolate mofetil<br>• Azathioprine |
| *mTOR inhibitors* |
| • Sirolimus<br>• Everolimus |
| *Corticosteroids* |

Reproduced with permission from Kennedy et al. [7]

suppressive agent should be patient specific. The most important adverse effects of generalized immunosuppression are cancer and infection, including opportunistic infections. Individual drugs have a specific profile of adverse effects.

### 19.5.4 Monitoring the Levels of Immunosuppressive Drugs

The avoidance of over-immunosuppression and under-immunosuppression is a major challenge in clinical practice. Patients are routinely monitored for signs of drug toxicity by means of serum drug levels including CNI concentrations, mammalian target of rapamycin inhibitor (mTORi) levels, and at certain centers, MMF/MPA concentrations. Nevertheless, extreme drug levels are helpful but not definitive in the diagnostic process. Moreover, dosing of immunosuppressive drugs remains rather empirical, and there is no test for biological activity of the drugs used in transplantation.

### 19.5.5 Conclusion

Kidney transplantation has greatly evolved and has seen many advances in immunosuppressive therapy, with an increasing number of immunosuppressive agents available for use in various combinations allowing for more options and personalization of immunosuppressive therapy. When selecting an induction immunosuppressive agent, a clinician must carefully consider several factors including immunological risk of the patient, the cumulative immunosuppression burden, concomitant maintenance immunosuppression, and additional patient factors including age and comorbidities such as cardiovascular disease, pulmonary disease, and prior cancer. T-cell-depleting agents such as rabbit ATG or alemtuzumab are associated with lower acute rejection rates but higher rates of leukopenia and infection as compared to basiliximab. An individual patient's risk of rejection should be carefully weighed against potential complications due to overimmunosuppression and/or drug-related toxicities. Maintenance immunosuppressive therapy has greatly evolved too. Although CNI-based therapy with tacrolimus, mycophenolate, with or without corticosteroids continues to be the standard (most commonly utilized) regimen ensuring low rates of acute rejection, the associated medication-related toxicities continue to contribute to morbidity and mortality.

## 19.6 Allograft Dysfunction

With a living donor kidney transplant, the graft usually begins to function soon after the vascular anastomosis is complete. Although immunosuppressive agents, surgical techniques, and histocompatibility tests have improved, allograft dysfunction remains the most common complication of renal transplantation [8].

### 19.6.1 Immediate Posttransplant Period

With a living donor kidney transplant, the graft usually begins to function soon after the vascular anastomosis is complete. Impairment of graft function is suggested by a decrease in urine output and/or a rise in creatinine levels. The definition of DGF varies among transplantation centers, and the most common definition is dialysis that is required within 7 days. On the other hand, the current definition of DGF does not enable clinicians to distinguish the causes of DGF from other types of graft dysfunction and can lead to misclassification of patients. Furthermore, there are different criteria for dialysis prescription among nephrologists. The main causes of DGF are listed in Table 19.3.

**Table 19.3** Main causes of DGF

| |
|---|
| *Prerenal* |
| • Hypotension, hypovolemia |
| • Arterial thrombosis, venous thrombosis |
| *Parenchymal* |
| • Acute tubular necrosis (Ischemia, drug) |
| • Rejection (hyperacute, acute) |
| • Thrombotic microangiopathy (CNIs, mTOR inhibitors) |
| • Recurrence of original disease (FSGS, HUS, primary hyperoxaluria) |
| *Postrenal* |
| • Ureteral obstruction (ureteral kinking, ureteral stenosis, blood clots, lymphocele) |
| • Urine leakage |
| • Urine fistula |

*DGF* delayed graft function, *CNI* calcineurin inhibitor, *mTOR* mammalian target of rapamycin, *FSGS* focal segmental glomerulosclerosis, *HUS* hemolytic uremic syndrome

**Table 19.4** Main measures for preventing DGF

| |
|---|
| *Donor* |
| • Normovolemia |
| • Maintain blood pressure |
| • Optimize cardiac output |
| • Adequate kidney perfusion |
| *Kidney perfusion* |
| • Selection of renal preservation solution[a] |
| • The use of pulsatile machine perfusion |
| *Cold ischemia time* |
| • Maintain <12–24 h when possible |
| *Ischemia-reperfusion injury* |
| • Multiple anti-inflammatory and antioxidant therapies[a] |
| *Recipient* |
| • Check blood volume |
| • Low-dose dopamine |
| • Loop diuretics |

*DGF* delayed graft function
[a]Requires more research

### 19.6.2 Management of DGF

Patients with DGF show longer hospitalization and are at a higher risk of occult rejection or other undiagnosed insults to the graft. Most studies suggest that patients with DGF have worse long-term outcomes than patients with immediate function. Great efforts should be made to reduce the damage during the transplantation process; these measures include optimal management of donors, a precise surgical technique, optimizing allograft perfusion, minimizing cold ischemia time, and ensuring adequate preparation of the recipient (Table 19.4).

**Table 19.5** Causes of allograft dysfunction in the early postoperative period

| |
|---|
| *Prerenal* |
| • Transplant artery stenosis |
| • Hypovolemia/hypotension |
| • Renal vessel thrombosis |
| • CNIs |
| *Parenchymal* |
| • Acute thrombotic microangiopathy |
| • Acute allergic interstitial nephritis |
| • Recurrence of primary disease |
| • Acute rejection |
| • Acute CNI nephrotoxicity |
| • Toxic/ischemic acute renal tubular necrosis |
| • Acute pyelonephritis |
| *Postrenal* |
| • Urine leaks |
| • Urinary tract obstruction |

*CNI* calcineurin inhibitor

### 19.6.3 Early Posttransplant Period

Early posttransplant allograft dysfunction is often defined as a sustained increase in plasma creatinine concentration, and the reasons are listed in Table 19.5 [9].

### 19.6.4 Late Posttransplant Period

There is an apparent overlap between the causes and assessment of acute allograft dysfunction in the late period (3–6 months after transplantation) and those of early acute dysfunction [9]. The reasons of late chronic allograft dysfunction are listed in Table 19.6.

### 19.6.5 Management of Late Allograft Dysfunction

The main focus of the current research in this field is the prevention of chronic allograft dysfunction. The medical history should be carefully

**Table 19.6** Reasons of late chronic allograft dysfunction [10]

| |
|---|
| *Prerenal* |
| • Heart failure |
| • Transplant renal artery stenosis |
| *Parenchymal* |
| • Chronic active antibody-mediated rejection (ABMR) |
| • Chronic active T-cell-mediated rejection (TCMR) |
| • Drug and radiocontrast nephrotoxicity |
| • Hypertension |
| • Interstitial fibrosis and tubular atrophy, no specific etiology |
| • Chronic BK virus nephritis |
| • Donor-related disease and/or perioperative injury |
| • Chronic CNI toxicity |
| • Chronic BK virus nephritis |
| • Late recurrence of primary disease |
| • Diabetic nephropathy |
| • New disease |
| *Postrenal* |
| • Urinary tract obstruction |

*CNI* calcineurin inhibitor (Reproduced with permission from Magee et al. [10])

examined, especially with respect to primary kidney disease, early posttransplantation course, acute rejection episodes, degree of hypertension, CNI levels, and compliance. Urinalysis and renal ultrasonography should be performed to rule out primary kidney disease and obstructive cause. Allograft biopsy is often performed because endogenous nephropathy is the leading cause of dysfunction [10].

If there is a histological evidence of acute TCMR components, pulsed steroids are usually prescribed, and baseline immunosuppression is increased. How to manage chronic TCMR is not clear. If there is evidence of an acute AMR component, plasmapheresis and/or IVIg protocol may be performed. How to manage chronic AMR is not clear either. In most cases, when allograft injury due to CNI toxicity, and with no evidence of active rejection, reducing the CNI dose is a reasonable action. Alternative medication such as MMF or sirolimus may be initiated as a replacement, but it is important to pay close attention to late acute rejection of patients. ACE-I/angiotensin receptor blockers are commonly used in renal transplantation although there are no randomized controlled trials. When GFR deteriorates, patients should be ready to resume dialysis. Erythropoietin, vitamin D therapy, and other ancillary measures should be applied. The "CKD management" of patients who fail in transplantation may be difficult due to the adverse effects of immunosuppressive agents [10].

## 19.7 Updated Banff Classification Categories

Among living and deceased donor transplant recipients, the incidence of acute rejection within the first year posttransplant decreased to 7.9% for both categories during 2013 and 2014. The development of donor-specific antibody (DSA) and AMR negatively affects graft survival, and the present-day diagnosis of AMR in the absence of peritubular capillary C4d staining has been incorporated into the Banff classification system [11]. Updated Banff classification categories are listed in Table 19.7.

## 19.8 Infection After Kidney Transplantation

Although the outcomes of renal transplant patients have improved over the years, this population continues to show significant morbidity and mortality due to infection. Infection accounts for 15–20% of deaths after transplantation, and it is the second most common cause of hospital admission among kidney transplant patients in the first year posttransplant [12]. Therefore, a transplantation team attempts to achieve a balance between preventing allograft rejection and maintaining immune system integrity for defense against pathogens. In addition to immunosuppressive agents, several factors contribute to a decrease in immune status, including uremia, nutrition, diabetes, dialysis, age, and ESRD-related malnutrition.

**Table 19.7** Updated Banff classification categories

| | |
|---|---|
| *Category 1*: Normal biopsy or nonspecific changes | |
| *Category 2*: Antibody-mediated changes | |
| Acute/active ABMR: three features are required | |
| Histological evidence of acute tissue injury (inflammation, TMA, ATN) | |
| Linear C4d staining | |
| Serological evidence of DSA | |
| Chronic active ABMR: three features are required | |
| Histological evidence of chronic tissue injury | |
| Linear C4d staining | |
| Serological evidence of DSA | |
| C4d staining without evidence of rejection | |
| *Category 3*: Borderline changes | |
| *Category 4*: TCMR | |
| Acute TCMR | |
| Grades | |
| IA | Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma) and foci of moderate tubulitis |
| IB | Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma) and foci of severe tubulitis |
| IIA | Mild to moderate intimal arteritis |
| IIB | Severe intimal arteritis comprising >25% of the luminal area |
| III | Transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation |
| Chronic active TCMR | |
| Chronic allograft arteriopathy | |
| *Category 5*: Interstitial fibrosis and tubular atrophy | |
| Grades | |
| I | Mild interstitial fibrosis and tubular atrophy (≤25% of cortical area) |
| II | Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area) |
| III | Severe interstitial fibrosis and tubular atrophy (>50% of cortical area) |
| *Category 6*: Other changes not considered to be rejection | |
| BK virus nephropathy | |
| Posttransplant lymphoproliferative disorders | |
| CNI nephrotoxicity | |
| Acute tubular injury | |
| Recurrent disease | |
| De novo glomerulopathy | |
| Pyelonephritis | |
| Drug-induced interstitial nephritis | |

*ABMR* antibody-mediated rejection, *TMA* thrombotic microangiopathy, *ATN* acute tubular necrosis, *DSA* donor-specific antibody, *TCMR* T-cell-mediated rejection, *CNI* calcineurin inhibitor

### 19.8.1 Pretransplant Recipient and Donor Evaluation

Before transplantation, appropriate evaluation and treatment of patients are required, starting with a detailed medical history taking and physical examination. The goal is to assess the condition or exposure that causes the candidate to be susceptible to future complications, especially those requiring treatment or prevention. Predonation kidney transplant donors have also been tested several times. Donors can harbor infectious diseases that can be transmitted to recipients via donor organs.

### 19.8.2 Timing of Posttransplant Infections

Infection after kidney transplantation is divided into three stages: 0–1 month, 1–6 months, and after 6 months. The recipients are susceptible to certain infections due to the different levels of immunosuppression and environmental factors in each period. Table 19.8 lists the timeline and relevant infectious microorganisms after a kidney transplant.

### 19.8.3 Evaluation of Fevers

Although a fever is not always present in an infected immunosuppressed patient, it remains the most common manifestation of an infection in a transplant patient. A number of clinical, laboratory, and radiological tests on a febrile transplant patient are recommended. Both infection and rejection can lead to fever in the transplant recipients, and the first differential diagnosis should be between infection and rejection. Medical tests for a renal transplant recipient with a fever are listed in Table 19.9, and Table 19.10 lists bacterial, viral, and fungal infections common among renal-transplant recipients.

**Table 19.8** Timeline and infectious organisms after a kidney transplant [13]

| 0–1 month | 1–6 months | After 6 months |
|---|---|---|
| Nosocomial infection<br>Pneumonia<br>Urinary tract infection<br>Bloodstream infections<br>Wound<br>Herpes viruses<br>Oral candidiasis | Cytomegalovirus<br>Polyomavirus<br>Pneumocystis<br>Cryptococcus<br>Nocardia<br>*Toxoplasma gondii*<br>Listeria monocytogenes<br>Candida species<br>Aspergillus species<br>Histoplasmosis<br>Coccidioidomycosis<br>Mycobacteria<br>Other herpes viruses<br>Hepatitides B and C | Community infections<br>Cytomegalovirus retinitis<br>Cryptococcus<br>Herpes virus<br>Polyomavirus<br>Mycobacteria |

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**Table 19.9** Medical tests for a renal transplant recipient with fever

| Rejection | Infection |
|---|---|
| • Creatinine<br>• Urinalysis<br>• Graft ultrasonography<br>• Renal biopsy | • Blood cell analysis<br>• Cultures (blood, urine, secretions)<br>• Chest X-ray imaging<br>• Echocardiogram<br>• Urinary ultrasonography (Graft, native kidney)<br>• Neurological evaluation<br>• Cerebrospinal fluid<br>• Cerebral CT<br>• Intestinal–hepatic tests<br>• CMV antigenemia<br>• Anti-legionella, -candida, or -mycoplasma antibodies |

**Table 19.10** Bacterial, viral, and fungal infections

| Bacterial infections | Viral infections | Fungal infections |
|---|---|---|
| • Urinary tract infections<br>• Sepsis<br>• Wound infections<br>• Nocardiosis<br>• Listeriosis | • Herpes virus infections<br>• Hepatitis viruses<br>• Influenza<br>• HIV<br>• Polyomaviruses | • Candidiasis<br>• Cryptococcus<br>• Aspergillosis<br>• Mucormycosis<br>• Histoplasmosis<br>• Coccidioidomycosis |

**Key Messages**

- Chronic rejection and overimmunosuppression remain significant clinical problems. The development of more specific treatments accompanied by reduction in toxicity requires further work.
- Antibody analysis is increasingly carried out posttransplant as a noninvasive predictor of acute and chronic alloimmune complications. Understanding the complexity and interactivity of these histocompatibility methods and their interpretation parameters is crucial for clinicians to formulate an appropriate treatment regimen.
- Comprehensive assessment and education of living kidney donors require communication among all members of the transplant team which is a complex and time-consuming process.
- Great effects should be paid to selection and preparation of kidney transplant recipients because of the risks of immunosuppressive therapy.
- Kidney transplantation has greatly evolved and has seen many advances in immunosuppressive therapy, with an increasing number of immunosuppressive agents available for use in various combinations allowing for more options and personalization of immunosuppressive therapy.
- DGF after kidney transplantation is usually defined as the need for dialysis during the first postoperative week, anuria, or failure of prompt azotemia resolution. DGF increases

the risk of allograft rejection by 50% as compared with prompt graft function.
- The development of DSA and AMR adversely affects graft survival. The modern diagnosis of AMR in the absence of peritubular capillary C4d staining has been incorporated into the Banff classification system.
- Although the outcomes of renal transplant patients have been great improved in recent years, infectious complications after a transplant may induce allograft injury or graft loss and are a major cause of morbidity and mortality.

## References


1. Hart A, et al. OPTN/SRTR 2015 annual data report: kidney. Am J Transplant. 2017;17(Suppl 1):21–116.
2. Lo P, et al. Preconditioning therapy in ABO-incompatible living kidney transplantation: a systematic review and meta-analysis. Transplantation. 2016;100(4):933–42.
3. Tinckam KJ. Basic histocompatibility testing methods. In: Core concepts in renal transplantation; 2012.
4. Anjum S, et al. Patterns of end-stage renal disease caused by diabetes, hypertension, and glomerulonephritis in live kidney donors. Am J Transplant. 2016;16(12):3540–7.
5. Lin J. Medical evaluation of the living kidney donor. In: Core concepts in renal transplantation; 2012.
6. Hart A, et al. Kidney. Am J Transplant. 2016;16(Suppl 2):11–46.
7. Kennedy CM, Magee CC. Immunosuppression in the renal transplant recipient. In: Lerma EV, Rosner M, editors. Clinical decisions in nephrology, hypertension and kidney transplantation. New York: Springer; 2013. p. 395–409.
8. Massie AB, et al. Early changes in kidney distribution under the new allocation system. J Am Soc Nephrol. 2016;27(8):2495–501.
9. Wu WK, et al. Delayed graft function and the risk of acute rejection in the modern era of kidney transplantation. Kidney Int. 2015;88(4):851–8.
10. Magee CC. Allograft dysfunction: diagnosis and management. In: Core concepts in renal transplantation; 2012.
11. Loupy A, et al. The Banff 2015 kidney meeting report: current challenges in rejection classification and prospects for adopting molecular pathology. Am J Transplant. 2017;17(1):28–41.
12. Martin-Gandul C, et al. The impact of infection on chronic allograft dysfunction and allograft survival after solid organ transplantation. Am J Transplant. 2015;15(12):3024–40.
13. Santos RD, Brennan DC. Prevention and management of infectious complications in kidney transplant recipients. In: Weir MR, Lerma EV, editors. Kidney transplantation: practical guide to management. New York: Springer; 2014. p. 301–18.