Current practices in the management of kidney transplant rejection: an Indian perspective

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ABSTRACT
Renal diseases like chronic kidney disease (CKD) and end-stage renal disease (ESRD) are a major healthcare burden in developing countries like India. Kidney transplantation is considered to be the most viable treatment option for such patients. In comparison to dialysis, renal transplantation is associated with reduced mortality and improved quality of life. However, a major challenge experienced in transplant procedures is transplant rejection. Four virtual advisory board meetings involving 30 nephrology experts were conducted to discuss the current therapeutic landscape of kidney transplant rejection in India and subsequent practice-based insights of the experts were garnered. The experts concurred on the need for appropriate screening including immunological profiling, diagnosis, and management of candidates for transplantation. While immunosuppressive therapy and strategies like plasmapheresis, intravenous immunoglobulin, corticosteroids, and rituximab have been well established in the treatment of transplant rejection, novel and emerging treatment modalities like interleukin-6 antagonists, imlifidase or complement inhibitors have shown promise and should be considered. Increased awareness among physicians about the development of newer immunosuppressive regimens with lower side effects that may improve long-term outcomes of kidney transplantation is warranted.

Keywords: Kidney transplant rejection, Antibody-mediated rejection, Crossmatch, Immunosuppressive therapy, Induction, Maintenance immunosuppression

INTRODUCTION

Current scenario of renal diseases in India
Chronic kidney disease (CKD) and ESRD are both associated with high morbidity and mortality.1 The exact magnitude of burden of these conditions in India is not known.2 However, ESRD imposes substantial economic and social burdens on patients and healthcare systems.3 According to an Indian population-based study, the crude and age-adjusted ESRD incidence rates were 151 and 232 per million population, respectively.2

Renal replacement therapies like dialysis or kidney transplantation are mandatory for ESRD.3 In India, the most feasible and suitable long-term treatment option is renal transplantation.2 Nevertheless, renal transplantation is associated with various challenges. Inadequate finances, lack of organized cadaver donor transplant programs as well as social and religious issues in certain areas are the major hindrances faced.4 It is estimated that almost 220,000 people need kidney transplantation in India, whereas, only ~7500 kidney transplantations are performed at 250 kidney transplant centers across the country.5 Of these, 90% are from living donors whereas 10% are from deceased donors.5 Additionally, prevention
of transplant rejection is one of the biggest post-transplant challenges in patients undergoing kidney transplantation. Rejection can be an acute, late acute, or chronic. Thus, effective management of transplant rejection remains a key unmet need. This review provides consensus on the appropriate management of kidney transplant rejection in India to facilitate long-term patient survival.

Four virtual advisory board meetings involving 30 nephrology experts were conducted during the months of June to September 2020. The experts discussed various aspects about existing clinical evidence and their practical experience with respect to management of kidney transplant rejection in India. Clinically relevant insights were drawn from advisory boards based on experts’ views.

An initial literature search was performed using databases PubMed and Google Scholar. Relevant articles were identified using the keywords kidney transplant rejection, antibody-mediated rejection, cross-match, immunosuppressive therapy, induction, and maintenance. The search was further refined for PubMed articles by excluding animal studies and studies in languages other than English. After screening, 33 suitable articles were identified and included in this document. This consensus article provides a collation of evidence-based literature and experts’ experience on present practices in the management of kidney transplant rejection. It is prepared in accordance with suggestions provided by the experts, and evidence highlighted is supported by consensus points.

OVERVIEW OF KIDNEY TRANSPLANTATION

Successful kidney transplantation is a better option compared to dialysis for improving the longevity of patients with CKD and/or ESRD. It also improves quality of life and has better survival advantages over dialysis. On the other hand, dialysis is time-consuming, expensive, and requires frequent hospital visits.

The goals for assessment of a renal transplant candidate include determining if any contraindications like unsuitable anatomy for technical success, high risk for perioperative mortality, active infection, active malignancy, or noncompliance exist; determining risk of recurrent renal disease that might cause loss of a transplanted kidney and identifying immunologic risk factors like donor-recipient ABO incompatibility, positive donor-recipient lympho-cytotoxic cross match, high panel reactive antibody level, complete human leukocyte antibody (HLA) mismatch between donor and recipient, early immunologic loss of another transplant, and systemic lupus erythematosus helps in the selection of induction and maintenance immunosuppression. Obtaining a history of allosensitizing events like previous transplant, blood transfusion, and pregnancy is equally important. In addition to the opinions of the transplant surgeon and nephrologist, input from specialties like dentistry, pharmacy, Transplant nurse coordination, nutrition, social services and financial counselling is routinely sought. A pretransplant urinary tract evaluation is also performed. Ultrasound assessment is routinely done for postvoid residual urine and upper tract abnormalities.

Consensus key points-1

According to the panel experts, kidney transplantation is currently the definitive treatment for patients with ESRD. Compared to dialysis, kidney transplantation is associated with reduced mortality and improved quality of life. The benefits of a transplant include increased life expectancy, cardiovascular benefits, and socioeconomic benefits.

KIDNEY TRANSPLANTATION REJECTION

The difficulties of chronic rejection and chronic allograft dysfunction often lead to graft loss and shortened long-term graft survival. Transplant rejection is an immunological response that results in inflammation with specific pathological changes in the allograft, due to the recipient immune system recognizing the non-self (foreign) antigen in the allograft. Transplant vasculopathy, which affects the large arteries as well as involves small peritubular capillaries, is the single most vital feature of chronic kidney transplant rejection. The most significant features of transplant vasculopathy include thickening of fibrointima of the blood vessels, infiltration of vessel walls with inflammatory cells, and breaks in the elastic layer of blood vessels.

Certain etiological factors known to be associated with an increased risk of rejection of the renal allograft after transplantation are tabulated in Table 1.

Pathophysiological mechanisms of the different types of rejection are summarized below:

Table 1: Etiological factors associated with increased risk of kidney transplant rejection.

| S. no. | Variables |
|-------|-----------|
| 1     | Prior sensitization-high panel reactive antibodies |
| 2     | Type of transplant (rejection rate is higher with deceased donor versus living-donor transplant) |
| 3     | Advanced age of the donor |
| 4     | Prolonged cold ischemia time |
| 5     | Human leukocyte antigen mismatch |
| 6     | Positive B cell crossmatch |
| 7     | ABO incompatibility |
| 8     | Recipient age (Younger recipients are at higher risk of rejection) |
| 9     | Recipient race (African Americans are at higher risk of rejection that Caucasians) |
| 10    | Delayed graft function |
| 11    | Therapy non-compliance |
| 12    | Previous episodes of rejections |

Hyperacute rejection: It is related to the presence of circulating antibodies in the recipient blood against the
donor antigen (usually ABO blood group or HLA antigen) before transplantation. These antibodies attack and destroy the transplanted organ immediately or within a few hours after allograft is revascularized.

**Acute T cell-mediated rejection:** Recipient lymphocytes become activated by recognition of foreign donor antigens in the transplanted organ by antigen-presenting cells (APCs) via direct, semi-direct or indirect pathways, which in turn results in activation and infiltration of T cells and subsequent damage to the allograft.

**Antibody-mediated rejection (AMR):** It is related to antibodies against foreign donor antigens, mainly HLA antigen, which causes damage to the allograft via activation of the complement-dependent pathway or by independent mechanisms involving NK cells, polymorphonuclear cells, platelets, and macrophages to attack allograft.

**Chronic rejection:** It is related to both immune and nonimmune-mediated factors. The key risk factor for chronic rejection is noncompliance with immunosuppressive medications. It can be either chronic AMR or chronic cellular rejection (uncommon).

The diagnostics for renal transplant rejection include:

**History, physical examination, and laboratory investigations:** Most patients who have acute rejection episodes are asymptomatic and have abnormal allograft dysfunction evidence on routine blood works. A sudden rise in serum creatinine to >25% of the baseline value might be suspected as allograft rejection. The specific workup for evaluating allograft dysfunction must include ruling out pre-and post-renal causes, complete blood workup to rule out thrombotic microangiopathy (TMA), electrolyte abnormality related to CKD, and acute kidney injury (AKI), and urine culture to rule out infection. Diagnostic workup must include assessments for proteinuria, and BK virus and cytomegalovirus (CMV) serology in clinically indicated patients.

**Monitoring for de novo donor-specific anti-HLA antibodies (DSA):** Monitoring for de novo DSA is recommended in settings like immunosuppression reduction by physician for any reason, known patient medication non-adherence, or at time of rejection episode.

**Renal biopsy:** The diagnosis of renal transplant rejection depends on interpretation of renal allograft biopsies. Percutaneous needle core biopsy is a definitive procedure by which essential diagnostic information on acute and chronic renal allograft dysfunction can be obtained.

**Banff classification:** The Banff classification of allograft pathology is an international consensus classification that provides a framework for reporting of rejection on renal allograft biopsies. The Banff diagnostic categories are as follows. Category 1: Normal biopsy or non-specific changes; category 2: Antibody-mediated changes; category 3: Suspicious (borderline) for acute T cell-mediated rejection; category 4: T cell-mediated rejection; category 5: Interstitial fibrosis and tubular atrophy; category 6: Other non-rejection changes.

**Consensus key points-2**

According to the panel experts, apart from the etiological causes (Table 1), other causes of kidney allograft loss include recurrent glomerular disease, fibrosis, calcineurin-inhibitor toxicity, and BK virus-associated nephropathy. Diagnosing rejection could include clinical evaluation, renal biopsy and Banff classification.

**CROSS MATCHING TECHNIQUES**

Immunogenetic profiling of transplant recipients and pre-transplant tissue crossmatch between potential donor and recipient is a must in modern-day renal transplantation. A pre-transplant crossmatch allows identification of pre-existing DSA in the recipient serum that would potentially react with donor antigens. It indicates possible immunological compatibility between the donor-recipient pair, thus enabling avoidance of major complications such as hyperacute rejection, AMR, and graft loss. It further allows prognostication of the prospective transplant and minimization of potentially catastrophic antibody-mediated allograft injury.

**Complement dependent cytotoxicity cross-match (CDC-XM):** CDC-XM was the first commonly used crossmatch technique implemented in routine clinical practice. It is an assay that measures cell bound antibody by its ability to bind with the complement and cause cell lysis. It detects all complement fixing IgG, IgM antibodies of HLA and non-HLA origins along with autoantibodies. Thus, it enables identification of recipient pre-sensitization to the donor kidney as well as the recognition of the association between a CDC-XM+ result and immediate graft loss. A CDC-XM+ result is usually assumed to be a contraindication to proceed with transplantation, unless it can be conclusively established that the result was not caused by IgG HLA alloantibodies.

**Flow-cytometry crossmatch (FCXM):** The FCXM was developed as a more sensitive assay than the standard CDC-XM for detection of anti-donor antibodies that mediate hyperacute rejection and graft loss during the early post-transplant period in renal transplant recipients. FCXM enabled identification of clinically relevant DSA even with a negative CDC-XM. Utilization of FCXM over anti-human globulin (AHG)-enhanced CDC-XM has significantly decreased the incidence of AMR and graft loss at 1 year. A negative FCXM rules out the possibility of immunologically significant DSA. Additionally, it has a higher specificity than CDC-XM as it detects only IgG and not IgM antibodies.
**Solid phase immunoassay (SPI):** The use of SPI has increased sensitivity and specificity, improved treatment of AMR and increased opportunities for transplantation. It is a predictive assay based on commercial kits of purified recombinant HLA molecules coated on a microtiter plate. Enzyme-linked immunosorbent assay (ELISA) or synthetic beads; (Luminex). SPI is specific for HLA antibodies and thus eliminates the false positives in CDC-XM and FCXM caused by non-HLA antibodies and autoantibodies. ELISA test is more sensitive than CDC-XM whereas Luminex is more sensitive than CDC-XM and FCXM both. The Luminex-SPI is now considered the benchmark in detecting immunologically significant DSAs. This comprises of a series of polystyrene microsphere beads to which target HLA antigens are attached after purification. Relevant beads are labelled with varying ratios of fluorescent dyes giving them a unique fluorescent signal. Test sera are added wherein, any DSA present in the sera would bind to appropriate HLA molecules on the beads. The resulting antigen-antibody binding can be evaluated via laser based fluorescent imaging quantified as mean fluorescent intensity (MFI). The assay can be taken a step ahead with the single antigen bead (SAB) test, where relevant beads are coated with a single cloned antigen. The SAB test is most specific detecting DSAs against the specific antigen.

**Virtual crossmatch (VXM):** The shift from ‘wet’ crossmatch to VXM based on Luminex assays has been a huge technological advancement in field of transplantation. This technique is based on comparison of anti-HLA antibodies of the recipient to the donor HLA antigens using bead technology. It predicts the eventual crossmatch and can assist in rapid identification of a suitable donor.

The combination of various assays helps exclude insignificant antibodies from risk assessment while enabling better prognostication and preparation when more significant antibodies are identified that can potentially complicate, though not preclude transplant.

**Consensus key points-3**

According to the panel experts, crossmatching is a vital tool for assessing the immune compatibility of a particular donor/recipient pairing. Complement dependent cytotoxicity remains mainstay of pre-transplant screening for HLA-specific antibodies. Flow crossmatch and Luminex bead assays allow identification of lower titer, and possibly clinically significant anti-HLA antibodies. Cut-off CDC value can be considered at 10 percentage. Single antigen assay can be considered in the second transplant.

**IMMUNOSUPPRESSIVE THERAPY**

Following kidney transplantation in ESRD patients, immunosuppressive therapy reduces the risk of kidney rejection and prolongs graft survival. The currently available immunosuppressive therapies could be categorized as: induction therapy, maintenance therapy and treatment for rejection.

**Induction therapy**

Induction therapy is intensive immunosuppression aimed at suppressing both cellular and humoral responses for preventing episodes of acute rejection. Initial intensive immunosuppression might be essential for preventing acute rejection and graft loss; immunosuppression may be subsequently reduced to minimize adverse events associated with immunosuppressive agents. Induction agents include lymphocyte-depleting antibodies such as thymoglobulin/rabbit anti-thymocyte globulin (rATG), and alemtuzumab; lymphocyte nondepleting antibodies like interleukin 2 receptor antibodies; and various other therapies (Table 2).

| Table 2: List of induction therapies used for immunosuppression. |
|---------------------------------------------------------------|
| **Induction agent** | **Description** |
| **Lymphocyte-depleting antibodies** | |
| Thymoglobulin<sup>10</sup> | Antilymphocyte polyclonal antibody that is derived by injecting rabbits with human thymocytes; works primarily by complement mediated depletion of T lymphocytes |
| Grafalon<sup>22</sup> | ATG produced by immunization of rabbits with the Jurkat human T-lymphoblastic cell line |
| Alemtuzumab<sup>10</sup> | Recombinant humanized monoclonal antibody directed against CD52 |
| Muromonab-cD3<sup>21</sup> | Mouse antibody that depletes T cells by binding to the T-cell-receptor-associated CD3 glycoprotein |
| Rituximab<sup>21</sup> | Chimeric monoclonal antibody against CD20 (antigen that is expressed on most B cells) |
| **Lymphocyte non-depleting antibodies** | |
| Basiliximab<sup>21</sup> | Chimeric monoclonal antibody that binds to the α chain of the IL-2R complex (CD25) |
| Daclizumab<sup>21</sup> | Humanized antibody that binds to the α chain of the IL-2R complex (CD25) |

Continued.
Use of induction agents in routine practice depends on various factors ranging from center-specific protocols to tailored immunosuppression based on recipient factors.\textsuperscript{10} The benefits and risks of each agent must be evaluated in every patient based on individual immunologic risk and susceptibility to infectious complications.\textsuperscript{10} It may be more beneficial to use more potent induction therapies like lymphocyte depleting agents in recipients that are at higher risk for rejection; however, using such agents may be of concern in recipients with chronic infections such as hepatitis B and/or C or human immunodeficiency virus (HIV).\textsuperscript{10} Reduced immunosuppression is also a feasible option for older recipients, Caucasian recipients, and those receiving living donor kidneys.\textsuperscript{10} Risk associated with acute rejection is variable, subject to certain conditions.\textsuperscript{25} Lower risk may be associated with zero HLA mismatch, live donor, Caucasian ethnicity, low level of panel reactive antibodies, absence of donor-specific antibodies, blood group compatibility, immediate graft function, short cold ischemia time, or first transplant.\textsuperscript{25} On the other hand, higher risk may be associated with increased number of HLA mismatches, younger recipient and older donor, African-American ethnicity, high level of panel reactive antibodies, presence of donor specific antibodies, blood group incompatibility, delayed onset of graft function, long cold ischemia time, or retransplant.\textsuperscript{25}

**Maintenance therapy**

The necessity of maintaining allograft recipients on immunosuppression is nearly universal.\textsuperscript{26} The development of DSAs and AMR could be effectively prevented by adequate maintenance of immunosuppression.\textsuperscript{27} Currently available maintenance therapies include the following:

**Corticosteroids:** Corticosteroids have been used in kidney transplantation since the early 1960s. However, long-term steroid use is associated with numerous adverse effects including hypertension, new onset diabetes after transplantation, osteoporosis, fractures, hyperlipidemia, and growth retardation.\textsuperscript{10} The development of potent maintenance and induction agents has led to increasing use of steroid-sparing strategies.\textsuperscript{10}

**Calcineurin inhibitors (CNIs):** CNI-based regimens involving cyclosporine A (CyA) or tacrolimus have been the mainstay of maintenance immunosuppression in all solid organ transplants.\textsuperscript{28} Recommended starting dose for cyclosporine is 6-10 mg/kg, whereas for tacrolimus it is 0.15-0.30 mg/kg.\textsuperscript{10} During the first 3 months post-transplant, a 12-hour tacrolimus trough in the range of 8-12 ng/mL can be aimed for, followed by a level of 6-10 ng/mL for 4-12 months.\textsuperscript{10} For cyclosporine, a 12-hour trough of 250-350 ng/mL is maintained for the first few months followed by a gradual reduction of target levels.\textsuperscript{10}

Mammalian target of rapamycin (mTOR) inhibitors: mTOR inhibitors, namely sirolimus and everolimus, block the response of T- and B-cell activation by cytokines, including IL-2, IL-4 and IL-6, and inhibit lipopolysaccharide-induced B-lymphocyte proliferation.\textsuperscript{27} Sirolimus is a macrocyclic with potent antitumor and immunosuppressive properties.\textsuperscript{26} On the other hand, everolimus was developed as a semisynthetic analog with similar antiproliferative and immunosuppressive properties as well as dependable bioavailability.\textsuperscript{26}

**Belatacept:** It is a recombinant fusion protein with an extracellular domain that consists of human cytotoxic T lymphocyte antigen-4 (CTLA-4) and the Fc fragment of human IgG.\textsuperscript{10} It inhibits the delivery of costimulatory signals by binding to CD28 receptor, and results in T-cell anergy.\textsuperscript{27} Studies like the BENEFIT and BENEFIT-EXT trials have established its efficacy as a CNI-free maintenance agent.\textsuperscript{10} Belatacept is the first approved immunosuppressant that enables effective and safe CNI avoidance, and it is the only therapy that has shown progressive improvement in glomerular filtration rate (GFR) in a CNI-sparing setting.\textsuperscript{27}

Mycophenolate mofetil (MMF) and mycophenolic acid (MPA): MMF is a prodrug that is hydrolyzed in the gut by esterases to the active moiety MPA.\textsuperscript{26} MPA inhibits inosine monophosphate dehydrogenase, a key enzyme involved in purine synthesis by the salvage pathway in T-cells and B-cells.\textsuperscript{26} A pooled analysis of trials with 1493 recipients exhibited significantly reduced acute rejection episodes with MMF with improved 1-year graft and patient survival.\textsuperscript{26}

Azathioprine: It is generally used in patients who are intolerant to MMF.\textsuperscript{10} Usual daily dose administered is 2-3 mg/kg once daily.\textsuperscript{10}

Mizoribine: It is an imidazole nucleoside agent with immunosuppressive effect resembling that of MMF.\textsuperscript{27} It has been reported to be specific for lymphocytes and
inhibits their proliferation without interfering with purine synthesis in other cell types.  

Consensus key points-4

According to the panel experts, immunosuppressive therapy aims at preventing acute rejection and optimizing the function of the transplanted kidney, while minimizing adverse effects of immunosuppression (such as increased risk of infection, cancer, diabetes, and cardiovascular disease). Risk stratification and choosing the right induction agent depend on various key donor-related, transplant-related, and recipient-related factors, with vigilant short- and long-term monitoring of hematological status. Lastly, maintenance therapy starts immediately after transplant and continues for life.

MANAGEMENT OF KIDNEY TRANSPLANT REJECTION

The major goal of almost all therapies for AMR are removing circulating DSAs and reducing DSA production. Currently available strategies for treating AMR include antibody depletion with plasmapheresis, immunoadsorption (IA), immunomodulation with intravenous immunoglobulin (IVIG), and T cell- or B cell-depleting agents. 

Treatment of early active AMR (≤30 days post-transplant)

The combination of plasma exchange (PLEX) and intravenous immunoglobulin (IVIG) with corticosteroids can be considered as standard of care. However, in certain centers, corticosteroids are reserved for patients with concomitant T-cell-mediated rejection (TCMR). Complement inhibitors (like eculizumab and a C1 esterase inhibitor), rituximab, or splenectomy depending on availability are recommended adjunctive therapies. In cases where concomitant TCMR is present, it must be treated.

Treatment of late active and chronic active AMR (≥30 days post-transplant)

In cases of chronic active AMR or chronic transplant vasculopathy, treatment aims at stabilizing or reducing the rate of decline in GFR, proteinuria, histological injury score, and DSA titer while minimizing drug toxicity. Using IVIG and PLEX, with/without rituximab, has not been proven to improve outcomes in patients with chronic active AMR and has to be balanced against increased risk of adverse events such as infection and cost. Treatment must aim at optimizing immunosuppression and supportive care, with reintroduction of steroids (if on a steroid-free regimen), maintenance of trough tacrolimus levels >5 ng/mL, and enhancement of medical management with emphasis on blood pressure, glucose, and lipid control.

Viral infections after renal transplantation

Viral infections are a significant cause of morbidity and mortality post-transplantation. Preventive measures like pretransplant screening, prophylactic antivirals, or post-transplant viral monitoring could limit the effect of infections in some cases. Cytomegalovirus (CMV) and BK infections are commonly seen in the first year post-transplantation. Therefore, screening protocols are crucial for detecting patients with increased risk of virus reactivation and early disease, and this must be initiated immediately after transplantation.

CMV infection: In kidney transplant recipients with signs and symptoms suspicious for CMV disease, laboratory confirmation is essential for establishing diagnosis. A biopsy with histopathologic examination of tissue is occasionally needed to diagnose tissue-invasive CMV disease. CMV can be prevented by prophylaxis or by preemptive treatment. Prophylaxis must be initiated immediately after transplantation. Treatment is always indicated for active CMV infection or tissue-invasive CMV disease. Intravenous ganciclovir is a gold standard for the treatment of CMV disease.

BK virus infection: BK virus, a member of the polyomaviridae family, is a notable cause of renal allograft impairment. Renal biopsy remains the gold standard for a definitive diagnosis of BK nephropathy. Many centers periodically screen patients for BK virus as evidence of over immunosuppression and to enable reduction of immunosuppression before irreversible renal damage occurs. The mainstay of treatment for polyoma virus infections has been reduction in immunosuppression.

Novel therapeutics

Anti-IL6R monoclonal antibody tocilizumab has exhibited a beneficial safety profile, reduced DSA levels, and stabilization of kidney function at two years after treatment initiation in patients with chronic AMR. Another potential IL-6 antagonist, clazakizumab, is being investigated in terms of efficacy and safety profile over tocilizumab. Proteasome inhibitor-based strategies like carfilzomib may be promising therapies in transplantation, but have shown variable results. Evidence suggests that carfilzomib is well tolerated and effective as a desensitization monotherapy in depleting plasma cells and reducing HLA antibody levels in combination with plasmapheresis. Another novel development for renal transplantation is imifidase, an endopeptidase derived from Streptococcus pyogenes, which has specificity for human IgG, and when infused intravenously, causes rapid cleavage of IgG. Imifidase could be a revolutionary novel therapy for desensitization in patients who otherwise might have no hope for receiving a life-saving transplant. Lastly, numerous complement inhibitors like compstatin are currently under development for addressing complement dysregulation. The role and efficacy of complement-targeting agents in the prevention and
treatment of rejection and other complement related conditions resulting in graft injury are currently under investigation. Complement inhibitors targeting C1 can be leveraged to treat AMR while sparing the alternative pathway, thereby potentially averting infection complications. In the future, targeted therapies that interfere with the complement cascade at various levels will prove to be valuable strategies to mitigate allograft injury, not just due to AMR, but also from ischemia-reperfusion injury and recurrent complement mediated glomerulopathies.

Consensus key points-5

The panel experts emphasized on the use of appropriate therapies for early and late AMR in accordance with recent evidence. They further added that screening and management of CMV and BK virus are crucial for achieving favorable outcomes following transplant.

CONCLUSION

This expert consensus paper highlights that appropriate diagnosis of transplant rejection includes clinical evaluation, renal biopsy, and Banff classification. Immunogenetic profiling of recipients and pre-transplant tissue crossmatch between potential donor and recipient are essential steps before transplantation. Post-transplant induction and maintenance immunosuppression are crucial in reducing the risk of graft rejection and prolonging graft survival. Kidney transplant rejection can be managed effectively with currently available strategies like plasmapheresis, immunoadsorption, immunomodulation with IVIG, and T cell-or B cell-depleting agents. Despite the development of promising therapies, novel strategies are required to enhance the overall management of kidney transplantation, its rejection, and improving long-term graft and patient survival.

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