9. Types of rejection

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9.1 Antibody-mediated rejection


- A consensus of expert opinion in regards to standard of care treatment for active and chronic active AMR after kidney transplantation


- This study is a retrospective analysis of a single center’s experience of using combination therapy (methylprednisolone, plasma exchange, and IVIG) including rituximab for post lung transplant AMR in Japanese patients.


- A case report detailing the use of Daratnumumab for treatment of therapy-refractory AMR in the context of ABO-incompatible kidney transplantation.


- This study is a retrospective analysis of a single center’s experience on the efficacy, safety, and DSA response to active AMR treatment modalities (corticosteroids, plasmapheresis, IVIG, and rituximab) in pediatric renal transplant recipients. The objective was to differentiate individual responses to active AMR treatment between class I and class II DSAs.


- This article summarizes the American Society of Transplantation community–wide discussion of Outstanding Questions in Transplantation, focusing on B–cell biology and donor–specific antibody prevention
  - This article reviews different strategies (IVIG plus rituximab, proteasome inhibition, complement blockade, novel agents in pipeline) in the management of late antibody mediated rejection including relevant clinical trial experiences

  - This article reviews the role of the complement system in antibody and T cell mediated rejection

  - Case report detailing the use of tocilizumab for the management of AMR in a cardiac transplant recipient

  - This clinical trial reports the results of a phase 2, randomized, multicenter, open-label, two-arm study evaluating the safety and efficacy of eculizumab in preventing acute antibody mediated rejection in sensitized recipients of living donor kidney transplants requiring pre transplant desensitization.

  - This clinical trial reports the results of an open-label, single-arm trial to evaluate the safety and efficacy of eculizumab in preventing acute AMR in recipients of deceased-donor kidney transplants with preformed donor-specific antibodies

  - Randomized, placebo-controlled trial investigating the role of boretzomib on preventing GFR decline through stopping the progression of DSA-positive AMR

  - A review that highlights recently developed AMR diagnostic criteria in lung transplantation, potential mechanisms that mediate the development of AMR, and discusses current and emerging treatment strategies for AMR.

  - This article discusses new advances, importance of immunosuppressive medication non adherence in dn DSA formation, associations between AMR, cellular rejection, changes in
glomerular filtration rate, and challenges of clinical trial design for the prevention and treatment of AMR.


- A systematic review through February 2017 that examines the treatments and outcomes for AMR.


- This is a Cochrane Systematic Review that reviewed the benefits and harms of a drug or drug combination for the treatment of antibody mediated rejection in kidney transplant recipients.


- This article reviews novel approaches (anti–CD20, proteasome inhibitors, IL–6 receptor blockade, complement inhibition) in the management of antibody mediated rejection.


- A systematic review and meta-analysis of clinical relevance of complement-activating anti-HLA DSAs across all solid organ transplant patients along with their transplant outcomes.


- A review article that explains the role of the endothelial cells and their active participation in rejection in solid organ transplant recipients.


- This review examines temporal relationships between key morphologic lesions of active and chronic ABMR in biopsies of human grafts.


- Review article regarding the updated 2017 Banff criteria for diagnosis of rejection in kidney transplants.


- Observational study of lung transplant recipients with AMR treated with carfilzomib.

- Demonstrated a multimodal approach to the treatment of suspected AMR in lung transplant recipients with a standardized protocol of plasma exchange, steroids, bortezomib, rituximab, and IVIG


- Review article regarding the clinical and histological manifestations of AMR and the immunopathological mechanisms contributing AMR and current therapies to treat it.


- A systematic review evaluates the evidence for rituximab use in the treatment of acute and chronic antibody-mediated renal transplant rejection


- Retrospective study evaluating the role of bortezomib in kidney transplant recipients that are refractory to conventional treatment


- In this phase III, multicenter, double-blind, placebo-controlled trial, we randomly assigned patients with biopsy proven AMR to receive rituximab (375 mg/m²) or placebo at day 5. All patients received PE, IVIg, and CS.


- Outcome of patients with transplant glomerulopathy (TG) is poor. Using B-cell targeting molecules represent a rational strategy to treat TG during chronic antibody-mediated rejection.


- This article is a scientific statement from the American Heart Association to provide heart transplant professionals with an overview of the current status of the diagnosis and treatment of AMR in the cardiac allograft based on recent consensus conferences and the published literature. It includes recommendations to facilitate evolving standardization and strategies for future study.

• Comprehensive review of AMR diagnosis and treatment. Includes a nice literature summary by treatment agent.


• Literature review of bortezomib in the treatment of antibody mediated rejection. Discusses mechanisms of action, basic science research, and current clinical trials


• This review discusses current diagnostic, pathologic, phenotypes, prevention strategies and novel treatment options for AMR


• The major outcome of the 2013 Banff conference is defining criteria for diagnosis of C4d-negative AMR and respective modification of the Banff classification.


• This review discusses HLA and non-HLA antibodies as well as non-complement dependent mechanisms of antibody toxicity


• This serum-based study details the potential role of non-HLA antibodies (MICA) and their impact on allograft survival.


• This review discusses the nature of anti-vimentin antibodies, their potential mechanisms of allograft damage and their impact on allograft survival.


• This retrospective study studied the impact of C1q-binding antibodies in combination with DSA and their impact on post-transplant renal allograft outcomes.


• This retrospective study addresses the outcomes of renal allografts undergoing early or late AMR while addressing some potential causes for late vs early AMR.

• This review discusses the mechanism of action as well as potential indications of rituximab in renal transplantation


• This systematic review addresses potential uses for eculizumab in renal transplantation (prevention, treatment, aHUS, etc)


• This review assesses and grades the available evidence for the treatment of acute AMR in kidney transplant recipients.


• This review highlights the roles of IVIg in highly sensitized patients, alone or in combination with rituximab and for the treatment of AMR


• This prospective trial demonstrates the potential role of eculizumab therapy in prevention AMR in sensitized renal transplant recipients
9.2 Chronic Rejection


- This study is a retrospective analysis of a single center’s experience on their use of bortezomib as adjunctive therapy for treatment of refractory biopsy proven chronic active antibody-mediated rejection in kidney transplant patients.


- An overview on chronic solid organ transplant rejection including etiology, epidemiology, pathophysiology, treatment and management of rejection


- Examined the impact of tocilizumab for chronic AMR in total IgG subclasses


- A review of clinical evidence regarding strategies to prevent chronic rejection after lung transplant


- Case series of renal transplant recipients with chronic AMR that were treated with tocilizumab
- Significant reductions in DSAs and stabilization of renal function were seen at 2 years


- Review article regarding the presentation, diagnosis, and management of both acute and chronic liver allograft rejection.


- This review discusses transplant glomerulopathy secondary to chronic anti-body mediated rejection and reviews both prevention strategies and treatment.


- This review discusses chronic antibody-mediated rejection and its progression to transplant glomerulopathy focusing on pathophysiology and potential therapy.

- This review details autoimmune, alloimmune and non-immune mechanisms of cardiac allograft rejection and coronaropathy


- This review discusses the role of DSA in chronic types of AMR, including indolent AMR, C4d negative AMR and late pathophysiologic effects of DSA.


- This review describes the clinical spectrum of lung allograft dysfunction and the bronchiolitis obliterans syndrome, their pathogenesis and auto/immune risk factors as well as non-immune factors.


- This review details multiple mechanisms of cellular and humoral kidney allograft rejection and integrates those in the context of chronic rejection.


- This review lays the bases of allo- and autoimmune responses in the context of chronic rejection for heart, lung, liver and kidney allografts.


- This review details immune and non-immune reasons for chronic liver allograft failure including disease recurrence and de novo autoimmune hepatitis.


- This review discusses the pathophysiologic processes underlying chronic renal allograft dysfunction from immune perspective but also recipient and donor characteristics. Prevention and treatment are also discussed.
9.3 Hyperacute Rejection


- This article reviews the current understanding of the mechanisms that drive surface expression of HLA antigens and proposes that an algorithm to combine HLA antibody and antigen levels in each donor–recipient pair could be used to better stratify transplant risk.


- A review article that explains accommodation in incompatible blood groups in kidney transplant patients


- A review article discussing the evidence that supports autoimmunity as a contributor to rejection and how to test for pre-existing immune responses that could occur


- Simultaneous liver-kidney transplant may protect the kidney allograft from hyper-acute rejection. However, patients with class II donor-specific antibodies should be closely monitored for both acute and chronic rejection of both organs.


- Review of hyperacute rejection of ABO-incompatible kidney allografts and current views on pre-transplant management to improve post-transplant outcomes


- Xenotransplantation was initially limited by hyperacute rejection. However, as genetic manipulation has largely allowed many of those issues to be resolved, the focus has shifted to overcoming the other barriers to xenotransplantation


- An immature immune system is more permissive of ABO-incompatible allografts. Hyperacute rejection may be avoided in infants who receive ABOi heart transplants.


- [Article in Spanish] The objective of the study is to evaluate the risk of graft failure. From the study, the authors concluded that evaluation of risk for graft failure should include the allosensibilization history of the receptor. The cytotoxicity crossmatch indicates a high risk of hyperacute rejection and is considered a contraindication. The Flow Cytometry crossmatch indicates an increase in the probability to loss the graft in the first year that is low for first transplants (>10%) but higher for retransplantation (>30%). The virtual crossmatch by solid phase indicates an increase in the probability to have an antibody mediated rejection (from 5% to 55%) but did not contraindicate always the transplant.

- One of the first descriptions of donor-specific antibodies causing hyper-acute rejection in kidney transplantation.
9.4 T-cell mediated rejection


- Case report of successfully using vedolizumab, a monoclonal antibody against α4β7+ integrin involved in gut-homing of T cells, for acute cellular rejection in intestinal transplant


- Review of HLA epitope matching as a new methodology for prediction of alloreactivity between donor and recipient HLA alleles
- HLA epitope matching offers a more precise assessment of donor-recipient HLA compatibility. Higher degrees of epitope match could correlate with prevention of acute graft rejection and graft failure.


- Prospective cohort of kidney recipients with biopsy proven acute TCMR receiving steroids
- Evaluated the clinical, histological, and immunological phenotypes at the time of acute TCMR and 3 months post-treatment


- Targeted proteomic analysis with proximity extension immunoassay is a promising minimally invasive technique to diagnose acute T-cell mediated rejection in kidney transplant recipients


- A case report of treating acute cellular rejection in a pregnant woman. The patient’s son was born premature via vaginal labor
- Successful outcomes can occur with close monitoring and daily dialysis in femal kidney transplant patients with resistant rejection


- This article reviews recent advances in our understanding of how the different T cell allorecognition pathways are triggered, consider how this generates effector alloantibody and cytotoxic CD8 T cell alloresponses and assess how these responses contribute to early and late allograft rejection


- A randomized controlled trial of 90 adult kidney transplant recipients who received varying doses of antithymocyte globulin (4.5 mg/kg in 3 days, vs 4.5mg/kg as a single dose, vs 6mg/kg in 3 days)

Review article that discusses the pathophysiology, diagnosis, and clinical presentation and treatment for ACR and AMR in lung transplant


Systematic review of studies providing functional and/or histological response rates to the treatment of acute cellular rejection after kidney transplantation. Banff grade 2B demonstrated worse prognosis compared to other histopathologic diagnoses of kidney rejection.


Extensive review of the literature to describe the utility and potential clinical benefit of gene expression (both proteomic and genomic transcripts) in diagnosis of multiple forms of kidney transplantation pathology


Review of the role regulatory T cells play in protecting a renal allograft from rejection or in predicting the clinical outcome of rejection.


Review and discussion of the role IL-17 and T-helper 17 cells play in allograft


Discussion of the use of antithymocyte globulin and alemtuzumab to control T-cell mediated renal allograft rejection


Review of the mechanisms of T-cell mediated allograft rejection and the treatment/management of ACR with different immunosuppressive agents. Also includes a history and discussion of developing T-cell mediated allograft tolerance.


This pivotal trial showed that rATG was superior to ATGAM in treating acute cellular rejection in renal transplantation.
9.5 Donor specific cell free DNA marker

- This is a validation study of myTAIHEART® a non-invasive DNA marker to assess heart transplant rejection in pediatric and adult recipients ≥ 2 months old and ≥ 8 days post-transplant.


- This is a systematic review of published literature investigating the use of cell free DNA in monitoring of graft health after solid organ transplantation.