9. Types of rejection

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9.1 Antibody-mediated rejection


- Retrospective study evaluating prevalence of de novo DSAs in adult liver transplant recipients on CNI-free maintenance regimen and their associations with allograft histopathologic abnormalities. Patients on CNI-free regimens had a higher prevalence of dn-DSA than standard regimens. Presence of dn-DSA but no CNI-free regimen was associated with abnormal histopathologic abnormalities.


- Single-center study evaluating different AMR treatment approaches and comparing treatment approaches in presence or absence of DSAs in kidney transplant recipients. Long-term IVIG was more favorable in patients with DSA-positive AMR while immunosuppression intensification was more effective in DSA-negative AMR.


- Retrospective cohort analysis of adult kidney transplant recipients post-COVID infection. Incidence of post-COVID DSA was low despite a decrease in immunosuppression during COVID infection.


- Review of current and future treatment options for AMR after pediatric kidney transplant.
   • Case report of an adult heart transplant recipient with symptomatic late DSA-positive AMR who fully recovered graft function following treatment with eculizumab, thymoglobulin, IVIG, and rituximab.

   • Case report of adult living donor liver transplant recipient who developed acute antibody mediated rejection after desensitization of pre-transplant antibodies treated with bortezomib and everolimus.

   • Retrospective cohort study of adult heart transplant recipients receiving intermittent IVIG for elevated DSAs.

   • Case series of adult liver transplant recipients who developed antibody mediated rejection as well as a review of literature describing antibody mediated rejection management strategies and outcomes after liver transplant.

   • Case report of acute AMR leading to acute liver failure in an adult liver transplant recipient.

   • Case report of acute anti-A/B AMR after ABO-incompatible kidney transplant that resolved with pulse corticosteroids, plasmapheresis, and bortezomib

   • A single-center retrospective study describing the management of AMR in lung transplant recipients.

A phase 2 randomized pilot trial of clazakizumab compared to placebo in renal transplant recipients with late antibody mediated rejection. Patients under active treatment displayed decreased DSA, but 5 (25%) patients developed serious infection.


An overview of the treatment options for non-HLA antibody-mediated rejection


A retrospective study of 8 patients who received additional eculizumab to 10 patients without. There were no significant differences seen between groups.


A review of recent advances in clinical diagnosis and treatment of antibody-mediated rejection in liver transplantation.


An extension of the RITUX-ERAH study, found that 7 years after ABMR, there was not benefit seen with the addition of rixutimab to plasma exchanges, IVIG, and steroids.


A cohort of 490 SOT recipients that received the influenza vaccine did not develop anti-HLA antibodies. Only 2 (0.4%) patients were diagnosed with graft rejection.


A discussion of emerging therapeutics for the prevention and treatment of AMR.


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 Daratumumab 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 bortezomib 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 to 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

- Literature review of the safety and utility tocilizumab and clazakizumab in the treatment of chronic antibody mediated rejection in kidney transplant recipients

- Case report of a kidney transplant recipient who received anti-thymocyte globulin for chronic antibody mediated rejection with improvement in pathologic findings and donor specific antibodies.


• A meta-analysis of 3 RCTs (SHITRIT, NOCTET, and 4EVERLUNG) compared mTORi with low-dose CNI compared to isolated CNI immunosuppression. Only 4EVERLUNG assessed chronic graft rejection, and did not show a significant difference in the onset of new-onset chronic rejection development between the groups. The mTORi-based group trended toward greater risk of death and acute graft rejection, although not statistically significant.


• A case report of facial retransplantation in a sensitized recipient that describes chronic AMR and recurrent ACR treatment with steroids, Thymoglobulin, bortezomib, eculizumab, alemtuzumab, IVIG, plasmapheresis, topical tacrolimus, and belatacept


• An overview on chronic kidney transplant rejection including etiology, epidemiology, pathophysiology, treatment, and management of rejection


• A single-arm, single-center phase I/II clinical trial administered bone marrow-derived mesenchymal stem cells (BM-MSCs) for cAMR. The median change in maximum DSA was –4310 at 2 years (p=0.0040).


• 15 kidney recipients with cAMR were treated with tocilizumab found early serological and histological improvements even in advanced transplant glomerulopathy.


• High quality transcriptomes generated from two chronic kidney transplant rejection 10iopsey samples showed increased immune cells and a novel subpopulation of myofibroblasts and comprehensively describes immune cell profiles.


• Tocilizumab reduces total IgG, IgG1-3, and anti-HLA-total IgG and IgG3 levels, suggesting that it suppresses Ig production in B cells nonspecifically, which may explain the benefit when used in cAMR.

• 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


- A meta-analysis 4256 patients from 21 trials on the effectiveness of induction dose of rituximab. Low dose rituximab (20mg) was more efficacious and reduced serious infection compared to the high dose regiments of rixutimab (200mg-500mg)

- Two case reports of suspected hyperacute and acute rejection following lung transplantation in patients with advanced COVID-19.


- A case of hyperacute rejection after living donor kidney transplant suspected to be mediated by increased IgG1 isoagglutinin subclass identified using flow cytometry.


- An RCT of 22 patients who underwent ABO-incompatible liver transplants were treated with mesenchymal stem cells transfusion (MSCT) or rituximab for AMR prophylaxis. MSCT group had less acute rejection, less biliary complications, and less infection. No significant difference was seen in 2-year graft and recipient survival between the groups.


- A case review of hyperacute fulminant graft dysfunction suspected to be mediated by non-HLA antibodies (AT1R antibodies and a positive endothelial cell crossmatch).


- A metaanalysis of ABO-incompatible living kidney transplant recipients who received a single 200mg dose or 375 mg/m² in rituximab groups. The 200mg dose showed similar rates of rejection, graft survival, and patient survival with lower incidence of infection after transplantation.


- 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


- 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


- Systematic review and meta-analysis of 12 studies reviewing BPAR histological findings (including Banff borderline) and impact of TCMR treatment strategies and outcomes for patients on tacrolimus/mycophenolate maintenance therapy

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


- An overview Tregs function in the liver and discussion of therapies that aim to increase Treg frequency and function in liver transplant patients.


- A systematic review of the incidence and outcomes of persistent TCMR after treatment in patient taking tacrolimus and mycophenolic acid. Persistent TCMR occurred frequently, with 39% of patients having BPAR within 2-9 months of the index TCMR.


- 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 female 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 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 derived cell free DNA marker


- Review article summarizing the review summarizes used tof DD-cfDNA, measurement of DD-cfDNA in clinical transplantation, approaches for improving sensitivity and specificity and long-term prospects as a transplant biomarker to supplement traditional organ monitoring and invasive biopsies


- Cross-sectional cohort study evaluating association between de novo donor-specific antibodies (dnDSAs) class and their mean fluorescence intensity (MFI) with donor-derived cell-free DNA (dd-cfDNA)


- Single-center prospective cohort study of pediatric deceased-donor-kidney transplant recipients assessed with sequential dd-cfDNA labs within 3 months. Patients were followed up for 1 year.


- Single and multicenter liver transplant recipient cohorts were used to assess the utility of dd-cfDNA to diagnose graft injury in liver transplant recipients (LTR) and as a predictive biomarker prior to alternative causes of allograft dysfunction


- In 51 lung transplant recipients, high risk bacteria and viral microbes (those known to increase the risk of allograft dysfunction) were associated with elevated dd-cfDNA (%).


- A study examining an assay that combines both dd-cfDNA (%) and absolute quantify of dd-cfDNA (copies/ml) in 41 patients, and found improved sensitivity, with minimal sensitivity decline for diagnosing rejection in renal transplants.


- Of 236 dd-cfDNA results from sensitized kidney transplants who underwent outpatient allograft biopsies for surveillance, sensitivity was 0% and sensitivity was 89% (compared to 28% and 96% respectively in clinically indicated biopsies).
- A review of the clinical utility of dd-cfDNA in renal transplantation.

- In a cohort of 14 patients that developed grade 3 primary graft dysfunction following lung transplant, the amount of cfDNA (especially nuclear DNA) in ex vivo lung perfusion was elevated compared to the 48 patients who did not develop primary graft dysfunction.

- A review of dd-cfDNA in solid organ transplants, including a discussion of the utility among different organ tissues, commercially available assays, contraversies, and future directions.

- A review of the evidence and future directions of the use of dd-cfDNA in monitoring acute rejection in heart and lung transplants.

- A case of elevated dd-cfDNA in a liver transplant recipient that had graft-versus host disease.

- Adding dd-cfDNA in DSA-positive renal allograft recipients significantly improved diagnostic accuracy.

- Elevated total cfDNA in heart transplant recipients predicted death and treatment for infection. Elevated donor fraction was associated with histopathologic acute rejection and CAV, but total cfDNA was not.

- A systematic review of cfDNA’s use for detecting rejection in heart transplants.

- In the DART cohort, both dd-cfDNA (≥1%) and dd-cfDNA variability (≥0.34%) in the first post-transplant year were associated with decline in cGFR ≥25% in the second year. Patients with de novo DSAs also had higher dd-cfDNA levels compared to patients who did not have DSA.


- A review of dd-cfDNA for detecting rejection in kidney transplantation.


- A post hoc analysis of simultaneous blood gene expression profiles and donor-derived cfDNA assays in 428 samples paired with surveillance biopsies. Dd-cfDNA detected more antibody-mediated rejection whereas gene expression profile detected more cellular rejection.


- Ventricle-specific differentially methylated regions of chromosome 9 and 12 detected in the cfDNA of heart transplant patients increased with biopsy-proven rejection grade.


- 67 pediatric kidney recipients underwent dd-cfDNA (AlloSure) monitoring for either routine testing or for suspicion of rejection. Dd-cfDNA >1% was diagnostic of rejection with a sensitivity of 86% and specificity of 100% (AUC: 0.996, 0.98-1.00; P=0.002). Given that neither DSA or AT1R positivity was statistically associated with biopsy-proven rejection, dd-cfDNA may be superior to these indicators.


- A review of the clinical relevance of DNA methylation changes regulating different immune pathways that can a role in acute or chronic graft rejection in kidney, lung, and heart transplant.


- Metaanalysis of the accuracy of dd-cfDNA found that dd-cfDNA is a useful marker for the diagnosis of AMR in recipients with suspected renal dysfunction. However, utility for diagnosing main rejection episodes was uncertain.

- 49 pediatric liver transplant recipients underwent dd-cfDNA monitoring for suspicion of rejection. Ddcf-DNA of 28.7% or greater yielded a sensitivity of 72.7% and specificity of 94.7%. There was a significant difference in dd-cfDNA distribution between whole and split livers.


- A metanalysis found patients with ABMR had significantly higher median dd-cfDNA fractions than patients without rejection or those with stable graft function. However, patients with TCMR did not have different median dd-cfDNA fractions compared to the other groups.


- 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.

9.6 Gene Expression Profiling


- Analysis of heart transplant recipients who received regular AlloMap testing as part of allograft rejection surveillance and enrolled in Outcomes AlloMap Registry (OAR) were analyzed. AlloMap scores for patients with CMV (but no ongoing rejection) were compared with those who were never infected with CMV


- Multicenter study validating TruGraf gene expression profiling to foridentification of subclinical acute rejection using peripheral blood paired with surveillance biopsies and strict clinical phenotyping algorithms


- Cardiac Allograft Rejection Gene Expression Observational II Study (CARGO II)
• Assessed validity of gene expression profiling test performance (AlloMap) in heart transplant population


• Invasive Monitoring Attenuation through Gene Expression (IMAGE) study
• Prospective, randomized, observational, multi-center, controlled trial showing non-inferiority of clinical outcomes in patients managed with gene expression profiling for rejection surveillance vs. patients monitored with conventional biopsy

9.6 Xenotransplantation


• 10-year review of human xenotransplantation cases with data collected from scientific journals, international congresses, internet searches, and declarations of International Xenotransplantation Association members
• Since last review (1995-2010) clinical activities were reduced but all were officially approved through local protocols /regulations


• Expert panel review of history of xenotransplantation


• Review article of first successful pig to heart xenotransplant


• Summarizes the challenges that swine leukocyte antigens (SLA) pose for xenotransplantation, and describes techniques for mutating target SLA amino acids.


• Xenotransplantation has been proposed as an approach to solve the problem of human organ shortage. This is a summary of the history of xenograft research, immunological mechanisms of hyperacute and acute xenograft rejection, and longest survival time of solid organs in preclinical models.


• This article summarizes data on Neu5Gc immunogenicity and its potential impact on limiting xenotransplantation in humans.

- 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.