9. Types of rejection

Table of Contents

9.1 Antibody-mediated rejection

Meszaros M, et al (2022). Impact of calcineurin inhibitor-free immunosuppression on de novo donor-specific antibody formation in liver transplant recipients. Liver International. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35184373/

- 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 not CNI-free regimen was associated with abnormal histopathologic abnormalities.

Koslik MA, et al (2022). Differential Treatment Effects for Renal Transplant Recipients With DSA-Positive or DSA-Negative Antibody-Mediated Rejection. Frontiers in Medicine. 9: 816555. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35174191/

- 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.

Masset C, et al (2022). Occurrence of de novo Donor Specific Antibodies after Covid-19 in kidney transplant recipients is low despite immunosuppression modulation. Kidney International Reports. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35155848/

- 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.

Bertacchi M, et al (2022). Antibody-mediated rejection after kidney transplantation in children; therapy challenges and future potential treatments. Clinical Transplantation. E14608. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35137982/

- Review of current and future treatment options for AMR after pediatric kidney transplant.

Yerly P, et al (2022). Complement blockade with eculizumab to treat acute symptomatic humoral rejection after heart transplantation. Xenotransplantation. 29(1): e12726. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35001433/

- 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.

Komagome M, et al (2022). Refractory Acute Antibody Mediated Rejection in Liver Transplant After Desensitization of Preformed Donor Specific Antibody-Validity of Bortezomib and Everolimus: A Case Report. Transplantation Proceedings. 54(1): 147-152. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34974892/

- 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.

Yopes M, et al (2022). Chronic intermittent intravenous immunoglobulin in heart transplant recipients with elevated donor-specific antibody levels. Clinical Transplantation. 36(2): e14524. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34705286/

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

Baradaran H, et al (2022). Antibody-Mediated Rejection in Adult Liver Transplant Recipients: A Case Series and Literature Review. Journal of clinical pharmacology. 62(2):254-271. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34480762/

- 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.

Robinson TJ, et al (2022). Acute liver failure secondary to acute antibody mediated rejection after compatible liver transplant: A case report. World journal of hepatology. 14(1):287-294. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35126855/

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

Lee JH, et al (2022). Acute Anti-A/B Antibody-Mediated Rejection After ABO-Incompatible Kidney Transplantation Treated With Bortezomib and Plasmapheresis: A Case Report. Transplantation Proceedings. S0041-1345(21)00922-2. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35067375/

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

Neuhaus, K., et al (2022). Antibody-Mediated Rejection Management Following Lung Transplantation. *The Annals of pharmacotherapy*, *56*(1), 60–64. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33899550/

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

Doberer, K., et al (2021). A Randomized Clinical Trial of Anti-IL-6 Antibody Clazakizumab in Late Antibody-Mediated Kidney Transplant Rejection. *Journal of the American Society of Nephrology : JASN*, *32*(3), 708–722. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33443079/

- 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.

Kardol-Hoefnagel, T., & Otten, H. G. (2021). A Comprehensive Overview of the Clinical Relevance and Treatment Options for Antibody-mediated Rejection Associated With Non-HLA Antibodies. *Transplantation*, *105*(7), 1459–1470. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33208690/

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

Kittleson, M. M.,et al (2021). Eculizumab for antibody-mediated rejection in heart transplantation: A case-control study. *Clinical transplantation*, e14454. Advance online publication. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34402096/

- A retrospective study of 8 patients who received additional eculizumab to 10 patients wihtout. There were no significant differences seen between groups.

Lee, B. T., Fiel, M. I., & Schiano, T. D. (2021). Antibody-mediated rejection of the liver allograft: An update and a clinico-pathological perspective. *Journal of hepatology*, *75*(5), 1203–1216. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34343613/

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

Bailly, E., et al (2020). An extension of the RITUX-ERAH study, multicenter randomized clinical trial comparing rituximab to placebo in acute antibody-mediated rejection after renal transplantation. *Transplant international; 33*(7), 786–795. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32279367/

- 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.

Cordero, E., et al (2020). Effect of Influenza Vaccination Inducing Antibody Mediated Rejection in Solid Organ Transplant Recipients. *Frontiers in immunology*, *11*, 1917. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33123119/

- 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.

Jordan, S. C., et al (2020). The role of novel therapeutic approaches for prevention of allosensitization and antibody-mediated rejection. *Am J Transpl;*, *20 Suppl 4*, 42–56. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32538536/

- A discussion of emergying therapeutics for the prevention and treatment of AMR.

The 2019 Expert Consensus from the Transplantation Society Working Group (2020). Recommended Treatment for Antibody-mediated Rejection after Kidney Transplantation. *Transplantation*. 2020 Jan 8. doi: 10.1097/TP.0000000000003095. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31895348

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

Yamanashi K, Chen-Yoshikawa TF, Hamaji M, et al (2020). Outcomes of combination therapy including rituximab for antibody-mediated rejection after lung transplantation. *Gen Thorac Cardiovasc Surg*.

2020;68(2):142–149. doi:10.1007/s11748-019-01189-1. Retrieved from: https://europepmc.org/article/med/31435872

- 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.

Spica D, et al (2019). Daratumumab for Treatment of Antibody-Mediated Rejection after ABO-Incompatible Kidney Transplantation. Case Rep Nephrol Dial. 2019;9(3):149–157. Published 2019 Nov 13. doi:10.1159/000503951. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6902247/

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

Kincaide E, et al (2019). Impact of active antibody-mediated rejection treatment on donor-specific antibodies in pediatric kidney transplant recipients. *Pediatr Transplant*. 2019;23(8):e13590. doi:10.1111/petr.13590. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31617318

- 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.

Chong AS, et al (2019). Outstanding questions in transplantation: B cells, alloantibodies, and humoral rejection. *Am J Transplant* 2019; 19: 2155-2163. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30803121

- 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

Bohmig GA, et al (2019). The therapeutic challenge of late antibody-mediated kidney allograft rejection. *Transpl Int* 2019; 32: 775-788. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30955215

- 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

Grafals M, Thurman JM (2019). The Role of Complement in Organ Transplantation. *Front Immunol*. 2019; 10:2380. Published 2019 Oct 4. doi:10.3389/fimmu.2019.02380. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31636644

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

January S, Pottebaum A, Raymer D, Lavine K (2019). Tocilizumab for antibody-mediated rejection in setting of cardiac allograft vasculopathy. *J Heart Lung Transpl*. 2019 Apr; 38(4): S38-S39. Retrieved from: https://www.jhltonline.org/article/S1053-2498(19)30080-4/fulltext

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

Marks WH, et al (2019). Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living -donor kidney transplant recipients requiring desensitization therapy: A randomized trial [published online ahead of print March 19, 2019]. *Am J Transplant*. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30887675

- 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.

Glotz D, et al (2019). Safety and efficacy of eculizumab for the prevention of antibody-mediated rejection after deceased-donor kidney transplantation in patients with preformed donor-specific antibodies. *Am J Transplant.* (2019) 19:2865–75. doi: 10.1111/ajt.15397. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31012541

- 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

Eskandary F, et al (2018). A randomized trial of bortezomib in late antibody-mediated kidney transplant rejection. *J Am Soc Nephrol*. 2018 Feb; 29 (2): 591-605. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29242250

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

Hulbert AL, Pavlisko EN, Palmer SM (2018). Current challenges and opportunities in the management of antibody-mediated rejection in lung transplantation. *Curr Opin Organ Transplant*. 2018;23(3):308–315. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29742565

- 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.

Velidedeoglu E, Cavaille-Coll MW, Bala S, Belen OA, Wang Y, Albrecht R (2018). Summary of 2017 FDA public workshop: antibody mediated rejection in kidney transplantation. *Transplantation*. 2018; 102(6):e257–64. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29470345

- 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

Wan SS, Ying TD, Wyburn K, Roberts DM, Wyld M, Chadban SJ (2018). The Treatment of Antibody-Mediated Rejection in Kidney Transplantation: An Updated Systematic Review and Meta-Analysis. *Transplantation*. 2018;102(4):557-568. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29315141

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

Bajpai NK, et al (2018). Interventions for treating antibody-mediated acute rejection in kidney transplant recipients. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD013033. DOI: 10.1002/14651858.CD013033. Retrieved from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013033/abstract

- 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.

Montgomery RA, Loupy A, Segev DL (2018). Antibody-mediated rejection: new approaches in prevention and management. *Am J Transplant*. 2018; 18(Suppl 3):3–17. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29292861

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

Bouquegneau A, et al (2018). Complement-activating donor-specific anti-HLA antibodies and solid organ transplant survival: A systematic review and meta-analysis. *PLoS Med*. 2018; 15(7):e1002637. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29799874

- 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

Cross AR, Glotz D, Mooney N (2018). The role of the endothelium during antibody-mediated rejection: from victim to accomplice. *Front Immunol*. 2018; 9:106. Retrieved from: Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29434607.

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

Haas M (2018). The relationship between pathologic lesions of active and chronic antibody-mediated rejection in renal allografts. *Am J Transplant* 2018; 18: 2849. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30133953

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

Haas M, et al (2018). The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am J Transplant*. 2018;18(2):293–307. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29243394

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

Ensor Cr, et al (2017). Proteasome inhibitor carfilzomib-based therapy for antibody-mediated rejection of the pulmonary allograft: use and short-term findings. *Am J Transplant*. 2017 May; 17(5): 1380-1388. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28173620.

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

Vacha M, et al (2017). Antibody depletion strategy for the treatment of suspected antibody-mediated rejection in lung transplant recipients: does it work? *Clin Transpl*. 2017 Mar; 31 (3): e12886. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27988971.

- 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

Valenzuela NM, Reed EF (2017). Antibody-mediated rejection across solid organ transplants: manifestations, mechanisms, and therapies. *J Clin Invest*. 2017;127(7):2492-2504. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28604384

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

Macklin PS, Morris PJ, Knight SR (2017). A systematic review of the use of rituximab for the treatment of antibody-mediated renal transplant rejection. *Transplant Rev (Orlando).* 2017;31(2):87-95. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28187998

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

De Sousa-Amorim E, et al (2016). Bortezomib for refractory acute antibody-mediated rejection in kidney transplant recipients: a single-centre case series. *Nephrology (Carlton)*. 2016 Aug; 21 (8): 700-704. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26492594.

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

Sautenet B, Blancho G, Buchler M, et al (2016). One-year results of the effects of rituximab on acute antibody mediated rejection in renal transplantation: RITUX-ERAH, a multicenter double-blind randomized placebo-controlled trial. *Transplantation* 2016; 100: 391 – 399. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26555944

- 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.

Bachelet T, Nodimar C, Taupin J, et al (2015). Intravenous immunoglobulins and rituximab therapy for severe transplant glomerulopathy in chronic antibody mediated rejection: a pilot study. *Clin Transplant* 2015; 29: 439-446. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25739833

- 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.

Colvin MM, Cook JL, Chang P, et al (2015). Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association. *Circulation*. 2015;131(18):1608–1639. doi:10.1161/CIR.0000000000000093. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25838326

- 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.

Kim M, Martin ST, Townsend KR, Gabardi S (2014). Antibody-mediated rejection in kidney transplantation: a review of pathophysiology, diagnosis, and treatment options. *Pharmacotherapy* 2014; 34 (7): 733- 744. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24753207

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

Ejaz NS, Alloway RR, Halleck F, Durr M, Budde K, Woodle ES (2014). Review of bortezomib treatment of antibody-mediated rejection in renal transplantation. *Antioxid Redox Signal*. 2014; 21 (17): 2401-18. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24635140

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

Djamali A, Kaufman DB, Ellis TM, Zhong W, Matas A, Samaniego M (2014). Diagnosis and Management of Antibody-Mediated Rejection: Current Status and Novel Approaches. *Am J Transplant*. 2014. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24401076

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

Haas M, Sis B, Racusen LC, Solez K, Glotz D, et al (2014). Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant*. 2014; 14(2): 272-283. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24472190

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

Valenzuela NM, McNamara JT, Reed EF (2014). Antibody-mediated graft injury: complement-dependent and complement-independent mechanisms. *Curr Opin Organ Transplant*. 2014; 19:33-40. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24316758

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

Sapák M, Chreňová S, Tirpáková J, et al (2014). Donor non-specific MICA antibodies in renal transplant recipients. *Immunobiology*. 2014; 219:109-12. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24054943

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

Rose ML (2013). Role of anti-vimentin antibodies in allograft rejection. *Hum Immunol*. 2013;74:1459-62. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23777935

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

Loupy A, Lefaucheur C, Vernerey D, et al (2013). Complement-binding anti-HLA antibodies and kidney-allograft survival. *N Engl J Med*. 2013; 369:1215-26. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24066742

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

Dörje C, Midtvedt K, Holdaas H, et al (2013). Early versus late acute antibody-mediated rejection in renal transplant recipients. *Transplantation*. 2013; 96:79-84. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23632391

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

Barnett AN, Hadjianastassiou VG, Mamode N (2013). Rituximab in renal transplantation. *Transpl Int*. 2013; 26:563-75. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23414100

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

Barnett AN, Asgari E, Chowdhury P, Sacks SH, Dorling A, Mamode N (2013). The use of eculizumab in renal transplantation. *Clin Transplant*. 2013; 27:E216-29. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23516966

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

Roberts DM, Jiang SH, Chadban SJ (2012). The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. *Transplantation*. 2012; 94:775-83. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23032865

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

Jordan SC, Toyoda M, Kahwaji J, Vo AA (2011). Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. *Am J Transplant*. 2011; 11:196-202. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21219579

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

Stegall MD, Diwan T, Raghavaiah S, et al (2011). Terminal Complement Inhibition Decreases Antibody-Mediated Rejection in Sensitized Renal Transplant Recipients. *Am J Transplant* 2011; 11:2405-2413. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21942930

- This prospective trial demonstrates the potential role of eculizumab therapy in prevention AMR in sensitized renal transplant recipients

9.2 **Chronic Rejection**

Sharma R (2022). Anti-Interleukin 6 Therapeutics for Chronic Antibody-Mediated Rejection in Kidney Transplant Recipients. *Exp Clin Transplant*. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34981708/

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

Tanaka R et al (2022). Clinical effect of rabbit anti-thymocyte globulin for chronic active antibody-mediated rejection after kidney transplantation. *CEN Case Rep*. 11(1): 79-83. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34374932/

- 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.

Sharma R et al (2022). Interleukin 6 Receptor Blockage to Treat Chronic Active Antibody Mediated Rejection in Kidney Transplant: A Case Report With Review of Relevant Literature. *Exp Clin Transplant*. 20(1): 91-93. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33605198/

- Case report and review of literature regarding using of tocilizumab for treatment of chronic antibody mediated rejection in kidney transplant recipients.

de Souza, A. R., et al (2021). Mammalian Target of Rapamycin Inhibitors Vs Calcineurin Inhibitors in Chronic Graft Rejection After Lung Transplantation: A Systematic Review and Meta-Analysis. *Transplantation proceedings*, *53*(10), 3056–3064.

- A metanalysis of 3 RCTs (SHITRIT, NOCTET, and 4EVERLUNG) compared mTORi with low-dose CNI compared to isolated CNI immunosuppresion. 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, althogh not statistically significant.

Kauke, M., et al (2021). Full facial retransplantation in a female patient-Technical, immunologic, and clinical considerations. *Am J Transpl: 21*(10), 3472–3480.

- 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

Hassanein M, Augustine JJ (2021). Chronic Transplantation Rejection. [Updated 2021 July 25]. In: StatPearls [Internet]. StatPearls Publishing; 2021. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31747169/

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

Wei, Y., et al (2021). Efficacy and Safety of Bone Marrow-Derived Mesenchymal Stem Cells for Chronic Antibody-Mediated Rejection After Kidney Transplantation- A Single-Arm, Two-Dosing-Regimen, Phase I/II Study. *Frontiers in immunology*, *12*, 662441. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34248942/

- 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).

Lavacca, A., et al (2020). Early effects of first-line treatment with anti-interleukin-6 receptor antibody tocilizumab for chronic active antibody-mediated rejection in kidney transplantation. *Clinical transplantation*, *34*(8), e13908. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32415711/

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

Liu Y, et al (2020). Single-cell analysis reveals immune landscape in kindeys of patients with chronic transplant rejection. Theranostics, 10(19), 8851-8862.

- High quality transcriptomes generated from two chronic kidney transplant rejection 10iopsies compared to normal samples showed increased immune cells and a novel subpopulation of myofibroblasts and comprehensively describes immune cell profiles.

Shin, B. H., et al (2020). Impact of Tocilizumab (Anti-IL-6R) Treatment on Immunoglobulins and Anti-HLA Antibodies in Kidney Transplant Patients With Chronic Antibody-mediated Rejection. *Transplantation*, *104*(4), 856–863. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31385933/

- 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.

Larpparisuth N, et al (2019). Efficacy of Bortezomib as an Adjunctive Therapy for Refractory Chronic Active Antibody-Mediated Rejection in Kidney Transplant Patients: A Single-Center Experience.

Transplant Proc. 2019;51(10):3293–3296. doi: 10.1016/j.transproceed.2019.07.022. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31732214

- 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.

Justiz Vaillant AA, Waheed A, Mohseni M (2019). Chronic Transplantation Rejection. [Updated 2019 Oct 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan.

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

Shin B, et al (2019). Impact of tocilizumab (anti-IL-6R) treatment on immunoglobulins and anti-HLA antibodies in kidney transplant patients with chronic antibody-mediated rejection. *Transpl*. 2019 Aug; doi: 10.1097/TP.0000000000002895. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31385933.

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

Van Herck A, et al (2017). Prevention of chronic rejection after lung transplantation. *J Thorac Dis.* 2017;9(12):5472–5488. doi:10.21037/jtd.2017.11.85. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29312757

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

Choi J, et al (2017). Assessment of tocilizumab (anti-interleukin-6 receptor monoclonal) as a potential treatment for chronic antibody-mediated rejection and transplant glomerulopathy in HLA-sensitized renal allograft recipients. *Am J Transplant.* 2017 Sep; 17 (9): 2381-2389. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28199785.

- 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

Choudhary NS, et al (2017). Acute and chronic rejection after liver transplantation: what a clinician needs to know. *J Clin Exp Hepatol*. 2017;7(4):358-366. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29234201

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

Remport A, et al (2015). Better understanding of transplant glomerulopathy secondary to chronic anti-body mediated rejection. *Nephrol Dial Transplant*. 2015; 30: 1825-33. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25473123

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

Schinstock CA, Stegall M, Cosio F (2014). New insights regarding chronic antibody-mediated rejection and its progression to transplant glomerulopathy. *Curr Opin Nephrol Hypertens*. 2014; 23(6): 611-8. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25295960

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

Costello JP, Mohanakumar T, Nath DS (2013). Mechanisms of Chronic Cardiac Allograft Rejection. *Tex Heart Inst J* 2013; 40:395-399. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24082367

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

Loupy A, Hill GS, Jordan SC (2012). The Impact of donor-specific anti-HLA antibodies on late kidney allograft failure. *Nat Rev Nephrol* 2012; 8:348-357. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22508180

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

Knoop C, Estenne M (2011). Chronic Allograft Dysfunction. *Clin Chest Med* 2011; 32:311-326. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21511092

- 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.

Nankivell B, Alexander SI (2010). Rejection of the Kidney Allograft. *N Engl J Med* 2010; 363:1541-1462. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20925547

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

Seetharam A, Tiriveedhi V, Mohanakumar T (2010). Alloimmunity and autoimmunity in chronic rejection. *Curr Opin Organ Transplant* 2010; 15:531-536. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20613527

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

Desai M, Neuberger J (2009). Chronic Liver Allograft Dysfunction. *Transplant Proceed* 2009; 41:773-776. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/19328977

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

Joosten SA, et al (2005). Chronic renal allograft rejection: Pathophysiologic considerations. *Kidney Int* 2005; 68:1-13. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/15954891

- 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

Lee, H. R., et al (2021). Effect of rituximab dose on induction therapy in ABO-incompatible living kidney transplantation: A network meta-analysis. *Medicine*, *100*(10), e24853. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33725841/

- 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)

Pan, J., et al (2021). Imaging Findings for Identifying and Evaluating Complications after Lung Transplantation in Patients with Advanced COVID-19: Two Case Reports. *Current medical imaging*, 10.2174/1573405617666210917125045. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34533448/

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

Yang JJ, et al (2021). Hyperacute rejection in ABO-incompatible kidney transplantation: Significance of isoagglutinin subclass. *Transpl. Immunol.* 2021, 69, 101484. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34678463/

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

Zhang, Y., et al (2021). A novel MSC-based immune induction strategy for ABO-incompatible liver transplantation: a phase I/II randomized, open-label, controlled trial. *Stem cell research & therapy*, *12*(1), 244. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33863383/

- A RCT of 22 patients who underwent ABO-incompantible 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.

Billa C, et al (2020). Hyperacute graft dysfunction in an orthotopic heart transplant in the prescence of non-HLA antibodies. *Am J Transplant.* 2020, 20(2), 593-599. Retrieved from: Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31400258/

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

Hwang, S. D., Lee, J. H., Kim, K., Lee, S. W., & Song, J. H. (2020). Effect of Rituximab Used as Induction in Patients with ABO Mismatch Kidney Transplant: A Systematic Review and Meta-analysis. *Transplantation proceedings*, *52*(10), 3125–3128. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32553506/

- A metanalysis 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.

Carey BS, Poulton KV, Poles A (2019). Factors affecting HLA expression: A review. *Int J Immunogenet*. 2019;46(5):307–320. doi:10.1111/iji.12443. Retrieved from: Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31183978

- 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.

Garcia de mattos barbosa M, Cascalho M, Platt JL (2018). Accommodation in ABO-incompatible organ transplants. *Xenotransplantation*. 2018;25(3):e12418. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29913044

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

Bharat A, Mohanakumar T (2017). Immune Responses to Tissue-Restricted Non-major Histocompatibility Complex Antigens in Allograft Rejection. *J Immunol Res.* 2017;2017:6312514. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28164137

- 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

O'Leary, JG, et al. (2013). Impact of donor-specific antibodies on results of liver transplantation. *Curr Opin Organ Transplant*, 18, 279-84. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/%2023591739

- 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.

Yaich, S. (2013). ABO-Incompatible kidney transplantation. *Saudi J Kidney DisTranspl*, 24, 463-72. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23640616

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

West, LJ. (2011). ABO-incompatible hearts for infant transplantation. *Curr Opin Organ Transplant,* 16, 548-54. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21836514

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

Ercilla MG, Martorell J (2010). Estudio inmunológico de la pareja donante-receptor [Immunologic study of the donor-receptor couple]. *Nefrologia*. 2010;30 Suppl 2:60–70. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21183964

- [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.

Kissmeyer-Nielsen, F, et al. (1966). Hyperacute rejection of kidney allografts, associated with pre-existing humoral antibodies against donor cells. *Lancet*, 2, 662-665. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/4162350

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

9.4 T-cell mediated rejection

Ho J, Okoli GN, Rabbani R, et al. Effectiveness of T cell–mediated rejection therapy: A systematic review and meta-analysis. American J Transplantation. 2022;22(3):772-785.

- 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

Justiz Vaillant AA, Misra S & Fitzgerald BM (2021). Acute Transplant Rejection. In StatPearls. StatPearls Publishing.

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

Hann, A., Oo, Y. H., & Perera, M. (2021). Regulatory T-Cell Therapy in Liver Transplantation and Chronic Liver Disease. *Frontiers in immunology*, *12*, 719954. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34721383/

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

Ho, J., et al (2021). Effectiveness of T cell-mediated rejection therapy: A systematic review and meta-analysis. *Am J Transpl*, 10.1111/ajt.16907. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34860468/

- 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.

Trentadue G, et al (2020). Safe and successful treatment of acute cellular rejection of an intestine and abdominal wall transplant with vedolizumab. *Transplant Direct*. 2020 Jan 17;6(2):e527. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/32095513

- 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

Kumru Sahin G, et al (2020). Critical evaluation of a possible role of HLA epitope matching in kidney transplantation. *Transplantation Reviewers (Orlando)* 2020 Apr;34(2):100533. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/32007300

- 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.

Boutou Y, et al (2019). Response to treatment and long-term outcomes in kidney transplant recipients with acute T cell-mediated rejection. *Am J Transpl*. 2019 Jul; 19 (7): 1972-1988. Retrieved from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.15299.

- 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

Van der Zwan M, et al (2019). Targeted proteomic analysis detects acute T Cell mediated kidney allograft rejection in belatacept treated patients. *Ther Drug Monit*. 2019 Apr;41(2):243-248. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30883517

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

Balaha M, et al (2019). Thymoglobulin-Resistant T-Cell mediated rejection in a pregnant renal transplant recipient: case report and review of the literature. *Exp Clin Transplant*. 2019 Jan;17(Suppl 1):159-163. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30777545

- 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

Siu JHY, et al (2018). T cell Allorecognition Pathways in Solid Organ Transplantation. *Front Immunol*. 2018;9:2548. Published 2018 Nov 5. doi:10.3389/fimmu.2018.02548. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6230624/

- 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

Nafar M, et al (2017). The appropriate dose of thymoglobulin induction therapy in kidney transplantation. *Clin Transplant*. 2017 Jun;31(6). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28376289

- 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)

Benzimra M, Calligaro GL, Glanville AR (2017). Acute rejection. *J Thorac Dis.* 2017;9(12):5440-5457. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29312755

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

Lamarche C, et al (2016). Efficacy of acute cellular rejection treatment according to Banff score in kidney transplant recipients: a systematic review. *Transplant Direct.* 2016;2(12):e115. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27990480

- 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.

Ong S and Mannon RB (2015). Genomic and proteomic fingerprints of acute rejection in peripheral blood and urine. *Transplantation Reviews* 2015; 29: 60-67. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25542607

- 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

Franzese, O, et al. (2013). Regulatory T cells in the immunodiagnosis and outcome of kidney allograft rejection. *Clin Dev Immunol*, article ID 852395. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23843861

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

Abadja, F, et al. (2012). Significance of T helper 17 immunity in transplantation. *Curr Opin Organ Transplant*, 17, 8-14. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22186097

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

Van den Hoogen, MWF, et al. (2012). Anti-T-cell antibodies for the treatment of acute rejection after renal transplantation. *Expert Opin Biol Ther*, 12, 1031-42. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22583145

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

Getts, DR, et al. (2011). Current landscape for T-cell targeting in autoimmunity and transplantation. *Immunotherapy*, 3, 853-70. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21751954

- 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.

Gaber AO, et al (1998). Results of the double-blind, randomized, multicenter, Phase III clinical trial of thymoglobulin versus ATGAM in the treatment of acute graft rejection episodes after renal transplantation. *Transplantation* 1998; 66(1): 29–37. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/9679818

- 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

Edwards RL, Menteer J, Lestz RM, Baxter-Lowe LA. Cell-free DNA as a solid-organ transplant biomarker: technologies and approaches. Biomarkers in Medicine. Published online February 23, 2022:bmm-2021-0968.

- 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

Butiu M, Obrisca B, Sibulesky L, et al. Donor-derived cell-free dna complements de novo class ii dsa in detecting late alloimmune injury post kidney transplantation. Transplantation Direct. 2022;8(2):e1285.

- 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)

Nie W, Su X, Liu L, et al. Dynamics of donor-derived cell-free dna at the early phase after pediatric kidney transplantation: a prospective cohort study. Front Med. 2022;8:814517.

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

Levitsky J, Kandpal M, Guo K, Kleiboeker S, Sinha R, Abecassis M. Donor-derived cell-free DNA levels predict graft injury in liver transplant recipients. American J Transplantation. 2022;22(2):532-540.

- 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

Bazemore, K., et al (2021). Donor derived cell free DNA% is elevated with pathogens that are risk factors for acute and chronic lung allograft injury. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*, *40*(11), 1454–1462. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34344623/

- 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 (%).

Bunnapradist, S., et al (2021). Using both the Fraction and Quantity of Donor-Derived Cell-Free DNA to Detect Kidney Allograft Rejection. *Journal of the American Society of Nephrology : JASN*, *32*(10), 2439–2441. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34162734/

- 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.

Chang, J. H., et al (2021). Donor-derived cell-free DNA and renal allograft rejection in surveillance biopsies and indication biopsies. *Clinical transplantation*, e14561. Advance online publication. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34913202/

- Of 236 dd-cfDNA results from sensitized kidney transplants who underwent outpatient allograft biopsies for surveillance, sensitivity was 0% and sensivitiy was 89% (compared to 28% and 96% respectively in clinically indicated biopsies).

Chopra, B., & Sureshkumar, K. K. (2021). Emerging role of cell-free DNA in kidney transplantation. *World journal of experimental medicine*, *11*(5), 55–65. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34877265/

- A review of the clinical utility of dd-cfDNA in renal transplantation.

Kanou, T., et al (2021). Cell-free DNA in human ex vivo lung perfusate as a potential biomarker to predict the risk of primary graft dysfunction in lung transplantation. *The Journal of thoracic and cardiovascular surgery*, *162*(2), 490–499.e2. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32928548/

- 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.

Kataria, A., Kumar, D., & Gupta, G. (2021). Donor-derived Cell-free DNA in Solid-organ Transplant Diagnostics: Indications, Limitations, and Future Directions. *Transplantation*, *105*(6), 1203–1211. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33534526/

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

Keller, M., & Agbor-Enoh, S. (2021). Donor-Derived Cell-Free DNA for Acute Rejection Monitoring in Heart and Lung Transplantation. *Current transplantation reports*, 1–8. Advance online publication. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34754720/

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

Lewis, D., et al (2021). High levels of donor-derived cell-free DNA in a case of graft-versus-host-disease following liver transplantation. Am J Transpl; [online ahead of print.] Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34825479/

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

Mayer, K. A., et al (2021). Diagnostic value of donor-derived cell-free DNA to predict antibody-mediated rejection in donor-specific antibody-positive renal allograft recipients. *Transplant international : official journal of the European Society for Organ Transplantation*, *34*(9), 1689–1702. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34448270/

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

Scott, J. P., et al (2021). Total Cell-Free DNA Predicts Death and Infection Following Pediatric and Adult Heart Transplantation. *The Annals of thoracic surgery*, *112*(4), 1282–1289. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33039362/

- 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.

Sharma, D., et al (2021). Cell-free DNA in the surveillance of heart transplant rejection. *Indian journal of thoracic and cardiovascular surgery*, *37*(3), 257–264. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33967413/

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

Sawinski, D. L., et al (2021). Association between dd-cfDNA levels, de novo donor specific antibodies, and eGFR decline: An analysis of the DART cohort. *Clinical transplantation*, *35*(9), e14402. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34184326/

- 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.

Oellerich, M., et al (2021). Liquid biopsies: donor-derived cell-free DNA for the detection of kidney allograft injury. *Nature reviews. Nephrology*, *17*(9), 591–603. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34031575/

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

Park, S., et al (2021). Combining blood gene expression and cellfree DNA to diagnose subclinical rejection in kidney transplant recipients. *Clinical Journal of the American Society of Nephrology*, *16*(10), 1539-1551. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34620649/

- 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.

Pattar, S., et al (2021). Identification of cell-free DNA methylation patterns unique to the human left ventricle as a potential indicator of acute cellular rejection. *Clinical transplantation*, *35*(6), e14295. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33756005/

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

Puliyanda, D. P., et al (2021). Donor-derived cell-free DNA (dd-cfDNA) for detection of allograft rejection in pediatric kidney transplants. *Pediatric transplantation*, *25*(2), e13850. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33217125/

- 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.

Vasco, M., et al (2021). Clinical epigenetics and acute/chronic rejection in solid organ transplantation: An update. *Transplantation reviews (Orlando, Fla.)*, *35*(2), 100609. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33706201/

- 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.

Xiao, H., et al (2021). Diagnostic Accuracy of Donor-derived Cell-free DNA in Renal-allograft Rejection: A Meta-analysis. *Transplantation*, *105*(6), 1303–1310.

- Metanalysis 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.

Zhao, D., et al (2021). Preliminary clinical experience applying donor-derived cell-free DNA to discern rejection in pediatric liver transplant recipients. *Scientific reports*, *11*(1), 1138. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33441886/

- 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.

Wijtvliet, V., et al (2020). Donor-derived cell-free DNA as a biomarker for rejection after kidney transplantation: a systematic review and meta-analysis. *Transplant international : official journal of the European Society for Organ Transplantation*, *33*(12), 1626–1642. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32981117/

- 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.

North PE, et al (2020). Cell-free DNA donor fraction analysis in pediatric and adult heart transplant patients by multiplexed allele-specific quantitative PCR: Validation of a rapid and highly sensitive clinical test for stratification of rejection probability. *PLoS One* 2020 Jan 13;15(1):e0227385. Retrieved from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0227385

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

Knight SR, Thorne A, Lo Faro ML (2019). Donor-specific Cell-free DNA as a Biomarker in Solid Organ Transplantation. A Systematic Review. *Transplantation*. 2019;103(2):273–283. doi: 10.1097/TP.0000000000002482. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30308576

- 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

Kanwar MK, Khush KK, Pinney S, et al. Impact of cytomegalovirus infection on gene expression profile in heart transplant recipients. The Journal of Heart and Lung Transplantation. 2021;40(2):101-107.

- 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

Friedewald JJ, Kurian SM, Heilman RL, et al. Development and clinical validity of a novel blood-based molecular biomarker for subclinical acute rejection following kidney transplant. Am J Transplant. 2019;19(1):98-109.

- 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

Crespo-Leiro MG, Stypmann J, Schulz U, et al. Clinical usefulness of gene-expression profile to rule out acute rejection after heart transplantation: CARGO II. Eur Heart J. 2016;37(33):2591-2601.

- Cardiac Allograft Rejection Gene Expression Observational II Study (CARGO II)

- Assessed validity of gene expression profiling test performance (AlloMap) in heart transplant population

Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-expression profiling for rejection surveillance after cardiac transplantation. N Engl J Med. 2010;362(20):1890-1900.

- 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

Hu X, Geng Z, Gonelle C, Hawthrone WJ, Deng S, Buhler L. International Human Xenotransplantation Inventory: A 10-y Follow-up [published online ahead of print, 2022 Jan 4]. Transplantation. 2022;10.1097/TP.0000000000004016. doi:10.1097/TP.0000000000004016

- 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

Siems C, Huddleston S, John R. (2022). A brief history of xenotransplantation. The Annals of Thoracic Surgery. 2022;113(3):706-710.

- Expert panel review of history of xenotransplantation

Shah AM, Han JJ. (2022). First successful porcine to human heart transplantation performed in the United States. Artificial Organs. Published online February 28, 2022:aor.14203.

- Review article of first successful pig to heart xenotransplant

Ladowski, J. M., Hara, H., & Cooper, D. (2021). The Role of SLAs in Xenotransplantation. *Transplantation*, *105*(2), 300–307. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32433239/

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

Lu T, et al (2020). Xenotransplantation: Current Status in Preclinical Research. *Front Immunol.* 2019; 10: 3060. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6989439/

- 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.

Tector, AJ, Mosser M, Tectom M, Bach JM (2020). The Possible Role of Anti-Neu5Gc as an Obstacle in Xenotransplantation. *Front Immunol.* 2020, 11,622. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32351506/

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

Ekser, B, et al. (2012). Clinical xenotransplantation: the next medical revolution? *Lancet*, 379, 672-83. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22019026

- 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.