9. Types of rejection

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9.1 Antibody-mediated rejection

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, Junker T, Dickenmann M, 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, Hitchman K, Hall R, Yamaguchi I, Ding Y, Crowther B (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, Rothstein DM, Safa K, Riella LV (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, Eskandary F, Doberer K, Halloran PF (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, Mamode N, Montgomery R, 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. https://doi.org/10.1111/ajt.15364. 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, Russ G, Rostaing L, Legendre C, Tufveson G, Chadban S, 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, Regele H, Baumann L, Bond G, Kozakowski N, 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. Doi:10.1097/MOT.0000000000000537 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, Bajpayee A, Charan J, Pareek P, Elhence P, Kirubakaran R (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, Loheac C, Aubert O, 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: 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, Loupy A, Lefaucheur C, 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. doi:10.1111/ajt.14625. 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, Yousem SA, Marrari M, Morrell MR, Mangiola M, 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, Chery G, Hulbert A, Byrns J, Benedetti C, 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, Revuelta I, Diekmann F, Cofman F, Lozano M, 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. 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

Larpparisuth N, Skulratanasak P, Premasathian N, Vongwiwatana A (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. Retrieved from: https://www.ncbi.nlm.nih.gov/books/NBK535435/

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

Shin B, Everly M, Zhang H, Choi J, Vo A, 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, Verleden SE, Vanaudenaerde BM, Verleden GM, Vos R (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, Aubert O, Vo A, Loupy A, Haas M, 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, Saigal S, Bansal RK, Saraf N, Gautam D, Soin AS (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, Ivanyi B, Mathe Z 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, Supkens YWJ, van Kooten C, Paul LC (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

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: https://www.ncbi.nlm.nih.gov/pubmed/31183978

- This articles 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

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

.

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. doi:10.3265/Nefrologia.pre2010.Nov.10692. 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.

iKissmeyer-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

Trentadue G, Kats-Uqurlu G, Blokzijl T, 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, Unterrainer C, Susal C, 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, Vigliette D, Pieveani D, Louis K, 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, Hesselink D, 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, Al-Otaibi T, Gheith O, 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, Surendrakumar V, Richards JA, Pettigrew GJ (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, Dalili N, Poor-Reza-Gholi F, 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, Cote J, Senecal L, 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, First MR, Tesi RJ, 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 specific cell free DNA marker

North PE, Ziegler E, Mahnke D, 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. doi: 10.1371/journal.pone.0227385. 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.