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3.1 Induction Therapy

Best LM, et al (2020). Induction immunosuppression in adults undergoing liver transplantation: a network meta-analysis. Cochrane Database Syst Rev. 2020 Jan 16;1:CD013203. doi: 10.1002/14651858.CD013203.pub2. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31978255

- Cochrane review of 25 randomized clinical trials evaluating induction regimens (glucocorticoids, anti-thymocyte globulin, basiliximab, daclizumab, alemtuzumab, or no induction) in liver transplant recipients. Low-certainty evidence suggests basiliximab induction reduces mortality and graft failure compared with corticosteroid induction.

Bittermann T, Hubbard RA, Lewis JD, Goldberg DS (2019). The use of induction therapy in liver transplantation is highly variable and is associated with posttransplant outcomes. Am J Transplant. 2019 Dec;19(12):3319-3327. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31243887

- Retrospective review comparing non-depleting induction vs depleting induction in 69,349 liver transplant recipients utilizing UNOS data. Only non-depleting induction was associated with a reduction in acute rejection. Both forms of induction were associated with a reduction in patient and graft loss, however, absolute difference was minimal.

Lange NW, Salerno DM, Sammons CM, Jesudian AB, Verna EC, Brown RS Jr (2018). Delayed calcineurin inhibitor introduction and renal outcomes in liver transplant recipients receiving basiliximab induction. Clin Transplant. 2018 Dec;32(12):e13415. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30276862

- This retrospective review of 210 liver transplant recipients from 2007 through 2015 at New York Presbyterian Hospital/Columbia University assessed the impact of delaying CNIs with use of basiliximab induction on renal function between 4 groups with varying degrees of AKI posttransplant. By delaying therapeutic CNI (therapeutic levels of 6-10) by about 14 days posttransplant in all 4 groups with varying degrees of AKI, there was no difference in renal function past 90 days posttransplant.

Iesari S, Ackenine K, Foguenne M, et al (2018). Tacrolimus and Single Intraoperative High-dose of Anti-T-lymphocyte Globulins Versus Tacrolimus Monotherapy in Adult Liver Transplantation: One-year Results of an Investigator-driven Randomized Controlled Trial. Ann Surg. 2018;268(5):776-783 Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30307410

- This is a randomized controlled trial comparing tacrolimus monotherapy (TAC, n = 109) and tacrolimus plus a single, intraoperative, high-dose (9mg/kg), rabbit anti-T-lymphocyte globulin. The primary endpoint evaluated was immunosuppression minimization to monotherapy with other endpoints including biopsy-proven rejection, clinical rejection, and patient and graft survival.

Zhang GQ, Zhang CS, Sun N, Lv W, Chen BM, Zhang JL (2017). Basiliximab application on liver recipients: a meta-analysis of randomized controlled trials. HBPD INT. 2017;16(2):139-146. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28381376

- Meta-analysis of 6 randomized controlled trials conducted from 1998 – 2015 examining the use of basiliximab induction in liver transplant recipients vs. steroid induction alone. Basiliximab induction was found to significantly reduce the incidence of post-transplant diabetes, in addition to lower observed rates of hypertension and biopsy prove acute rejection.

Petite SE, Bollinger JE, Eghtesad B (2016). Antithymocyte Globulin Induction Therapy in Liver Transplant: Old Drug, New Uses. Ann Pharmacother. 2016;50(7):592-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27147705

- MEDLINE literature search involving 9 studies reviewing the use of rabbit antithymocyte globulin (rATG) induction therapy in liver transplant recipients. Patients receiving rATG induction tended to have improved renal function compared with patients not receiving induction. Rejection rates tended to be lower in recipients administered rATG.

Au KP et al (2015). Clinical factors affecting rejection rates in liver transplantation. Hepatobiliary Pancreat Dis Int. 2015;14(4):367-73 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26256080

- This retrospective review of 788 liver transplant patients studied the relationship between acute cellular rejection (ACR) and various clinical factors. Liver transplant recipients with older age, chronic hepatitis B virus infection, living donor liver transplantation and use of interleukin-2 receptor antagonist on induction have fewer ACR.

Yoo MC et al (2015). Steroid-free Liver Transplantation Using Rabbit Antithymocyte Globulin Induction in 500 Consecutive Patients. Transplantation. 2015; 99(6):1231-5. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25539464

- This report demonstrated the benefits of a steroid-free immunosuppression protocol using rabbit antithymocyte globulin (RATG) induction in orthotopic liver transplantation (OLT) with tacrolimus minimization 500 recipients

Halldorson JB et al (2015). Differential rates of ischemic cholangiopathy and graft survival associated with induction therapy in DCD liver transplantation. Am J Transplant. 2015;15(1):251-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25534449

- This single center study used a Multivariable analysis demonstrating induction agents to be independently associated with graft survival and ischemic cholangiopathy free graft survival when analyzed against variables including donor age, fWIT, donor cold ischemia time and transplant era.

Garcia-SM et al (2014). Impact of anti-thymocyte globulin during immunosuppression induction in patients with hepatitis C after liver transplantation. Dig Dis Sci. 2014;59(11):2804-12. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24865255

- This study evaluated the 1- and 2-year patient survival and HCV recurrence rate in patients receiving ATG during the induction phase of immunosuppression after liver transplantation.

Kubal CA et al (2014). Crossmatch-positive liver transplantation in patients receiving thymoglobulin-rituximab induction. Transplantation. 2014;97(1):56-63. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24030603

- This study reviewed the role of induction immunosuppression in positive crossmatch in liver transplantation. With the use of rabbit anti-thymocyte globulin ± rituximab induction, overall low rejection rates can be achieved in positive crossmatch liver transplantation.

Penninga L et al (2014). Antibody induction versus placebo, no induction, or another type of antibody induction for liver transplant recipients. Cochrane Database Syst Rev. 2014;(6):CD010253 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24901467

- Cochrane review of 19 randomized clinical trials assessing immunosuppression with T-cell specific antibody induction compared with placebo, no induction, or another type of antibody induction in liver transplant recipients.

Penninga L et al (2014). Antibody induction versus corticosteroid induction for liver transplant recipients. Cochrane Database Syst Rev. 2014;(5):CD010252. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24880007

- Cochrane review of 10 randomized clinical trials assessing immunosuppression with T-cell specific antibody induction versus corticosteroid induction in liver transplant recipients.

Turner AP et al (2013). Induction immunosuppression in liver transplantation: a review. Transpl Int. 2013 Jul;26(7):673-83. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23651083

- A review of antibody induction agents in liver transplantation, particularly the use of basiliximab in adults with renal function impairment allowing for delayed introduction of calcineurin-inhibitors.

Rostaing, L et al. (2012). Review article: use of induction therapy in liver transplantation. Transplant Reviews, 26(4), 246-260. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22863028.

- Review of rationale, mechanisms, safety and evidence supporting various induction agents used in liver transplantation. Includes tables summarizing RCTs on induction.

Neumann, U et al. A Randomized Multicenter Study Comparing a Tacrolimus-Based Protocol with and without Steroids in HCV-Positive Liver Allograft Recipients. Journal of Transplantation, 2012, 1-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22690326.

- Comparison of induction with tacrolimus + daclizumab vs. tacrolimus + steroids. Primary endpoint, median HCV viral load at 12 months, was similar between groups.

Mangus, R et al. (2012). Immunosuppression induction with rabbit antithymocyte globulin with or without rituximab in 1000 liver transplant patients with long-term follow-up. Liver Transplantation, 18(7), 786-795. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22237953.

- Retrospective, single-center study comparing 3 induction methods: 1) rATG given in OR (n=166), 2) rATG given 48 hrs post-transplant (n=266), and 3) rATG given 48 hrs post-tranpslant + rituximab given 72 hrs post-transplant. No significant difference in 5-year survival was found between groups.

Ghanekar, A et al. (2012). Routine induction therapy in living donor liver transplantation prevents rejection by may promote recurrence of hepatitis C. Transplant Proceedings, 44, 1351-1356. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22664014.

- Retrospective study in 184 LDLT patients who received either rATG or basiliximab for induction. Results showed significantly lower rates of rejection but higher rates of HCV recurrence in the rATG group.

Klintmalm, G et al. (2011). A randomized, multicenter study comparing steroid-free immunosuppression and standard immunosuppression for liver transplant recipients with chronic hepatitis C. Liver Transplantation, 17(12), 1394-1403. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21850690.

- Prospective RCT in 295 HCV patients comparing steroid-free induction (tacrolimus + mycophenolate mofetil + daclizumab) to tacrolimus + steroids and tacrolimus + mycophenolate mofetil + steroids. No significant differences found in ACR, HCV recurrence, patient survival, or graft survival at 2 years.

Levitsky, J et al. (2011). Alemtuzumab induction in non-hepatitis C positive liver transplant recipients. Liver Transplantation, 17(1), 32-27. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21254342.

- Retrospective case-control study comparing induction with alemtuzumab (n= 55) vs tacrolimus + steroid taper (n= 85). Alemtuzumab was associated with less hypertension and rejection but a higher rate of infections (due to increased number of viral infections). No significant differences in graft survival, patient survival, ACR, or renal dysfunction.

Selzner N, Grant DR, Shelev I, Levy GA. (2010). The immunosuppressive pipeline: meeting unmet needs in liver transplantation. Liver Transplantation, 16, 1359-1372. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21117245.

- Explores novel molecular targets for induction and maintenance immunosuppression, including CNI- free regimens.

Boillet, O et al. (2009). Thymoglobulin induction in liver transplant recipients with a tacrolimus, mycophenolate mofetil, and steroid immunosuppressive regimen: a five-year randomized prospective study. Liver Transplantation, 15(11), 1426-1434. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19877264.

- Comparison of thymoglobulin induction (n=44) or no induction (n=49). No difference found in ACR or long-term survival, but higher rate of leukopenia in thymoglobulin group.

Bajjoka, I et al. (2008). Preserving renal function in liver transplant recipients with rabbit anti-thymocyte globulin and delayed calcineurin inhibitors. Liver Transplantation, 14, 66-72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18161842.

- Retrospective study comparing rATG induction and delayed CNI initiation (n=118) versus early initiation of CNI (n= 80). All patients received MMF and steroids. Patients in the rATG group had significantly lower serum creatinine and a trend toward lower rates of ACR at 12 months post-transplant.

Nair S, Loss G, Cohen AJ, Eason JD. (2006). Induction with rabbit anti-thymocyte globulin versus induction with corticosteroids in liver transplantation: impact on recurrent hepatitis C virus infection. Transplantation, 81(4), 620-623. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16495812.

- HCV patients were randomized to receive either rATG (n=33) or methylprednisolone (n=31) induction. No significant difference was shown in patient survival or HCV recurrence rates at 6 months post-transplant.

Fung, J et al. (2005). Immunosuppression in liver transplantation: beyond calcineurin inhibitors. Liver Transplantation, 11(3), 267-280. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15719409.

- Review of induction and maintenance immunosuppressant strategies, focusing on potential for CNI sparing regimens.

Eason JD, Loss GE, Blazek J, Nair S, Mason AL. (2001). Steroid-free liver transplantation using rabbit anti-thymocyte globulin induction: results of a prospective randomized trial. Liver Transplantation, 7(8), 693-697. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11510013.

- First reported RCT comparing induction with rATG (n=36) versus methylprednisolone (n=35). Showed a trend toward lower rates of ACR, post-transplant diabetes and HCV recurrence in the rATG group.

3.2 Maintenance therapy

3.2.1 Calcineurin Inhibitors

Lim TY, et al (2020). Sequential Cohort Analysis After Liver Transplantation Shows de Novo Extended Release Tacrolimus Is Safe, Efficacious, and Minimizes Renal Dysfunction. Transplant Direct. 2020 Jan 17;6(2):e528. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32095514

- Single-center, prospective sequential cohort analysis comparing clinical outcomes of liver transplant recipients receiving tacrolimus IR or de novo tacrolimus ER (Astagraf XL). Tacrolimus ER was associated with a reduction in new-onset CKD stage 3-4 compared with tacrolimus IR. Incidence of biopsy-proven acute rejection, patient and graft survival were similar between groups.

Lin SD, Lee Krishnamoorthy T, Kumar R, Lim RT (2019). Tacrolimus Monotherapy in Recipients of Liver Transplant: A Single-Center Experience. Transplant Proc. 2019 Jul - Aug;51(6):1920-1922. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31399176

- Single-center retrospective review evaluating outcomes of early tacrolimus monotherapy (<6 months post-transplant) in 100 liver transplant recipients. Compared with patients transitioned to monotherapy after 6 months post-transplant, there were no differences in rejection, CMV infection, renal impairment, or patient survival at 5 years follow-up.

Adam R, Karam V, Cailliez V, et al (2019). Improved Survival in Liver Transplant Patients Receiving Prolonged-release Tacrolimus-based Immunosuppression in the European Liver Transplant Registry (ELTR): An Extension Study. Transplantation. 2019;103(9):1844-1862. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31343568

- Retrospective analysis of European Liver Transplant Registry of long-term liver transplantation outcomes with prolonged-release tacrolimus (Astagraf) versus immediate-release tacrolimus-based immunosuppression. Analysis comprised up to 8-year data collected in an extension of the previously published ELTR study.

Lee EC, Kim SH, Park SJ (2018). Safety and Efficacy of Once-Daily Prolonged-Release Tacrolimus in Living Donor Liver Transplantation: An Open-Label, Prospective, Single-Arm, Phase 4 Study. Ann Transplant. 2018;23:713-720. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30310047

- This is a phase 4 single-arm open-label prospective study assessing the efficacy and safety of conversion from twice-daily tacrolimus to once-daily prolonged-release tacrolimus in living donor LT recipients. Adherence was evaluated during outpatient visits after tacrolimus conversion, as well as acute rejection, graft loss, or patient death after Tac conversion

Shin MH, Song GW, Lee SG, et al (2018). Once-daily, prolonged-release tacrolimus vs twice-daily, immediate-release tacrolimus in de novo living-donor liver transplantation: A Phase 4, randomized, open-label, comparative, single-center study. Clin Transplant. 2018;32(9):e13376. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30098071

- Randomized, open-label, comparative, single-center, Phase 4, 24-week study comparing pharmacokinetics, safety, and efficacy of once-daily, prolonged-release tacrolimus with twice-daily, immediate-release tacrolimus in adult de novo living-donor liver transplant recipients in Korea.

Levy G, et al. (2014). REFINE: a randomized trial comparing cyclosporine A and tacrolimus on fibrosis after liver transplantation for hepatitis C. American Journal of Transplantation, 14(3):635-46. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24456049.

- Multicenter, prospective, randomized, trial evaluating fibrosis development 12 months post-transplant for hepatitis C virus cirrhosis in 356 liver transplant recipients receiving either cyclosporine or tacrolimus. Fibrosis score >2 at month 12 was similar among both groups.

Boudjema K, et al. (2011). Reduced-dose tacrolimus with mycophenolate mofetil vs. standard-dose tacrolimus in liver transplantation: a randomized study. American Journal of Transplantation, 11(5), 965-76. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21466650.

- The prospective, randomized, multicenter trial evaluated the impact of reduced-dose tacrolimus in combination with mycophenolate mofetil (experimental) compared to standard dose tacrolimus (control) in 195 liver transplant recipients. Rate of acute graft rejection and occurrence of renal dysfunction, arterial hypertension, or diabetes were lower in the experimental group.

Neuberger JM, et al. (2009). Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the 'ReSpECT' study. American Journal of Transplantation, 9(2), 327-36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19120077.

- Prospective, randomized trial evaluating standard dose tacrolimus in combination with corticosteroids (n=183); reduced-dose tacrolimus, mycophenolate mofetil (MMF), and corticosteroids (n=170); and daclizumab induction with delayed introduction of reduced-dose tacrolimus, MMF, and corticosteroids (n=172) in liver transplant recipients who were without renal dysfunction in the pre-transplant setting. Estimated glomerular filtration rate decreased the least in the daclizumab induction group. Patient and graft survival were similar among all groups.

Beckebaum S, et al. (2009). Combined mycophenolate mofetil and minimal dose calcineurin inhibitor therapy in liver transplant patients: clinical results of a prospective randomized study. Transplantation Proceedings, 41(6), 2567-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19715976.

- Liver transplant recipients with chronic renal dysfunction are randomized to receive either calcineurin inhibitor therapy (N=30) or mycophenolate mofetil (MMF) in combination with reduced dose calcineurin inhibitor therapy (N=60). Serum creatinine significantly decreased and estimated glomerular filtration rate increased in the MMF group.

Wiesner RH. (1998). A long-term comparison of tacrolimus (FK506) versus cyclosporine in liver transplantation: a report of the United States FK506 Study Group. Transplantation, 66(4), 493-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9734494.

- Randomized, multicenter trial evaluating tacrolimus compared to cyclosporine maintenance therapy in 529 liver transplant recipients. Biopsy-proven acute rejection at one year following transplant was significantly lower in the tacrolimus group. There was no difference in patient survival at 5 years following transplant.

3.2.2 Antimetabolites

Aguiar D, et al (2017). Conversion from Calcineurin Inhibitor-Based Immunosuppression to Mycophenolate Mofetil in Monotherapy Reduces Risk of De Novo Malignancies After Liver Transplantation. Annals of transplantation. 2017 Mar 17;22:141-147. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28302995

- Retrospective review of adult liver transplant recipients at a Spanish center evaluating malignancy rates in patients maintained a mycophenolate monotherapy regimen. Patients converted to an immunosuppression regimen of mycophenolate monotherapy experienced less de novo malignancy, non-melanoma skin cancer and other malignancies compared to recipients with maintenance immunosuppression with calcinuerin inhibitors.

Schmeding M, et al. (2011). Mycophenolate mofetil monotherapy in liver transplantation: 5-year follow-up of a prospective randomized trial. Transplantation, 92(8), 923-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21832958.

- The prospective, randomized trial evaluates maintenance immunosuppression consisting of either calcineurin inhibitor monotherapy or mycophenolate mofetil (MMF) monotherapy in 150 liver transplant recipients. Although no significant difference in acute rejection was identified between groups, the MMF monotherapy group had a trend to higher rejection rates. Chronic rejection was absent in both study groups and 5-year survival was similar among both groups.

3.2.3 mTOR Inhibitors

Nogueras López F, et al (2020). Impact of Everolimus-based Immunosuppression on Renal Function in Liver Transplant Recipients. Transplant Proc. 2020 Mar;52(2):556-558. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32035673

- Single-center, retrospective study evaluating renal function of 66 liver transplant recipients who received de novo everolimus in combination with tacrolimus minimization or withdrawal for baseline renal dysfunction. With 24 month follow-up, eGFR was significantly and persistently greater than baseline eGFR.

Grigg SE, Sarri GL, Gow PJ, Yeomans ND (2019). Systematic review with meta-analysis: sirolimus- or everolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. Aliment Pharmacol Ther. 2019;49(10):1260-1273. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30989721

- Systematic review with meta-analysis: sirolimus- or everolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma

Saliba F, Duvoux C, Dharancy S, et al (2019). Early Switch From Tacrolimus to Everolimus After Liver Transplantation: Outcomes at 2 Years (CERTITUDE). Liver Transpl. 2019 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31631501

- Two-year follow up of the SIMCER trial (early conversion from CNI to everolimus in combination with mycophenolate and prednisone). Continuation of everolimus was associated with preservation of renal function, however, only approximately 50% of patients were able to continue to everolimus therapy due to safety or efficacy concerns.

Jeng LB, Lee SG, Soin AS, et al (2018). Efficacy and safety of everolimus with reduced tacrolimus in living-donor liver transplant recipients: 12-month results of a randomized multicenter study. Am J Transplant. 2018;18(6):1435-1446. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29237235

- Randomized multicenter, open-label study evaluating 284 living-donor liver transplant patients starting everolimus + reduced tacrolimus or continue standard tacrolimus. The primary endpoint was treated BPAR, and graft loss or death at 12 months posttransplant

Charlton M, Rinella M, Patel D, Mccague K, Heimbach J, Watt K (2017). Everolimus Is Associated With Less Weight Gain Than Tacrolimus 2 Years After Liver Transplantation: Results of a Randomized Multicenter Study. Transplantation. 2017;101(12):2873-2882. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28817434

- Randomized multi-center study of patients in one of the following groups (1) everolimus + reduced tacrolimus (2) tacrolimus control (3) Tacrolimus elimination. Post hoc analysis completed evaluating weight change at 12 and 24 months, as well as vital signs, lipids, and laboratory parameters at 12 and 24 months.

Saliba F, Duvoux C, Gugenheim J, et al (2017). Efficacy and Safety of Everolimus and Mycophenolic Acid With Early Tacrolimus Withdrawal After Liver Transplantation: A Multicenter Randomized Trial (SIMCER). Am J Transplant. 2017;17(7):1843-1852.Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28133906

- Randomized multi-center open-label trial of de novo liver transplant recipients receiving either to everolimus with low-exposure tacrolimus discontinued by month 4 or to tacrolimus-based therapy, both with basiliximab induction and enteric-coated mycophenolate sodium with or without steroids. Everolimus was associated with a significant improvement in renal function compared with CNI at 28 weeks post-transplant, however, a higher incidence of treated biopsy-proven acute rejection was observed.

Sterneck M, Kaiser GM, Heyne N, et al (2016). Long-term follow-up of five yr shows superior renal function with everolimus plus early calcineurin inhibitor withdrawal in the PROTECT randomized liver transplantation study. Clin Transplant. 2016 Jun;30(6):741-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27160359

- Five-year follow up of the PROTECT study (early conversion from CNI to everolimus vs CNI). Conversion to everolimus resulted in better renal function and comparable patient and graft outcomes with long-term follow up.

Sterneck M, et al. (2014). Everolimus and early calcineurin inhibitor withdrawal: 3-year results from a randomized trial in liver transplantation. American Journal of Transplantation, 14(3), 701-10. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24502384.

- Prospective, randomized trial in 203 liver transplant recipients receiving either everolimus with corticosteroids or cyclosporine/tacrolimus with corticosteroids. Glomerular filtration rate was significantly higher in the everolimus group by month 35 following randomization. No difference in biopsy-proven acute rejection, graft loss and death was seen between groups.

Asrani SK, et al. (2014). De novo sirolimus and reduced-dose tacrolimus versus standard-dose tacrolimus after liver transplantation: the 2000-2003 phase II prospective randomized trial. American Journal of Transplantation, 14(2), 356-66. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24456026.

- Phase II, multicenter, randomized trial in 222 liver transplant recipients who received either standard-dose tacrolimus with corticosteroids or sirolimus, reduced-dose tacrolimus, in combination with corticosteroids. Patient and graft survival were significantly lower in the sirolimus group. Similar rates of acute cellular rejection were seen among both study groups.

Teperman L et al. (2013). Calcineurin inhibitor-free mycophenolate mofetil/sirolimus maintenance in liver transplantation: the randomized spare-the-nephron trial. Liver Transplantation, 19(7), 675-89. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23775875.

- Mycophenolate mofetil (MMF) and sirolimus combination therapy (n=148) is compared to MMF and calcineurin inhibitor (CNI) combination therapy (n=145) for preserving renal function in liver transplant recipients. The sirolimus group had a significantly greater improvement in glomerular filtration rate and increased rates of biopsy-proven acute rejection compared to CNI group. Patient survival was similar between both groups.

Saliba F, et al. (2013). Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. American Journal of Transplantation, 13(7), 1734-45. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23714399.

- Multicenter, prospective, randomized trial evaluating everolimus with reduced-dose tacrolimus; standard-dose tacrolimus; or tacrolimus elimination in 719 liver transplant recipients. Composite endpoint of biopsy-proven acute rejection, graft loss or death was similar in the reduced-dose tacrolimus and standard-dose tacrolimus groups at 24 months. Patients in the tacrolimus elimination group experienced higher rates of treated biopsy proven acute rejection.

Fischer L, Klempnauer J, Beckebaum S, et al (2012). A randomized, controlled study to assess the conversion from calcineurin-inhibitors to everolimus after liver transplantation--PROTECT. Am J Transplant. 2012 Jul;12(7):1855-65. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22494671

- Multicenter, open-label, RCT evaluating the effect of early conversion from CNI to everolimus (4 weeks post-transplant) on renal function in 203 liver transplant recipients. At 1 year post-transplant there was no difference in renal function, acute rejection, graft loss, or mortality in patients who transitioned to everolimus compared with those who continued on CNI.

De Simone P, et al (2012). Everolimus with Reduced Tacrolimus Improves Renal Function in De Novo Liver Transplant Recipients: A Randomzied Controlled Trial (H2304). American Journal of Transplantation 2012; 12: 3008-3020. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22882750

- Prospective, multicenter, open-label study comparing three immunosuppression regimens in de novo liver transplant recipients: (i) everolimus with tacrolimus elimination, (ii) everolimus with reduced-exposure tacrolimus, and (iii) standard exposure tacrolimus. Group ii and iii had a similar composite outcome of treated biopsy proven acute rejection (tBPAR), graft loss or death at 12 months but group ii had less tBPAR than group iii. Group ii had improved GFR compared to group iii but had more discontinuation due to adverse events.

Asrani SK, et al. (2010). Use of sirolimus in liver transplant recipients with renal insufficiency: a systematic review and meta-analysis. Hepatology, 52(4), 1360-70. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20815021.

- Eleven randomized controlled trials and observational trials are included in the meta-analysis to evaluate the impact of sirolimus on renal function in liver transplant recipients. Sirolimus use

was associated with improved renal function. Sirolimus use was not associated with patient death, graft failure, and rejection.

3.2.4 Co-Stimulation Blockade

Klintmalm GB, Feng S, Lake JR, et al (2014). Belatacept-based immunosuppression in de novo liver transplant recipients: 1-year experience from a phase II randomized study. Am J Transplant. 2014 Aug;14(8):1817-27. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25041339

- Phase II RCT evaluating de novo belatacept in liver transplant recipients. Patients were randomized to one of five treatment arms (1. basiliximab + belatacept high dose [HD] + mycophenolate mofetil (MMF), 2. belatacept HD + MMF, 3. belatacept low dose [LD] + MMF, 4. tacrolimus + MMF, or 5. tacrolimus alone). Due to an increase in death and graft loss with belatacept users, the study was terminated early after 12 months.

LaMattina JC, et al. (2014). Safety of belatacept bridging immunosuppression in hepatitis C-positive liver transplant recipients with renal dysfunction. Transplantation, 97(2), 133-7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24342980.

- Retrospective review evaluating the use of belatacept at a single center in seven liver transplant recipients with hepatitis C virus. Patient survival, graft survival, and biopsy-proven acute rejection episode are among the endpoints evaluated.

3.2.5 Other

Khorsandi SE, Heaton N (2016). Optimization of immunosuppressive medication upon liver transplantation against HCC recurrence. Translational gastroenterology and hepatology. 2016 Apr 6;1:25. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28138592

- Review of evidence evaluating the impact of immunosuppression agents on hepatocellular cancer recurrence and oncological survival.

Watt KD, et al. (2012). Impact of sirolimus and tacrolimus on mortality and graft loss in liver transplant recipients with or without hepatitis C virus: an analysis of the Scientific Registry of Transplant Recipients Database. Liver Transplantation, 18(9), 1029-36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22641474.

- The current study analyzes the Scientific Registry of Transplant Recipients Database to identify risk factors for mortality and graft loss in liver transplant recipients with or without hepatitis C virus indication for transplant.

Klintmalm GB, et al. (2011). A randomized, multicenter study comparing steroid-free immunosuppression and standard immunosuppression for liver transplant recipients with chronic hepatitis C. Liver Transplantation, 17(12), 1394-403. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21850690.

- Prospective, randomized, multicenter trial evaluating tacrolimus and corticosteroid (N=77); tacrolimus, corticosteroid, and mycophenolate mofetil (N=72); and daclizumab induction with tacrolimus and mycophenolate mofetil (N=146) in liver transplant recipients. No difference in acute cellular rejection, hepatitis C virus recurrence, or patient/graft survival was found among all study groups.

3.3 ABO-Incompatible Liver Transplantation

Sun C, et al (2020). The management and outcomes of ABO-incompatible pediatric liver transplantation: Experience of a single Chinese center. J Pediatr Surg. 2020 Feb 24. pii: S0022-3468(20)30151-2. doi: 10.1016/j.jpedsurg.2020.01.059.

- Retrospective review of 71 pediatric liver transplant recipients of ABO-incompatible grafts who received management with IVIG and/or plasmapheresis pending anti-ABO titer levels. Compared with ABO-compatible transplant recipients, there were no differences in surgical complications, graft or patient survival at 3-year follow-up.

Yadav DK,et al (2019). ABO-Incompatible Adult Living Donor Liver Transplantation in the Era of Rituximab: A Systematic Review and Meta-Analysis. Gastroenterol Res Pract. 2019 Jun 11;2019:8589402. doi: 10.1155/2019/8589402. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6594289/

- Systematic review and meta-analysis of 9 studies (retrospective or prospective) evaluating the safety and effectiveness of rituximab in ABO-incompatible living donor liver transplantation. No differences were observed when comparing graft or patient survival at 1, 3, or 5 years' post-transplant for ABOi vs ABOc groups, however, ABOi transplant recipients had higher rates of biliary complications, CMV infection and AMR.

Lee EC, Kim SH, Park SJ (2017). Outcomes after liver transplantation in accordance with ABO compatibility: A systematic review and meta-analysis. World J Gastroenterol. 2017;23(35):6516-6533. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29085201.

- Systematic review and meta-analysis of 21 retrospective studies including 8247 total patients (1494 ABO-incompatible and 6753 ABO-compatible liver transplant recipients). ABOi transplant recipients were noted to have lower 1, 3, and 5-year graft survival, as well as an increased incidence of AMR, chronic rejection, CMV, and surgical complications, as compared to ABO-compatible recipients.

Kim, J. M. et al. (2016), Case-matched comparison of ABO-incompatible and ABO-compatible living donor liver transplantation. British Journal of Surgery, 103: 276–283. Retrieved from http://onlinelibrary.wiley.com.ezproxy.galter.northwestern.edu/doi/10.1002/bjs.10048/full

- Forty-seven ABO-I LDLT procedures were included. Ninety-four patients who had ABO-C LDLT were selected as a comparator group. The incidence of cytomegalovirus, bacterial and fungal infections during the first 3 months was similar after ABO-I LDLT and ABO-C LDLT. The 1-, 2- and 3-year patient survival rates after ABO-I LDLT and ABO-C LDLT were 89% *vs* 87%, 85% *vs* 83%, and 85% *vs* 79% respectively.

Song, G.-W, et al. (2016). ABO-Incompatible Adult Living Donor Liver Transplantation Under the Desensitization Protocol With Rituximab. American Journal of Transplantation, 16: 157–170. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26372830

- Retrospective review of 235 adult patient undergoing adult donor living donor liver transplantation. The desensitization protocol included a single dose of rituximab and total plasma exchange. Three-year graft and patient survival rates were comparable to those of the ABOc group, however, 17 patients experienced AMR that manifested as diffuse intrahepatic biliary stricture; six cases required retransplantation, and three patients died.

Morimoto, H (2016). Different sensitivity of rituximab-treatment to B-cells between ABO-incompatible kidney and liver transplantation. Human Immunology, 77(6), 456-463. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27085793

- Study showing B-cell and T-cell immune responses in both KT and LT recipients. Investigated the kinetics of proportions of peripheral blood B-cell subsets in transplant recipients to compare the susceptibility to rituximab of ABO-I KT and LT. Rituximab has differing B-cell sensitivity between KT and LT recipients and a minimal effect on the alloreactive T-cell responses in KT and LT recipients.

Ikegami, T et al. (2016). Feasible usage of ABO incompatible grafts in living donor liver transplantation. Hepatobiliary Surgery and Nutrition, 5(2), 91–97. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4824747/

- Five year follow up study of 19 patients receiving ABOi-LDLTs using plasmapheresis and rituximab for desensitization. ABOi-LDLTs had increased incidence of cytomegalovirus infection (52.6% vs. 22.9%), other post-transplant complications including bacterial sepsis and acute rejection were not different. The 5-year graft survival rate was 87.9% in ABOi-LDLTs and 80.3% in non-ABOi-LDLTs.

Zhou, J. et al. (2015). ABO-incompatible liver transplantation for severe hepatitis B patients. Transplantation International, 28: 793–799. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/tri.12531/full

- Retrospective review of 22 patients with severe Hepatitis B(SHB) in whom were performed emergency liver transplantation from ABO-incompatible donors. Although the 1-, 3-, 5-year graft and patient survival rates of ABOi were lower than that of ABO-compatible group, the results suggested that ABOi liver transplantation might be a life-saving procedure for patients with SHB

as a promising alternative operation when ABO-c donors are not available and bridges the second opportunity for liver retransplantation.

Yasuda, M et al. (2015). The changes in treatment strategies in ABOi living donor liver transplantation for acute liver failure. The Journal of Medical Investigation. 2015;62(3-4):184-7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26399345

- Review of changes in treatment strategies in ABOi LDLT for acute liver failure. The desensitization protocol for ABOi barrier included Case #1; local infusion + plasma exchange (PE), Case #2; local infusion + rituximab + PE, Case #3 and #4; rituximab + PE, and Case #5; rituximab + PE under high-flow continuous hemodiafiltration. The patients of Case #2 and #3 received rituximab within 7 days before LDLT and experienced antibody-mediated rejection. Rituximab-based ABOi-LDLT given at least 2 weeks prior to transplant, most-recently under high-flow hemodiafiltration for treating encephalopathy, is a feasible option for applying LDLT for ALF.

Detry, O. (2015). Should ABO-incompatible deceased liver transplantation be reconsidered? Transplantation International, 28: 788–789. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25847352

- A retrospective review of the literature highlighting results in ABO-incompatible deceased donor liver transplantation in adult recipients. Both groups conclude that ABOi DDLT might be life-saving and might be used in urgent cases.

Thorsen, T. et al. (2015). Liver transplantation with deceased ABO-incompatible donors is life-saving but associated with increased risk of rejection and post-transplant complications. Transplantation International, 28: 800–812. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25736519

- Uncontrolled, retrospective, observational study in 61 patients receiving ABOi LT. Results show non-A2 grafts are associated with inferior graft survival and increased risk of rejection, vascular and biliary complications. ABOi LT performed with A2 grafts is associated with good long-term graft survival and can be used safely in urgent cases.

Egawa, H et al. (2014). Impact of rituximab desensitization on blood-type-incompatible adult living donor liver transplantation: a Japanese multicenter study. American Journal of Transplantation, 14(1), 102-14. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24279828.

- Uncontrolled, retrospective, observational study in 381 ABO-incompatible living-donor liver transplant (LDLT) recipients comparing desensitization with or without rituximab. Rituximab was associated with significantly lower rates of antibody-mediated rejection (AMR).

Muth, B et al. (2013). Use of apheresis in solid organ transplantation. Journal of Infusion Nursing, 36(5), 329-333. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24006111.

- Overview of use of apheresis, including management of associated complications.

Tanabe M et al. (2010). Current progress in ABO-incompatible liver transplantation. European Journal of Clinical investigation 20, 943-949. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20636381.

- Review article describing mainly progress in ABO-incompatible liver transplant since 1998, highlighting improved survival seen since the introduction of rituximab prophylaxis in 2003.

Stewart, Z et al. (2009). ABO-incompatible deceased donor liver transplantation in the United States: a national registry analysis. Liver Transplantation, 15, 883-893. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19642117.

- Analysis of UNOS data in ABO-incompatible liver transplants from 1990-2006 (N= 667 adults; N= 326 infants/ pediatrics), identifying trends that may be useful in guiding allocation of incompatible organs.

Testa, G et al. (2008). Adult living-donor liver transplantation with ABO-incompatible grafts. Transplantation, 85(5), 681-686. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18337660.

- Report of 5 ABO-incompatible LDLT recipients treated with plasmapheresis and IVIG pre-transplant, followed by thymoglobulin induction splenectomy. At 43 months post-transplant, 4 of 5 patients were alive with their original grafts. The 5th patient died of multi-organ failure 4 months after transplant; cause of organ failure was not determined. Overall results suggest favorable outcomes in ABO-incompatible LDLT.

Egawa, H et al. (2007). B-cell surface marker analysis for improvement of rituximab prophylaxis in ABO-incompatible adult living donor liver transplantation. Liver Transplantation 13: 579-588. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17394164.

- Prospective study in 30 ABO-incompatible LDLT patients treated with hepatic artery infusion (HAI) only or HAI with rituximab prophylaxis. Rituximab was associated with a trend toward lower rates of humoral rejection and lower peak IgG titers.

Hanto D et al. (2003). ABO-incompatible liver transplantation with no immunological graft losses using total plasma exchange, splenectomy, and quadruple immunosuppression: evidence for accommodation. Liver Transplantation 9(1), 22-30. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12514769.

- Retrospective study of 14 ABO-incompatible liver transplants treated with a protocol including total plasma exchange pre- and post-transplant, splenectomy at time of transplant and quadruple immunosuppression. Five-year patient and graft survival rates were 71.4% and 61.2%, respectively. No antibody-mediated rejections occurred.

3.4 Management of Rejection

Del Bello A, et al (2020). Outcome of Liver Transplant Patients With Preformed Donor-Specific Anti-Human Leukocyte Antigen Antibodies. Liver Transpl. 2020 Feb;26(2):256-267. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31612580

- Multi-center, retrospective analysis of 142 liver transplant recipients with preformed DSAs evaluating impact of induction therapy and transplant outcomes. Preformed DSA was associated with significantly higher rates of acute rejection but not patient survival.

Vionnet J, Sempoux C, Pascual M, Sánchez-fueyo A, Colmenero J (2019). Donor-specific antibodies in liver transplantation. Gastroenterol Hepatol. 2019; Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31810796

- Review article of the impact of pre-formed donor specific antibodies and de novo anti-human leukocyte antigen donor-specific antibodies in liver transplantation, as well as strategies to overcome the issue

Charlton M, Levitsky J, Aqel B, et al (2018). International Liver Transplantation Society Consensus Statement on Immunosuppression in Liver Transplant Recipients. Transplantation. 2018;102(5):727-743. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29485508

- Recommendations of the International Liver Transplantation Society (ILTS) Consensus guidelines on T-cell mediated rejection and antibody mediated rejection in liver transplant recipients are presented in this consensus findings article.

Kim PT, Demetris AJ, O'Leary JG. (2016). Prevention and treatment of liver allograft antibody-mediated rejection and the role of the 'two-hit hypothesis'. Current Opinions in Organ Transplant, 21(2):209-18. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26918881

- This article review prevention and treatment strategies for acute and chronic antibody-mediated rejection (AMR).

Del Bello A, et al. (2016). Donor-specific antibodies and liver transplantation. Human Immunology, 77(11): 1063-1070. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26916836

- This article reviews the implications and impact of preformed and de novo DSAs in liver transplantation and outlines potential management.

Oleary, J et al. (2014). The Role of Donor-Specific HLA Alloantibodies in Liver Transplantation. American Journal of Transplantation, 14, 779-787. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24580828

- This article addresses the concerns surrounding the misunderstandings of the role of donor specific antibodies in liver transplantation. Experts were consulted to pool common theories and clinical experience. The findings suggest that AMR is typically overlapped with ACR in liver transplantation and those patients undergoing simultaneous liver-kidney transplant are at higher risk for AMR post-transplant. DSA identification prior to transplant which persist post-liver transplant increase the risk for AMR as well.

Hubscher, S et al. (2012). Antibody-mediated rejection in the liver allograft. Current Opinions in Organ Transplant, 17, 280-286. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22569512.

- This article reviews the pathology of antibody-mediated rejection (AMR) focusing on recent studies which have improved our understanding of the clinicopathological features and diagnostic approaches.

Fosby, B et al. (2012). Recurrence and rejection in liver transplantation for primary sclerosing cholangitis. World Journal of Gastroenterology, 18, 1-15. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22228965.

- This review article focuses on the epidemiology, pathogenesis, treatment and the possible influence of rejection on the risk of recurrent disease in the liver allograft.

Levitsky, J et al. (2012). Risk for Immune-Mediated Graft Dysfunction in Liver Transplant Recipients With Recurrent HCV Infection Treated With Pegylated Interferon. Gastroenterology, 142, 1132-1139. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22285805.

- 52 liver transplant recipients with hepatitis C were assessed for the incidence of, risk factors for, and outcomes of PEGIGD. PEG-IGD has high morbidity and mortality and is not associated with increased rates of virologic response and is recommended to be avoided due to an increased risk of rejection.

Paterno F, Shiller M, Tillery G, O'Leary JG, Susskind B, Trotter J, Klintmalm GB (2012). Bortezomib for acute antibody-mediated rejection in liver transplantation. Am J Transplant. 2012 Sep;12(9):2526-31. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22681986

- Case report of three liver transplant recipients with ABO-compatible refractory AMR. Treatment with bortezomib resulted in normalization of liver function tests, resolution of C4d deposition and decrease in DSA.

Togashi, J et al. (2011). Basiliximab as therapy for acute rejection after liver transplantation for hepatitis C virus cirrhosis. Bioscience Trends, 5, 57-60. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21572248.

- Due to the controversy in utilizing steroids in liver transplant recipients experiencing rejection due to reactivation of diseases, basiliximab was studied. Authors concluded that basiliximab can be safely used as rescue therapy for ACR without significant adverse effects in patients who underwent liver transplantation for HCV cirrhosis.

Neil, D et al. (2010). Current views on rejection pathology in liver transplantation. European Society for Organ Transplantation, 23, 971–983. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20723179

- This article addresses the differences between acute and chronic rejection with regard to pathophysiology and clinical presentation. A discussion on antibody-mediated rejection is also present in this review.

Shaked A, et al. (2009). Incidence and Severity of Acute Cellular Rejection in Recipients Undergoing Adult Living Donor or Deceased Donor Liver Transplantation. American Journal of Transplantation, 9, 301-308. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19120082.

- This review article discusses risk factors for acute rejection and different management strategies from different transplant centers. The reported incidence of acute cellular rejection is also reported.

3.5 Hepatic Diseases

3.5.1 Acute Hepatic Necrosis

Stravitz RT, Lee WM (2019). Acute liver failure. Lancet. 2019;394(10201):869-881. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31498101.

- Review article describing common causes, diagnosis, management, prognosis, as well as long-term outcomes after transplant. A brief review of available evidence is also included.

Wang, D et al. (2013). Advances in the management of acute liver failure. World Journal of Gastroenterology, 19, 7069-7077. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24222950

- Review article which focuses on etiologies of acute liver failure and the management of various complications. The role of liver transplantation in this population is also discussed.

Gulmez, S et al. (2013). Transplantation for Acute Liver Failure in Patients Exposed to NSAIDs or Paracetamol (Acetaminophen). Drug Safety, 36, 135-144. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23325533

- Study designed to estimate population rates of NSAID associated acute liver failure leading to transplantation. 9479 patients total across 52 centers were registered for transplantation with 600 of them actually leading to transplantation. Of these 600, 301 had received either NSAID or paracetamol therapy within 30 days of transplantation.

Banares, R et al. (2013). Extracorporeal Albumin Dialysis With the Molecular Adsorbent Recirculating System in Acute-on-Chronic Liver Failure: The RELIEF Trial. Hepatology, 57, 1153-1162. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23213075

- 189 patients were randomized to receive molecular adsorbent recirculating system (MARS) or to standard medical therapy. No significant difference was seen between the two groups with respect to 28-day survival. When confounders were controlled, patients who received MARS also did not have a significantly beneficial effect over standard medical therapy. However, in patients with severe HE, MARS may have a role in decreasing the grade of diseases more rapidly than standard medical therapy without additional adverse effects.

Lee W, et al. (2012). Introduction to the Revised American Association for the Study of Liver Diseases Position Paper on Acute Liver Failure 2011. Hepatology. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22213561

- Guidelines review from the American Association for the Study of Liver Diseases. Etiology of acute liver failure and therapeutic management are discussed.

Reuben, A et al. (2010). Drug-Induced Acute Liver Failure: Results of a U.S. Multicenter, Prospective Study. Hepatology, 52, 2065-2076. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20949552

- Cases of idiosyncratic drug-induced liver failure are discussed. Long-term outcomes, such as transplant-free survival and overall survival are also discussed as well.

Lee, W et al. (2009). Intravenous N-Acetylcysteine Improves Transplant-free Survival in Early Stage Non-Acetaminophen Acute Liver Failure. Gastroenterology, 137, 856-864. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19524577

- 173 patients with non-acetaminophen induced acute liver failure were stratified to receive either intravenous NAC (N=81) or placebo (N=92). Overall survival was 70% in the NAC group and 66% in the placebo group (p=0.283). Transplant-free survival however, was significantly better in those that received NAC (40%) vs. those that received placebo (27%); p=0.043. This benefit was seen in patients with coma grades I-II, suggesting that more advanced coma grades (worse encephalopathy) did not benefit from NAC with regards to survival.

Larson, A et al. (2005). Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study. Hepatology, 42, 1364-1372. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16317692

- Review article which discusses the epidemiology of acute liver failure secondary to acetaminophen toxicity. Overall survival, median dose ingested, and intentional vs. unintentional overdose data are discussed.

Schiodt F, et al. (2003). Viral Hepatitis-Related Acute Liver Failure. American Journal of Gastroenterology, 98, 448-453. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12591067

- Review article which discusses the incidence of viral-hepatitis induced acute liver failure. This article discusses the incidence of transplant free-survival rate as well as transplant rate differentiation between different subsets of viral hepatitis.

3.5.2 Biliary Atresia

Uto K, Inomata Y, Sakamoto S, Hibi T, Sasaki H, Nio M (2019). A multicenter study of primary liver transplantation for biliary atresia in Japan. Pediatr Surg Int. 2019;35(11):1223-1229. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31535197

- Multi-center study conducted of the first nationwide survey in Japan to assess the status of primary liver transplant for biliary atresia in over 2800 patients.

Kasahara M, Umeshita K, Sakamoto S, Fukuda A, Furukawa H, Uemoto S (2017). Liver transplantation for biliary atresia: a systematic review. Pediatr Surg Int. 2017;33(12):1289-1295. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28983725

- Systematic review of liver transplantation for biliary atresia.

Davenport, M et al. (2013). Steroids in biliary atresia: Single surgeon, single centre, prospective study. Journal of Hepatology, 59, 1054-1058. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23811305

- This primary article observes the difference in outcomes in patients with biliary atresia who received steroid therapy vs. those that did not. 153 infants underwent portoenterostomy. Afterwards, patients were divided into three groups, low dose steroid (prednisolone 2mg/kg/day), high dose steroid (prednisolone 5mg/kg/day), and no steroids. A significant difference was seen between groups with respect to decreases in bilirubin and AST between the high dose steroids vs. no steroid groups. There was also an increase in the clearance of jaundice between those patients that received steroids and those that did not. This study supports the use of steroids in infants immediately post portoenterostomy.

Moreira, R et al. (2012). Biliary Atresia A Multidisciplinary Approach to Diagnosis and Management. Archives of Pathology and Laboratory Medicine, 136, 746-760. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22742548

- This review article discusses the diagnosis and management of biliary atresia. The main points of discussion include pathophysiology, kasai's procedure, and the role of liver transplantation.

Davenport, M et al. (2007). Randomized, Double-Blind, Placebo-Controlled Trial of Corticosteroids After Kasai Portoenterostomy for Biliary Atresia. Journal of Hepatology, 46, 1821-1827. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17935230

- This clinical trial evaluated the use of steroids as adjuvant therapy after Kasai's procedure. Patients were randomized to receive placebo or 2mg/kg/day of prednisolone on day 7 to 21 and then 1mg/kg/day on day 22 to day 28. There was a statistically significant difference in bilirubin levels with much lower levels seen in the steroid group at 1 month (66 vs. 92 mmol/L; p=0.06). However, no difference was seen at 6 months (p=0.56) or 12 months (p=0.3). The need for liver transplantation at 6 and 12 months was also not statistically significant (p=0.99, p=0.47, respectively). The authors concluded that the rates of reduction in bilirubin were only apparent in the immediate post-operative period (1 month), but did not sustain a long term effect.

3.5.3 Malignant Neoplasms

Verna EC, et al (2020). Liver transplantation for hepatocellular carcinoma: Management after the transplant. Am J Transplant. 2020 Feb;20(2):333-347. doi: 10.1111/ajt.15697. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/31710773

- This review discusses risk factors for HCC recurrence, surveillance modalities, HCC prevention and treatment strategies after liver transplantation.

Kulik L, Heimbach JK, Zaiem F, et al (2018). Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. Hepatology. 2018;67(1):381-400. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28859222

- Systematic review and meta-analysis of 63 studies including pre-liver transplant patients with hepatocellular carcinoma. Reviews data available describing outcomes of various approaches to HCC management, including observation vs. therapy, transplant alone vs. transplant with bridging, and transplant without down-staging vs. transplant following down staging to within Milan Criteria.

Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ (2018). Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol. 2018;15(2):95-111. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5819599/

- Extensive review of cholangiocarcinoma, including epidemiology, anticipated outcomes, standards of care based on anatomical subtype, surgical approach and consideration of transplant, use of newer immunotherapies, and emerging investigational therapies.

Geissler EK, Schnitzbauer AA, Zülke C, et al (2016). Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomized, Multicenter, Open-Label Phase 3 Trial (SiLVER Trial). Transplantation. 2016;100(1):116-25. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26555945.

- Randomized, open-label study of 525 liver transplant recipients with hepatocellular carcinoma (HCC) randomized to maintenance immunosuppression incorporating either sirolimus or continuing standard of care. The primary endpoint of recurrence free survival (RFS) occurred in 218 (85.2%) of the treatment/sirolimus group and 233 (92.5%) of the control group at 1-year post-transplant (p=0.01). However, this difference became non-significant at 2 –years. Benefit in RFS was most pronounced in those considered low-risk based on Milan Criteria.

Yao, D et al. (2014). A review of the clinical diagnosis and therapy of cholangiocarcinoma. Journal of International Medical Research 1-14. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24366497

- This review article serves as a reference for the diagnosis and clinical management of cholangiocarcinoma. Being the second most common primary hepatic malignancy worldwide, this article will provide a reference as to the common treatment strategies.

Pompili, M et al. (2013). Bridging and down staging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. World Journal of Gastroenterology, 19, 7515-7530. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24282343

- This review article describes various strategies for managing hepatocellular carcinoma before and after liver transplantation. Treatment strategies such as radiofrequency ablation, transarterial chemoembolization, and other therapies are described in detail. Many primary articles are also referenced throughout this review. This will serve as a reference for those who wish to expand their exposure to standard management of HCC pre and post-liver transplantation.

Cheah,Y et al. (2012). Liver Transplantation for Hepatocellular Carcinoma: An Appraisal of Current Controversies. Liver Cancer, 1, 183–189. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24159583

- This review article describes criteria for liver transplantation in patients with HCC and discusses Milan criteria. Other areas discussed include living donor liver transplantation for HCC and expanding Milan criteria in the setting of an increased incidence of HCC. Many patients are unable to undergo surgical resection due to location of tumors or due to high perioperative mortality risk. This article describes alternative strategies in managing this patient population.

Finn. (2012). Current and Future Treatment Strategies for Patients with Advanced Hepatocellular Carcinoma: Role of mTOR Inhibition. Liver Cancer, 1, 247-256/ Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24159589

- This review article discusses the role of mTOR inhibitors in patients with advanced HCC. The mechanism of the anti-proliferative effect that mTOR inhibitors possess to have positive outcomes in patients with HCC is explained

Lewandowski, R et al. (2009). A Comparative Analysis of Transarterial Downstaging for Hepatocellular Carcinoma: Chemoembolization Versus Radioembolization. American Journal of Transplantation, 9, 1920-1928. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19552767

- This primary article evaluates the use of chemoembolization (TACE) vs. radioembolization (Y90) for the management of HCC. The objective of this study was to see if the effects of TACE vs. Y90 were better or worse in downstaging HCC to allow patients to be listed for liver transplantation. 43 patients were treated with TACE and 43 patients were treated with Y90 procedures. Median tumor size at baseline was similar (5.7cm vs. 5.6cm) in TACE vs. Y90 groups. Event-free survival was significantly better in the Y90 group (17.7 vs. 7.1 months; p=0.0017). Overall survival was also significantly better in the Y90 group (41.6 vs. 19.2 months, p=0.008). The authors concluded that Y90 seemed to provide better downstaging response rates than TACE.

Maddala, Y et al. (2004). Drop-Out Rates of Patients with Hepatocellular Cancer Listed for Liver Transplantation: Outcome with Chemoembolization. Liver Transplantation, 10, 449-455. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15004776

- This primary article discusses the use of chemoembolization in patients with HCC on the waiting list for liver transplantation. The aim of this study was to assess the dropout rate of patients who were removed from the waiting list due to resolution of disease from chemoembolization. The dropout rate at 6 months was 15% (8 patients dropped out of the waiting list out of 54 total). This study reflects alternative options to the management of HCC aside from liver transplant, due to the rising incidence of disease and lack of transplantable organs.

3.5.4 Metabolic Diseases

VanWagner LB, et al (2020). Blood pressure control according to clinical practice guidelines is associated with decreased mortality and cardiovascular events among liver transplant recipients. Am J Transplant. 2020 Mar;20(3):797-807. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31730286

- Longitudinal cohort study of 602 liver transplant recipients assessing the effect of blood pressure control on cardiovascular events and mortality. Achieving blood pressure control (<140/<90 mmHg) was associated with a reduction in cardiovascular events and improved survival.

Cotter TG, et al (2020). Nonalcoholic Steatohepatitis After Liver Transplantation. Liver Transpl. 2020 Jan;26(1):141-159. doi: 10.1002/lt.25657. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31610081/

- This review discusses pre- and post-transplant management considerations for patients with end stage liver disease due to NASH.

Sheka AC, et al (2020). Nonalcoholic Steatohepatitis: A Review. JAMA. 2020 Mar 24;323(12):1175-1183. doi: 10.1001/jama.2020.2298. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/32207804

- This review discusses the epidemiology, diagnosis and management of NASH.

Jenssen T, Hartmann A (2019). Post-transplant diabetes mellitus in patients with solid organ transplants. Nat Rev Endocrinol. 2019;15(3):172-188. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30622369

- This review discusses current evidence on PTDM in patients receiving kidney, heart, liver and lung transplants.

Wong VW, Singal AK (2019). Emerging medical therapies for non-alcoholic fatty liver disease and for alcoholic hepatitis. Transl Gastroenterol Hepatol. 2019;4:53. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31463412

- This review article discussed the novel therapeutic agents and current status of ongoing clinical trials with agents for the treatment of non-alcoholic fatty liver disease and/or alcoholic hepatitis.

Mitchell EL, Khan Z (2017). Liver Disease in Alpha-1 Antitrypsin Deficiency: Current Approaches and Future Directions. Curr Pathobiol Rep. 2017;5(3):243-252. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29399420

- Review of the liver disease caused by alpha-1 antitrypsin deficiency. This review includes a discussion on pathogenesis, epidemiology, diagnostic testing, and recent therapeutic developments.

Kanwar, P et al. (2014). Metal Storage Disorders Wilson Disease and Hemochromatosis. Med Clin N Am, 98, 87-102. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24266916

- This review article discusses the details of diagnosis, treatment, stratification, and survival data in patients with Wilson's disease and hemochromatosis.

Said, A et al. (2013). Non-alcoholic fatty liver disease and liver transplantation: Outcomes and advances. World Journal of Gastroenterology, 28, 9146-9155. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24409043

- This review article discusses the details of treatment of NAFLD and recurrence after transplantation. The incidence of transplantation rates as well as long-term outcomes after transplant is discussed.

Teckman, J et al. (2013). Liver Disease in Alpha-1 Antitrypsin Deficiency: Current Understanding and Future Therapy. COPD, 10, 35-43. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23527737

- This review article discusses the details of diagnosis, pathophysiology, and clinical management of alpha-1-antitrypsin deficiency and its effect on the liver.

Janczyk, W et al. (2013). Omega-3 fatty acids for treatment of non-alcoholic fatty liver disease: design and rationale of randomized controlled trial. BMC Pediatrics, 13, 85. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23702094

- The primary outcome of the trial is the number of patients who decreased ALT activity by ≥0, 3 of upper limit of normal. Results are not published yet, but the discussion of the rationale for omega-3-fatty acids is discussed. Other primary articles are referenced as well

Deugnier, Y et al. (2011). Pathology of Hepatic Iron Overload. Seminars in Liver Disease, 31, 260-271. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21901656

- The description of diagnosis and etiologies are presented in this review article. Genetic variations of disease are also discussed as well as some treatment options.

Gan, E et al. (2011). Natural History and Management of HFE-Hemochromatosis. Seminars in Liver Disease, 31, 293-301. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21901659

- This review articles discusses commonly raised issues relating to the current natural history, diagnosis, and management of HH patients.

Johncilla, M et al. (2011). Pathology of the Liver in Copper Overload. Seminars in Liver Disease, 31, 239-244. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21901654

- This review article discusses copper iron overload and its mechanism in causing liver injury.

Rosencrantz R, et al. (2011). Wilson Disease: Pathogenesis and Clinical Considerations in Diagnosis and Treatment. Seminars in Liver Disease, 31, 245-259. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21901655

- This review article discusses the details of diagnosis, treatment, stratification, and survival data in patients with Wilson's disease.

3.5.5 Cholestatic Liver Disease/Cirrhosis and Non-Cholestatic Cirrhosis

Montano-Loza AJ, Hansen BE, Corpechot C; Global PBC Study Group (2019). Factors Associated With Recurrence of Primary Biliary Cholangitis After Liver Transplantation and Effects on Graft and Patient Survival. Gastroenterology. 2019 Jan;156(1):96-107.e1. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30296431

- Multicenter, international cohort study assessing incidence and risk of PBC recurrence after liver transplantation. PBC recurred in 22% at 5 years and 36% at 10 years post-transplant. Risk factors for recurrence included age <50 years at time of diagnosis, age <60 years at time of transplant, tacrolimus use, and elevated bilirubin or alkaline phosphatase at 6 months post-transplant.

Pena Polanco NA, Levy C, Martin EF (2017). Cholestatic Liver Diseases After Liver Transplant. Clin Liver Dis. 2017 May;21(2):403-420. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28364821

- Review article that discusses disease recurrence post-transplant and outcomes associated with disease recurrence.

Bosch A, Dumortier J, Maucort-Boulch D, et al (2015). Preventive administration of UDCA after liver transplantation for primary biliary cirrhosis is associated with alower risk of disease recurrence. J Hepatol. 2015 Dec;63(6):1449-58. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26282232

- Multi-center retrospective cohort study evaluating preventative administration of ursodeoxycholic acid (UDCA) on PBC recurrence post-transplant in 90 liver transplant recipients. Preventative UDCA was associated with reduced risk of PBC recurrence after transplant.

Liou IW. (2014). Management of end-stage liver disease. The Medical Clinics of North America, 98(1):119-52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24266918

- The current article reviews various complications associated with end-stage liver disease and treatments for managing complications.

Bjornsson ES, et al. (2013) Drug-induced cholestasis. Clinics in Liver Disease, 17(2), 191-209. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23540497

- The current article describes risk factors, pathophysiology, and drugs more commonly associated with drug-induced cholestasis occurrence.

Hirschfield GM, et al. (2010) Pathogenesis of cholestatic liver disease and therapeutic approaches. Gastroenterology, 139(5), 1481-96. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20849855

- The current article reviews the pathophysiology of cholestasis at the molecular level and provides a brief description of treatment options for managing cholestasis.

Neuberger J (2003). Liver transplantation for primary biliary cirrhosis: indications and risk of recurrence. J Hepatol. 2003 Aug;39(2):142-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12873808

- Review article that discusses PBC, outcomes after transplant and PBC recurrence post-transplant.

Hofmann AF. (2002) Cholestatic liver disease: pathophysiology and therapeutic options. Liver, 22 Suppl 2:14-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12220297

- The current article reviews the pathophysiology of the development of cholestasis and treatment options for managing cholestasis.