3. Liver transplantation

3.1. Induction therapy

Petite SE et al. Antithymocyte Globulin Induction Therapy in Liver Transplant. Annals of Pharmacotherapy, 50 (7), 592-598 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. 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. 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. 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. 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. 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 reviwed 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. 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. 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. 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. (2012). 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

De Simone P, et al. Everolimus with Reduced Tacrolimus Improves Renal Function in De Novo Liver Transplant Reicpients: A Randomzied Controlled Trial. American Journal of Transplantation 2012; 12: 3008-3020.

- 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.

Aguiar D, et al. 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.

Khorsandi SE, Heaton N. 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.

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.

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.

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 pretransplant setting. Estimated glomerular filtration rate decreased the least in the daclizumab induction group. Patient and graft survival were similar among all 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

3.3. ABO-Incompatible Liver Transplantation

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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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.

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.

3.5. Hepatic diseases

3.5.1. Acute hepatic necrosis

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.

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.

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.

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.

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.

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.

3.5.2. 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

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.

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.

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.

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.

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.

3.5.4. Metabolic diseases

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.

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.

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.

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.

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.

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.

3.5.5. Cholestatic liver disease/cirrhosis and non-cholestatic cirrhosis

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.

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.

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.

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.