4. Intestine transplantation

4.1. Induction/maintenance therapy

Fishbein TM, et al. (2002). Intestinal transplantation before and after the introduction of sirolimus. Transplantation, 10, 1538-1542. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12042637

- Mount Sinai Hospital, single center, retrospective review of a before and after immunosuppression regimen with the addition of sirolimus on graft and patient survival in adult and pediatric intestinal transplants
- Group 1 (tacrolimus, steroids and antibody induction) had 57.9% graft survival compared to Group 2 (tacrolimus, steroids, basiliximab, and sirolimus) had 91.7% graft survival, $p<0.04$

Nishida S, et al. (2002). Induction therapy for adult small bowel transplant with Campath-1H. Transplantation Proceedings 2002; 34: 1889-91. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/12176616

- A total of 14 small bowel transplants performed at the University of Miami/Jackson Memorial Medical Center using Campath-1H for induction therapy. A comparison of three induction groups: group 1, tacrolimus plus steroid bolus and cycle; group 2, daclizumab; and group 3, Campath-1H.
- Patient and graft survival were improved in group 3. Overall, 85% of patients were alive at the time of publication and 7

Sudan DL, et al. (2002). Basiliximab reduces the incidence of acute rejection after intestinal transplantation. Transplant Proceedings, 34, 940-941. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12034250

- Prospective study from the University of Nebraska Medical Center assessing addition of basiliximab for induction to a tacrolimus and prednisone immunosuppression maintenance regimen
- Basiliximab reduced the incidence of acute rejection (86% vs. 36%, p<0.01) and the median number of acute rejection episodes (3 vs. 0, p<0.01) without increasing the risk for infection

Garcia M, et al. (2004). Campath-1H Immunosuppressive Therapy Reduces Incidence and Intensity of Acute Rejection in Intestinal and Multivisceral Transplantation. Transplantation Proceedings. 2004, 36, 323-324.
Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15050146

- Retrospective review of 78 patients who underwent isolated intestinal, multivisceral transplantation and retransplant (n=9) from 1998 to 2002, and received induction immunosuppression with alemtuzumab (n =27) or daclizumab (n =51). There was an overall reduced incidence of acute cellular rejection (ACR) in patients receiving alemtuzumab (19.1%) compared with those receiving daclizumab (32.8%). The mean grade of ACR in alemtuzumab patients compared with daclizumab patients was significantly lower (P <. 01) during the first 6 weeks posttransplant. Patient and graft survival was not statistically significantly different between the two groups.

Farmer DG, et al. (2004). Induction therapy with interleukin-2 receptor antagonist after intestinal transplantation is associated with reduced acute cellular rejection and improved renal function. Transplant proceedings, 36(2), 331-2. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15050149

- Survival and rejection outcomes are retrospectively reviewed in 27 pediatric or adult intestinal transplant recipients receiving no induction, OKT3, or an interleukin-2 receptor

antagonist followed by standard maintenance triple therapy at the Dumont-UCLA Transplant Center. Patient and graft survival were higher in the interleukin-2 receptor agonist group compared to the OKT3 and no induction groups. Acute rejection episodes were significantly lower in the interleukin-2 receptor antagonist group compared to the no induction group.

Reyes J, et al. (2005). Intestinal transplantation under tacrolimus monotherapy after perioperative lymphoid depletion with rabbit anti-thymocyte globulin (thymoglobulin). American Journal of Transplantation, 5(6), 1430-6. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15888051

- Tacrolimus monotherapy following rabbit antithymocyte globulin 5 mg/kg induction is evaluated in 36 pediatric or adult intestinal transplant recipients at the University of Pittsburgh Medical Center. Patient and graft survival was 100% and 94% at one and two years, respectively.

Nishida S, et al. (2006). Intestinal transplantation with alemtuzumab (Campath-1H) induction for adult patients. Transplantation proceedings, 38(6), 1747-9. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16908270

- Survival and rejection outcomes are retrospectively reviewed in 76 adult intestinal transplant recipients receiving steroids, daclizumab, or OKT-3 versus alemtuzumab induction therapy at the University of Miami/Jackson Memorial Medical Center. Patient survival at one year was higher and rate of acute rejection episodes was significantly lower in the alemtuzumab group when compared to the non-alemtuzumab group.

Lauro A, et al. (2007). Twenty-five consecutive isolated intestinal transplants in adult patients: a five-yr clinical experience. Clinical Transplantation 2007; 21: 177-185. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17425742

- A review of 25 isolated intestinal transplants in adults for short gut syndrome, chronic intestinal pseudo-obstruction, Gardner syndrome, radiation enteritis and massive intestinal angiomatosis. Three protocols were used for immunosuppression: daclizumab for induction, tacrolimus and steroids as maintenance (protocol 1), alemtuzumab for induction and low-dose tacrolimus as maintenance (protocol 2), or thymoglobulin for induction and low-dose tacrolimus as maintenance (protocol 3).
- Two- and five- year patient survival rates were 80% and 66%, respectively. Two- and five-year graft survival rates were 76% and 64%, respectively. Induction therapy reduced the amount of postoperative immunosuppressive agents.

Vianna RM, et al. (2008). Induction immunosuppression with thymoglobulin and rituximab in intestinal and multivisceral transplantation. Transplantation, 85(9), 1290-3. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18475186

- Retrospective review evaluating the use of antithymocyte globulin in combination with rituximab induction therapy followed by tacrolimus and steroid taper maintenance therapy in 27 adult intestinal/multivisceral transplant recipients at Indiana University. Patient and graft survival at one year was 81% and 76%, respectively, with the incidence of rejection similar to that published with the use of other immunosuppression therapies.

Abu-Elmagd KM, et al. (2009). Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Annals of surgery, 250(4), 567-81. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19730240

- The evolution of intestinal and multivisceral transplant at the University of Pittsburgh Medical Center are described. Patient and graft survival are evaluated in 453 pediatric or adult recipients throughout the three eras described. Patient and graft survival significantly decreased from one and ten years following transplant, further necessitating the development of more innovative techniques to decrease incidences of complications and prolong survival in intestinal/multivisceral transplant recipients.

Zanfi C, et al. (2010). Daclizumab and alemtuzumab as induction agents in adult intestinal and multivisceral transplantation: rejection and infection rates in 40 recipients during the early postoperative period. Transplant proceedings, 42(1), 35-8. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20172276

- Forty adult intestinal transplant recipients received either daclizumab induction followed by tacrolimus and prednisone maintenance therapy or alemtuzumab induction followed by low-dose tacrolimus therapy at the University of Bologna/Sant'Orsola-Malpighi Hospital. Patient and graft survival were higher in the daclizumab induction therapy group compared to the alemtuzumab group.

Trevizol AP, et al. (2012). Intestinal and multivisceral transplantation immunosuppression protocols--literature review. Transplantation Proceedings, 44(8), 2445-8. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23026616

- Retrospective review evaluating the use of three immunosuppression protocols that include daclizumab induction with tacrolimus and steroid maintenance (protocol 1), alemtuzumab induction with tacrolimus maintenance (protocol 2), and antithymocyte globulin in combination with rituximab induction with tacrolimus maintenance (protocol 3) in 211 adult intestinal/multivisceral transplant recipients at seven centers. Incidence of acute

cellular rejection was lowest with protocol 2. One- and three-year patient survival was higher with protocol 3. Rate of infection was lower in protocol 3 compared to protocols 1 and 2.

Lauro A, et al. (2012). Induction therapy in adult intestinal transplantation: reduced incidence of rejection with "2-dose" alemtuzumab protocol. Clinical Transplantation, 27, 567-70. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23815302

- Retrospective review evaluating a "2-dose" alemtuzumab protocol compared to two previously utilized protocols (daclizumab, and 4-dose alemtuzumab) in 42 adult intestinal transplantation recipients at the University of Bologna, Italy. No difference in early acute cellular rejection and death due to sepsis compared to patients receiving other regimens.

Ceulemans LJ, et al. (2015). Belgian multicenter experience with intestinal transplantation. Transplantation International, 28, 1362-70. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/26033472

- Retrospective review of intestinal and multivisceral transplantation at five centers in Belgium. Twenty four patients underwent transplantation, 17 of whom received basiliximab induction and 3 of whom received antithymocyte globulin induction. Rejection and mortality are not stratified by receipt of different induction or maintenance immunosuppression. Maintenance immunosuppression regimens and rejection treatment varied.

Grant D, et al. (2015). Intestinal transplant registry report: global activity and trends. American Journal of Transplantation, 15, 210-9. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/25438622

- Updated report from the Intestinal Transplant Registry, a database that receives information biannually from 82 contributing centers. A total of 2,699 patients are included in this report dating back to 1985, representing an estimated 95% of all cases ever performed. The use of any induction immunosuppression and the incorporation of sirolimus into maintenance immunosuppressive regimens were both associated with improved patient survival in a multivariable survival analysis

Chang HK, et al. (2016). Ten-year experience with bowel transplantation at Seoul St. Mary's Hospital. Transplantation Proceedings, 48, 473-8. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/27109981

- Retrospective review of intestinal and multivisceral transplantation at a single center in South Korea. Fifteen patients underwent transplantation; 2 patients received daclizumab induction, 2 patients received basiliximab, and 10 patients received an unspecified combination of antithymocyte globulin and basiliximab. Tacrolimus monotherapy was used for basic maintenance and an m-TOR inhibitor was used for renal dysfunction patients. Rejection and mortality are not stratified by receipt of different induction or maintenance immunosuppression. Seven cases of ACR were treated with rATG and 3 cases of AMR were treated with rituximab or rituximab and bortezomib.

Ramish D, et al. (2016). Long-term outcomes of intestinal and multivisceral transplantation at a single center in Argentina. Transplantation Proceedings, 48, 457-62. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/27109978

- Retrospective review of 42 patients who underwent either intestinal or multivisceral transplants at a single center in Argentina. Patients were prospectively divided into two immunologic risk categories: low and high risk. Low risk recipients (n=26) received induction therapy with basiliximab, while high risk recipients (n=13) received antithymocyte globulin. Both cohorts received maintenance immunosuppression with tacrolimus and steroids, but low risk patients received mycophenolate mofetil while high risk patients received sirolimus. A total of 68 episodes of rejection occurred in the low-risk population versus 15 episodes in the high risk group. Nine low-risk patients had an episode of rejection within 30 days (34%) versus 5 patients in the high risk group (38%). Patient and graft survival at 5 years in the low risk risk group were 59% and 51%, respectively, compared to 52% and 50% in the high risk group.

Lauro A, et al. (2007). Daclizumab and Alemtuzumab as induction agents in adult intestinal and multivisceral transplantation: a comparison of two different regimens on 29 recipients during the early post-operative period. Digestive and Liver Disease, 39, 253-256. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17275428

- Retrospective review of 29 adult intestinal and multivisceral transplant recipients comparing alemtuzumab (n=17) and daclizumab (n=12) induction. For maintenance, both groups used tacrolimus (goal 8-12 ng/mL and 15-20 ng/mL, respectively) and steroids were only used in the daclizumab group. In the alemtuzumab group 12% experienced acute

cellular rejection vs 42% in the daclizumab group. Patient and graft survival at 3-years were not different between groups (63.6% vs 81.8%).

Todo S, et al. (1993) Intestinal transplantation in humans under FK 506. Transplant Proc. 25(1 Pt 2):1198-9. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/7680148

- Clinical trial of intestinal transplant under FK506 (n=23). Eighty-eight percent of isolated small bowel recipients, 75% of combined intestine and liver recipients, and 100% of multivisceral transplant recipients were alive at follow-up. Of the 19 surviving patients, 14 are home and completely free of TPN.

Dazzi A, et al. (2007). Steroids in intestinal transplant. Clin Transplant, 21(2):265-8. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17425756

- Retrospective study comparing steroid doses in 25 intestinal/multivisceral transplant recipients. Patients with a mean prednisone dose higher than 20 mg/day had lower graft ($p=0.009$) and patient ($p=0.02$) survival. Infections were more frequent during steroid administration ($p=0.04$).

Horslen S, et al. (2002). Initial experience using rapamycin immunosuppression in pediatric intestinal transplant recipients. Transplantation Proceedings, 34: 934-935. Retrieved from: https://www.sciencedirect.com/science/article/pii/S0041134502026775?via%3Dihub

- Retrospective review of 16 pediatric intestinal transplant patients started on sirolimus for renal-sparing. The initial loading dose of sirolimus was 2 to 3 mg/m^2 followed by 1 mg/m^2 daily to achieve levels of 8-10 ng/ml. Some children required twice daily dosing to achieve

these levels. Tacrolimus was generally decreased 50% and adjusted according to blood level depending on the patient. Of the patients who had nephrotoxicity, 11/15 improved; 2 patients developed neutropenia leading to discontinuation; 2 patients did not improve. Rejection occurred in 1/16 patients. Graft loss occurred in 2/16 patients.

Andres AM, et al. (2010). The use of sirolimus as a rescue therapy in pediatric intestinal transplant recipients. Pediatr Transplanation, 14: 931-935. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20946188

- Retrospective review of 5 children transitioned to sirolimus for second-line therapy in 45 small bowel transplant recipients (1997-2009). Tacrolimus was discontinued in 4/5 patients due to refractory hemolytic anemia with decreased renal function and discontinued in 1/5 due to renal failure and unclear neutropenia. Tacrolimus-related side effects disappeared in all five although other immunosuppressants and splenectomy were used. Renal function and hematologic disorders seemed to improve. Four out of 5 patients were alive with excellent quality of life at the end of follow up (median follow up 18 months).

Barau C, et al. (2017). Pharmacokinetics of mycophenolic acid and dose optimization in children after intestinal transplantation. Ther Drug Monit, 39(1): 37-42. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=PMID%3A+27898598

- A pharmacokinetic study was conducted in 8 children (median 9.4 years) at a median time of 113 months after intestinal transplant. MMF was introduced at a low median starting dose of 687 mg/m^2/d. One of 3 patients who received MPS and 2/6 patients who received MMF had an MPA $AUC_{0\text{-}12}$ below 30 mg.h.L^{-1}. The median MMF dosage had to be increased by 91% to achieve $AUC_{0\text{-}12}$ above the defined target of 30 mg.h.L^{-1}. When used with tacrolimus and

steroids, an initial MMF dose of 600 mg/m^2 twice a day would be recommended for children after intestinal transplant to achieve similar MPA exposure to that of adults and children after transplantation of other organs.

Apostolov R, et al. (2017). Mycophenolate toxicity mimicking acute cellular rejection in a small intestinal transplant. World J Transplant, 7(1): 98-102. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=PMID%3A+28280702

- Enterocolitis can occur from MMF use and has been associated with multiple histologic features. This case presents a case of MMF toxicity in a small intestinal transplant recipient that presented with histological changes in the ileum mimicking persistent acute cellular rejection. Biopsies from the patient's native colon showed similar changes to that from the donor small bowel. MMF was stopped and complete resolution occurred over 3 weeks.

4.2. Management of rejection

4.2.1. Cellular rejection

Wu T, et al. (2003). A schema for histologic grading of small intestine allograft acute rejection. Transplantation, 75, 1241-1248. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12717210

- Schema for the assessment of the severity of small bowel acute rejection

Ruiz R, et al. (2004). Histological criteria for the identification of acute cellular rejection in human small bowel allografts: results of the pathology workshop at the VIII international small bowel transplant symposium. Transplantation Proceedings, 36,335-337. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15050150

- A standardized grading scheme for acute cellular rejection in small bowel transplantation

Pascher A, et al. (2005). Anti-TNF-alpha therapy for acute rejection in intestinal transplantation. Transplant Proc. 2005, 37(3), 1635-6. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15866693

- Retrospective review of 12 intestinal transplant recipients and 1 multivisceral transplant recipient who underwent infliximab rescue therapy for steroid- and OKT3- resistant rejection. Maintenance immunosuppression consisted of tacrolimus, sirolimus, daclizumab, steroids (n=10) or tacrolimus, alemtuzumab, and steroids (n=3).
- In 2 patients, severe acute rejection did not resolve despite steroid bolus therapy plus 5 to 10 days of OKT3 treatment. Treatment with infliximab (4 infusions of 3 mg/kg) induced a complete remission of histological and clinical signs of rejection. Two further patients with steroid-resistant rejection received two courses of infliximab (3 mg/kg) as antirejection therapy. All rejection episodes resolved completely.

Horslen SP. (2006). Optimal management of the post-intestinal transplant patient. Gastroenterology, 130, S163- S169. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16473067

- Report of a survey sent to the five most active intestinal transplant centers (University of Nebraska Medical Center, University of Pittsburgh Medical Center and Pittsburgh Children's Hospital, University of Miami, University of California Los Angeles, and Mount Sinai Hospital) on immunosuppression, management of acute rejection, feeding, and management of viral infections.
- Initial treatment for acute rejection in all centers was corticosteroid bolus, with the use of anti-lymphocyte antibodies reserved for severe or corticosteroid unresponsive rejection

Fishbein TM. (2009). Intestinal transplantation. New England Journal of Medicine, 361, 998-1008. Retrieved from:: http://www.ncbi.nlm.nih.gov/pubmed/19726774

- Review of the indications and surgical procedure of intestinal transplantation
- Summary of graft dysfunction, potential treatment options for rejection, and patient/graft survival

Garg M, et al. (2011). Intestinal transplantation: current status and future direction. Journal of Gastroenterology and Hepatology, 26, 1221-1228. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21595748

- Review article on indications and surgical procedure of intestinal transplantation
- Outlines post intestinal transplant management, monitoring and treatment for rejection, and patient/graft survival

Hibi T, et al. (2012). Citrulline level is a potent indicator of acute rejection in the long term following pediatric intestinal/multivisceral transplantation. American Journal of Transplantation, 12, S27-S32. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22812705

- Citrulline has been proposed as a marker for rejection following intestinal transplantation
- Prospective study collecting citrulline levels per protocol and during biopsy of intestine to correlate level with grading of acute cellular rejection in a pediatric patient population

Kim SY, et al. (2012). Chronic rejection in a small bowel transplant with successful revision of the allograft by segmental resection: case report. Transplantation Proceedings, 2012, 44, 1180-82. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22564659

- Case report of a 3 year old female who underwent living related intestinal transplant for short gut syndrome. Approximately five years post-transplant, she was admitted with severe dehydration thought to be secondary to rejection. A biopsy was performed at the site of an identified stricture, demonstrating nonspecific inflammatory reaction with fibrosis, diffuse hyalinosis, and mucosal surface flattening with loss of villi consistent with chronic rejection.
- Segmental resection was performed of the narrowed segment with end-to-end anastomosis. After a 10-day hospitalization, the patient was independent of parenteral nutrition and discharged home.

Lauro A, et al. (2013). Mortality after steroid-resistant acute cellular rejection and chronic rejection episodes in adult intestinal transplants: report from a single center in induction/preconditioning era. Transplantation Proceedings, 45, 2032-3. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23769102

- Fourteen patients experienced episodes of steroid-resistant acute cellular rejection. Three were successfully treated with OKT3, 1 patient with alemtuzumab, and 1 by antithymocyte globulin. Overall mortality among this cohort was 50%. Five patients experienced chronic rejection, among whom mortality was 60%; the two surviving patients were re-listed from transplantation. No difference in survival between steroid-resistant and steroid-sensitive populations.

Rao B, et al. (2016). A case report of acute cellular rejection following intestinal transplantation managed with adalimumab. Transplantation Proceedings, 48, 536-8. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/27109995

- A case of rejection is reviewed in which a patient, 10 months post-transplantation, failed to respond after receipt of methylprednisolone, basiliximab, and antithymocyte globulin.
- The patient subsequently initiated therapy on adalimumab, and continued therapy as an outpatient with subsequent biopsy-confirmed resolution of the rejection episode.

4.2.2. Antibody-mediated rejection

Fan J, et al. (2015). Eculizumab salvage therapy for antibody-mediated rejection in a desensitization-resistant intestinal re-transplant patient. American Journal of Transplantation, 2015, 15, 1995-2000. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/25649227

- Case report of a 15 year old male patient who underwent intestinal transplant for short gut syndrome secondary to blunt trauma. Eight years post-transplant, the patient experienced severe acute cellular rejection with an antibody-mediated component refractory to medical management. A second intestinal transplantation was performed which also failed due to rejection requiring a multivisceral transplantation. Patient received plasmapheresis, bortezomib and IVIG pre-operatively and eculizumab intra-operatively.
- All detected DSA were reduced to MFI < 3,000 and the patient was free of cellular and humoral rejection.

Cheng EY, et al. (2016). Prevalence and clinical impact of donor-specific alloantibody among intestinal transplant recipients. Transplantation, 2017, 101, 873-882. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/27490417

- Retrospective review of 109 intestinal transplant recipients at UCLA between 1991 and 2015 who had available pre- and post-transplantation HLA antibody testing. Among patients without pre-transplant DSA, 24 (25%) developed de novo DSA.
- Recipients with pre-transplant DSA experienced higher risks of graft loss and lower survival compared to patients without DSA. After detection of de novo DSA, patients exhibited poor graft survival rates, with 1- and 2-year failure rates of 10% and 28%, respectively.

Fujiwara S, et al. (2016). Effectiveness of bortezomib in a patient with acute rejection associated with an elevation of donor-specific HLA antibodies after small-bowel transplantation: case report. Transplantation Proceedings, 2016, 48, 525-7. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/27109992

- Case report of a 20 year old male patient who underwent intestinal transplantation for chronic intestinal obstruction secondary to hypoganglionosis. Patient experienced severe acute cellular rejection on POD16, which was managed with corticosteroids and ATG. Subsequently, C4d staining was positive and donor-specific class I and II HLA antibody were identified.
- Bortezomib was administered (1.6 mg/kg on POD28, 31, 35 and 38), resulting in symptomatic improvement, reduction in antibodies, and no future episodes of rejection.

Wu GS. (2016). Updates on antibody-mediated rejection in intestinal transplantation. World Journal of Transplantation, 2016, 6, 564-572. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5036126/

- Review summarizing current knowledge of antibody-mediated injury with potential solutions and emphasis on key areas requiring further research

- Focus on pre- and post-transplantation donor-specific antibodies and diagnostic criteria

Huard G, et al. (2017). Severe acute cellular rejection after intestinal transplantation is associated with poor patient and graft survival. Clinical Transplantation, 31, e12956. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28295657

- Retrospective review of 20 (15.9%) intestinal transplantations who experienced severe acute cellular rejection between 2000 and 2014 at Mount Sinai Medical Center of which 7 were in pediatric recipients.
- All patients received IV methylprednisolone with an increase in tacrolimus dosing of which only 4 responded to IV steroids deeming 16 patients to have steroid-resistant ACR. These 16 patients also received ATG with 11 requiring additional therapies including various combinations of MMF, rapamycin, IVIg, infliximab, rituximab, and plasmapheresis. Severe ACR episode resolved in 12 patients and uncontrolled led to graft enterectomy in 6 patients. Follow-up showed that 11 patients (55%) developed graft failure and 13 (65%) died after the severe ACR episode.

Wu GS, et al. (2017). Successful rescue of late-onset antibody-mediated rejection 12 years after living donor intestinal transplantation: a case report. Transplant Proceedings, 49, 232-236. Retrieve from: https://www.ncbi.nlm.nih.gov/pubmed/28104146

- Case report of 18 year old male who underwent a living-donor intestinal transplant for history of extensive intestinal resection secondary to acute bowel volvulus at Xijing Hospital in China and developed late-onset antibody-mediated rejection 12 years after transplantation.

- Twelve years after transplant, biopsy showed diffuse C4d deposition. After treatment failure to steroids and thymoglobulin, positive DSAs lead to suspicion of humoral rejection and treated with single-dose rituximab followed by large dose of IVIg for 3 weeks with the addition of mycophenolate mofetil. At 16 and 17 year follow-up exam, biopsy was negative for rejection. Patient was given rituximab every 10-12 months to maintain low (<2%) CD19-positive B-lymphocytes in peripheral blood.

Aberg F, et al. (2018). Severe allograft rejection in an intestinal transplant patient following oral immunoglobulin treatment for chronic norovirus infection: a case report. Clinical Case Reports, 6, 1232-1235. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6028366/

- Case report of 34 year old Caucasian male, who originally underwent intestinal transplantation 3 years prior due to chronic intestinal pseudo-obstruction from familial visceral myopathy, received a retransplant 18 months prior to publication. Later, patient developed norovirus gastroenteritis and started on oral IVIg after 3 months of unresolving norovirus.
- Four days after the end of IVIg oral treatment, biopsy showed grade 2-3 rejection in the small bowel and colon. Patient was initiated on high-dose steroids with persistent signs of rejection and then received 10-day course of ATG leading to resolution of rejection.

Lauro A, et al. (2018). Chronic rejection after intestinal transplant: where are we in order to avert it?. Digestive Diseases and Sciences, 63, 551-562. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29327261

- Review of experimental data and available data regarding chronic rejection among intestinal transplant recipients
- Emphasis on the etiology of CR, mechanisms, and target areas for clinical interventions

4.3. **Graft failure/retransplant**

Mazariegos GV, et al. (2008). Pediatric intestinal retransplantation: techniques, management, and outcomes. Transplantation, 86,1777-1782. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19104421

- Children's hospital of Pittsburgh, single center retrospective review of retransplantation of intestinal grafts
- Greater than 70% survival with a functioning graft at 56 months after retransplantation, with majority of patients receiving induction therapy with rabbit antithymocyte globulin, tacrolimus, and maintenance steroids

Desai CS, et al. (2012). Intestinal retransplantation: analysis of organ procurement and transplantation network database. Transplantation, 93, 120-125. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22113492

- A retrospective analysis of the United Network for Organ Sharing database on intestinal retransplantation of children and adults from 1987 to 2009
- Less favorable patient and graft survival after isolated intestinal retransplantation in adults vs. a primary transplant, as well as poor results in pediatrics after liver---intestinal retransplantation

Trevizol AP, et al. (2013). Intestinal and multivisceral retransplantation results: literature review. Transplant Proceedings, 45, 1133-1136. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23622645

- Literature review on multivisceral and intestinal retransplantation in regards to demographics, immunosuppression, rejection, infection, and graft and patient survival rates
- Acute cellular rejection is the main causes of graft loss and retransplantation is a possible option after primary graft loss

Lumketkai BN, et al. (2016). Mortality and rates of graft rejection or failure following intestinal transplantation in patients with vs without Crohn's disease. Clinical Gastroenterology and Hepatology, 14, 1574-82. Retrieved from: http:www.ncbi.nlm.nih.gov/pubmed/27374004

- Retrospective analysis of adults in the Scientific Registry of Transplant Recipients who received intestinal transplant in the US from May 1990 to June 2014, specifically comparing outcomes among recipients with or without Crohn's disease.
- Between the two populations, the risk of rejection or death was not statistically significantly different; the risk of graft failure was greater among patients transplanted for Crohn's prior to the year 2000, but this difference ceased to exist in patients transplanted after 2000

Nagai S. et al. (2017). Intestinal graft failure: should we perform the allograft enterectomy before or with retransplantation? Transplantation, 101, 411-420. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26901076

- Retrospective review of 221 intestinal and multivisceral transplantations at Indiana University Hospital from 2003 to 2014

- Patient survival was similar between patients who underwent an isolated graft enterectomy prior to transplant compared to those who underwent simultaneous enterectomy and retransplantation.

Kubal C, et al. (2018). Challenges with intestine and multivisceral re-transplantation: importance of timing of re-transplantation and optimal immunosuppression. Annals of Transplantation, 23, 98-104. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29402878

- Retrospective review of patients undergoing intestinal and multivisceral re-transplantation between 2005 and 2016 at Indiana University School of Medicine
- High rates of mortality was seen among re-transplanted recipients with the most common cause of death associated with compromised immune system (15/23 patients died at a median time of 12 months after re-transplant). Strategies to allow reconstitution of immune system include longer interval between re-transplantation and allograft specific immunosuppression.

4.4. Other post-transplant complications

4.4.1. Infectious

Guaraldi G, Cocchi S, Codeluppi M, et al. (2005). Outcome, incidence, and timing of infectious complications in small bowel and multivisceral organ transplantation patients. Transplantation 2005;80: 1742-1748. Retrived from: https://www.ncbi.nlm.nih.gov/pubmed/16378070

- Prospective study of 19 patients undergoing small bowel (SB) and multivisceral (MV) transplantations.

- A total of 100 episodes of infection were documented: 59 bacterial, 35 viral, and 6 fungal; 94%, 67% and 28% of patients developed at least one bacterial, viral and fungal infection, respectively. Median time of first bacterial infection was 11 days (IR=9-17), first viral infection was 91 days (IQ=65-101), and first fungal was 181 days (IQ-156-217). Larger cohorts are needed to address infection risk factors and long-term outcomes.

Kaufman S, et al. (2005). Characteristics of human calicivirus enteritis in intestinal transplant recipients. Journal of Pediatric Gastroenterology and Nutrition, 2005;40: 328-333. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15735487

- Case series of 5 pediatric patients who developed human calicivirus enteritis (type Miami beach) after intestinal transplantation. IV fluid therapy was necessary for ≥ 40 days in 3 of 5 infants for severe osmotic or secretory diarrhea. Virus excretion exceeded 80 days in two patients.

Ziring D, et al. (2005). Infectious enteritis after intestinal transplantation: incidence, timing, and outcome. Transplantation, 2005;79: 702-709. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15785377

- Single-center retrospective review of 33 intestinal transplantation recipients at Durmont-UCLA Transplant Center between 1991 and 2003 exploring infectious enteritis (IE).
- 13 of 33 (39%) developed 20 culture- or biopsy-proven episodes of IE.
- Infections were diagnosed a median of 76 days (32-1,800 days) after intestinal transplantation.
- There were 7 rejection episodes (at the approximate time of diagnosis of IE) and 2 graft losses. Three-year patient survival was 74%, with no deaths directly attributable to IE.

Akhter K, et al. (2012). Six-month incidence of bloodstream infections in intestinal transplant patients. Transplant Infectious Diseases, 2012;14: 242-247. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22093913

- Retrospective review of 56 adult and pediatric intestinal transplant recipients at Georgetown University Hospital between November 2003 and July 2007 to evaluate the incidence of post-transplant bloodstream infections.
- Bloodstream infections occurred in 34 of 56 patients, with a total number of 85 episodes. 65.9% of episodes were due to gram-positive organisms, 34.1% due to gram-negative organisms, and 2.4% due to fungi.
- Risk factors for development of bloodstream infections included inclusion of a liver graft and a pre-operative bilirubin > 5 mg/dL. Additionally, the incidence of bloodstream infections was more common in children than in adults (p=0.006).

Florescu DF, et al. (2012). Incidence, risk factors, and outcomes associated with cytomegalovirus disease in small bowel transplant recipients. Pediatric Transplantation 2012;16: 294-301. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22212495

- Retrospective review of 98 pediatric intestinal transplant recipients at the University of Nebraska Medical Center between January 2003 and December 2007.
- 7 of 98 (7%) patients experienced CMV disease and 11 of 98 (11%) patients experienced CMV viremia. A total of 24.5% of patients were CMV D+/R-.
- CMV disease was associated with an 11.1 times higher risk of death and shorter time-to-death after transplantation (303 days versus 1232 days); CMV enteritis further shortened the time-to-death (248 days versus 1212 days).

Timpone JG, et al. (2013). Infections in intestinal and multivisceral transplant recipients. Infectious Diseases Clinics of North America, 2013;27: 359-377. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23714345

- Multidrug-resistant bacteria and fungus are common causes of post-intestinal transplant infections, resulting in intra-abdominal, bloodstream, and other infections. The greatest risk for healthcare-associated infections occur immediately after transplantation, with opportunistic viral and fungal infections occurring later in the post-transplant period.

Avsar Y, et al. (2014) Small bowel transplantation complicated by cytomegalovirus tissue invasive disease without viremia. Journal of Clinical Virology, 2014, 60, 177-80. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24703746

- Case report of a 52 y/o female who underwent intestinal transplantation due to short gut syndrome (CMV D+/R+). CMV prophylaxis was continued for 100 days post-transplant. Approximately 3 months after discontinuation of CMV prophylaxis, the patient presented with odynophagia and emesis. Endoscopy revealed ulcerative esophagitis and gastritis and biopsy specimens were positive for typical inclusion bodies and CMV DNA. CMV serum samples were negative for CMV DNA.
- Treatment was initiated with IV ganciclovir and two doses of CMV IgG (Cytotect ®) 50 IU/kg administered one week apart. Following initial improvement and conversion to secondary prophylaxis, CMV tissue invasive disease recurred in the absence of CMV viremia. Treatment was re-initiated with CMV IgG 100 IU/kg/day for one week, foscarnet 180 mg/kg/day, and immunosuppression was modified to include low-dose tacrolimus and everolimus. Symptoms persisted, and repeat biopsy demonstrated acute cellular rejection that ultimately required graft explantation and resumption of TPN.

Silva JT, San-Juan R, Fernandez-Caamano B, et al (2016). Infectious Complications following small bowel transplantation. American Journal of Transplantation 2016; 16: 951-959. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26560685

- Retrospective analysis of 69 patients who underwent 87 SBT procedures between February 2004 to December 2013.
- 81 patients (93.1%) developed 263 episodes of infection, most commonly bacterial (47.5%). A total of 54 episodes of opportunistic infection (OI) occurred in 35 patients. Infection was the major cause of mortality in 17 of 24 deaths. Posttransplant renal replacement therapy and re-transplantation were identified as risk factors for the development of OI and invasive fungal disease.

Florescu DF, Sandkovsky U (2015). Fungal infections in intestinal and multivisceral transplant recipients. Curr Opin Organ Transplant. 2015;20(3):295-302. Retrieved from: https://www-ncbi-nlm-nih-gov/pubmed/25944228

- Review that highlights diagnostic and management issues associated with fungal infections in intestinal and multivisceral transplant recipients.
- Invasive candidiasis is the most common fungal infection in patients with intestinal and multivisceral transplants. Experience for diagnosis and management comes from case series and single centers. Diagnosis and management of infections caused by other pathogens such as Aspergillus, Cryptococcus, Mucor, and endemic mycoses is usually extrapolated from other solid organ transplant recipients.

Simkins JJ, Morillas-rodriguez JA, Morris MI, et al (2019). Bloodstream Infection caused by Enteric Organisms during the First 6 Months after Intestinal Transplant. Transpl Infect Dis. 2019;:e13064. Retrieved from: https://www-ncbi-nlm-nih-gov/pubmed/30865328

- Retrospective study (1/2009-5/2017) aimed to evaluate the incidence of BSI episodes due to enteric organisms during the first six months after intestinal transplant
- Fifty-five adult patients were analyzed. Twenty-eight (51%) patients developed a total of 51 episodes of BSI. Mean time from transplant to BSI: 85.5±58.8 days. The most common organisms were Klebsiella pneumoniae (33%), Enterococcus spp. (31%), and Candida spp. (18%). Twenty-three (45%) were multi-drug resistant. The most common sources were gut translocation (35%), central line infection(20%) and intra-abdominal abscess (14%).

4.4.2. Non-infectious

PTLD

Lauro A, Arpinati M, Pinna AD (2015). Managing the challenge of PTLD in liver and bowel transplant recipients. Br J Haematol 2015; 169(2):157-72. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25377273

- This review article discusses the incidence, risk factors, treatment, and complications of PTLD among liver and bowel transplant recipients.

Nalesnik M, Jaffe R, Reyes J, et al (2000). Posttransplant lymphoproliferative disorders in small bowel allograft recipients. Transplant Proceedings 2000;32: 1213. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2975486/

- 27 of 127 (21%) patients who received small bowel allografts developed PTLD. 22 cases in pediatric and 5 in adults.
- These results indicate that adult multivisceral transplant recipients are at high risk for developing PTLD. There was no significant difference in frequency based on EBV serostatus at the time of transplant. The actuarial survival for PTLD patients was 37% at 2 years.

Berney T, et al (2002). Successful treatment of posttransplant lymphoproliferative disease with prolonged rituximab treatment in intestinal transplant recipients. Transplantation 2002;74: 1000-1006. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12394845

- Retrospective review of 5 patients diagnosed with PTLD after intestinal transplantation at a single center in Miami, FL between 1999 and 2001. Median time to diagnosis of PTLD was 9 months (range 2 months to 5 years). Maintenance immunosuppression in all patients included tacrolimus and steroid-based immunosuppression.
- Once PTLD was diagnosed, immunosuppression was sharply decreased or discontinued based of severity, and rituximab was initiated at an initial dose of 125 mg/m^2, followed by a second dose of 250 mg/m^2 3 days later, and 375 mg/m^2 7 days after the second dose and once per week thereafter. Rituximab was continued until three consecutive negative readings of EBV PCR. After a median follow-up of 8 months (3 months to 2.5 years), no patient had evidence of residual PTLD.

Renal Dysfunction

Ueno T, Kato T, Gaynor J, et al (2006). Renal dysfunction following adult intestinal transplant under tacrolimus-based immunosuppression. Transplantation Proceedings 2006;38: 1762-1764. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16908274

- Analysis of 24 adult intestinal transplant patients between 1995 and 2002.
- Creatinine clearance decreased from a mean 114 mL/min per 1.73 m^2 to 49.6 mL/min per 1.73 m^2 at 2 years post-transplant. Renal function decreased significantly after intestinal transplantation in adults.

Boyer O, et al. (2013). Renal function and histology in children after small bowel transplantation. Pediatric Transplantation, 2013, 17, 65-72. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22882667

- Retrospective review of 27 children who underwent intestinal transplantation at a single center in France between 1994 and 2010 for whom complete renal function data was available out to one year post-transplant. Maintenance immunosuppression included tacrolimus, azathioprine and prednisone.
- A reduction in eGFR was observed in 17 patients (63%). Biopsies confirmed CNI toxicity in 11/14 evaluable patients.

Puttarajappa CM, et al. (2018). Outcomes of adult intestinal transplant recipients requiring dialysis and renal transplantation. Transplant Direct, 4(8):e377. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30255137

- Retrospective cohort study of 307 adult patients who underwent intestinal transplant at University of Pittsburgh between 1990 to 2014.

- During a median follow up of 5.7 years, 24.7% of patients required dialysis, 13.2% required long-term dialysis and 6% received renal transplant after intestinal transplant. One, 3-year, and 5-year ESRD risk was 2%, 7%, and 14%, respectively. Median patient survival after dialysis initiation was 6 months with a 3-year survival of 21%. Any dialysis (HR, 12.74; 95% CI 8.46-19.20; $P < 0.01$) and ESRD (HR, 9.53; 95% CI, 5.87-15.49; $P < 0.01$) was associated with higher mortality after adjusting for covariates. For renal transplant after IT, 1- and 3-year kidney and patient survivals were 70% and 49%, respectively.

Hypogammaglobulinemia

Quiros-Tejeira, RE. (2012). Immunological complications beyond rejection after intestinal transplantation. Current Opinion in Organ Transplantation, 2012, 17, 268-72. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22476219

- The large number of lymphoid cells in the allograft results in a greater incidence in graft-versus-host disease, which is reported to occur in 7-13% of intestinal transplant recipients
- Autoimmune hemolytic anemia and other cytopenias may develop due to passenger B lymphocytes from the allograft
- Inflammatory bowel disease (IBD)-like post-transplant disorder develops at a rate that is ten times greater than the general population, despite the use of anti-T-cell therapies
- Tacrolimus-based immunosuppressive regimens have been associated with the development of de novo food allergies after intestinal transplantation.

Farmer DG, et al. (2013). Incidence, timing, and significance of early hypogammaglobulinemia after intestinal transplantation. Transplantation, 2013, 95, 1154-9. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23407545

- Retrospective review of intestinal transplant recipients at UCLA between January 2007 and December 2011. Serum IgG was monitored weekly for two months following transplantation.
- Relative to pre-transplant serum IgG levels, post-transplant IgG levels were statistically significantly reduced; a total of 20 patients experienced 57 episodes of hypogammaglobulinemia in which 85% were administered IVIG.
- No significant associations were identified between hypogammaglobulinemia and either infections or acute cellular rejection.

Poole JA, Qiu F, Kalil AC, et al (2016). Impact of immunoglobulin therapy in intestinal transplant recipients with posttransplantation hypogammaglobulinemia. Transplantation Proceedings 2016;48: 479-484. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27109982

- Retrospective study of 23 intestinal transplant recipients with a diagnosis of hypogammaglobulinemia (HGG). There was no difference in survival based upon IgG level at last follow (IgG ≥ 400 mg/dL and IgG <400 mg/dL).
- No difference in survival based on number of IgG doses administered, total dose, or frequency. Overall, improved survival rates were not found in patients with severe HGG with immunoglobulin therapy to increase IgG levels to ≥ 400 mg/dL.

Graft-versus-host disease (GVHD)

Mazariegos GV, Abu-Elmagd K, Jaffe R, et al (2004). Graft versus host disease in intestinal transplantation. American Journal of Transplantation 2004;4: 1459-1465.

- Retrospective review of 23 intestinal transplant patients with suspected GVHD. 14patients had confirmed GCHD with histopathological criteria.
- The majority of cases resolved with steroid administration and optimization of immunosuppression.

Wu G, Selvaggi G, Nishida S, et al (2011). Graft-versus-host disease after intestinal and multivisceral transplantation. Transplantation 2011;91: 219-224.

- Retrospective study of 24 patients between March 1994 and July 2007. A total of 22 (9.1%) were diagnosed with GVHD, with a median time of onset of 75 days (range, 14-1408).
- Multivisceral graft recipients were more likely to develop GVHD than isolated small bowel, and the presence of recipient splenectomy was associated with the incidence of GVHD.
- A total of 16 patients with GVHD died during follow-up, and GVHD is therefore a fatal and progressive complication of small bowel transplantation.

Cromvik J, Varkey J, Herlenius G, et al (2016). Graft-versus-host disease after intestinal or multivisceral transplantation: A Scandinavian single-center experience. Transplantation Proceedings 2016;48: 185-190.

- Retrospective review of 26 patients who underwent intestinal or multivisceral transplantation between 1998 and 2014. 5 of 26 patients (19%) were diagnosed with GVHD, of which all were multivisceral transplant patients.
- Risk factors for the development of GVHD included underlying tumor diagnosis and neoadjuvant chemo- or brachytherapy prior to transplantation.

- All patients received high-dose corticosteroids as first line treatment, and survived their episodes of GVHD.

4.5. Intestinal disorders

4.5.1. Functional bowel problem

Longstreth GF, et al. (2006). Functional bowel disorders. Gastroenterology, 5, 1480-1491. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16678561

- Review article on definition, diagnosis, and treatment of functional bowel disorders, including irritable bowel syndrome, functional bloating, functional constipation, functional diarrhea, and unspecified functional bowel disorder

Bines JE. (2009). Intestinal failure: a new era in clinical management. Journal of Gastroenterology and Hepatology, 24, S86-92. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19799705

- Review article on intestinal failure highlighting the etiology of the disease and medical and surgical management

Shatnawei A, et al. (2010). Intestinal failure management at the Cleveland Clinic. Archives of Surgery, 145, 521-527. Retrieved from:: http://www.ncbi.nlm.nih.gov/pubmed/20566970

- Review article from the Cleveland Clinic on the institutional guidelines for the management of intestinal failure, including long-term home parenteral nutrition and related complications, intestinal rehabilitation, and small bowel transplant

Duggan CP, et al. (2017). Pediatric Intestinal Failure. New England Jouranl of Medicine, 17, 666-675. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28813225

- Review article addressing etiology and nutritional, pharmaceutical, and surgical therapies for pediatric intestinal failures

4.5.2. Short gut syndrome

Buchman AL, et al. (2003) AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology, 124, 1111-1134. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12671904

- Review article on short bowel syndrome
- Includes pathophysiology, medical management, complications, and the role of surgery for treatment

Jeppsesen PB. (2013). Modern treatment of short bowel syndrome. Current Opinion in Clinical Nutritional and Metabolic Care, 16, 582-587. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23924950

- Review article on the medical treatment for short bowel syndrome with the new agent teduglutide, a GLP-2 agonist
- GLP-2 is an amino acid secreted from the intestine after a meal as a feedback mechanism, which may be dysregulated in short bowel syndrome leading to accelerated motility, hypersecretion, diminished blood flow, and other associated symptoms of this disease.

Carroll R, et al. (2016). Management and complications of short bowel syndrome: an update review. Current Gastroenterology Reports, 18. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27324885

- Review article on dietary management and organ-specific complications including osteoporosis, nephrolithiasis, hepatic cholestasis, liver disease, lactic acidosis, and impact on quality of life.