4. Intestinal transplant

4.1. Immunosuppression

4.1.1 Induction/maintenance therapy

Santeusanio AD (2021). Tacrolimus time-in-therapeutic range is associated with freedom from acute rejection and graft failure following intestinal transplantation. Clin Transplant. 9, e14291. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33740822/

- Single-center, retrospective review from 2011-2018 on all intestinal allograft (non-liver) patients to assess tacrolimus time in therapeutic range to clinical outcomes of freedom of acute rejection or graft failure at 1 year post-transplant or to date of graft failure.
- Forty-seven patients were included in the study, 8 patients (17%) had a pre-transplant DSA > 2000 MFI. Graft survival at 1 year was 72.3%, 15 episodes of biopsy proven acute rejection occurred and 8 episodes of histological severe biopsy proven acute rejection occurred. Highest tacrolimus time in therapeutic range (>36%) led to more time free of rejection. Thirteen patients lost their graft within 1 year. Freedom from acute rejection and graft failure were all correlated to less tacrolimus time in therapeutic range suggesting a benefit for more frequent monitoring and dose adjustments to keep tacrolimus in therapeutic range.

Vianna R, et al. (2020). Association of more intensive induction with less acute rejection following intestinal transplantation: Results of 445 consecutive cases from a single center. Transplantation, 104(10), 2166-2178. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31929425/

- Retrospective review of 445 adult or pediatric intestinal transplant recipients in a single center. Patients were divided into 5 induction groups; Group 1(1994-1997) with 44 recipients received no/old induction (high-dose corticosteroids in 34), group 2 (1998-2011) with 159 recipients received anti-CD25 monoclonal antibody (daclizumab in 156), group 3 (2001-2011) with 113 recipients received alemtuzumab, group 4 (2006-2012) with 34 recipients received rATG, and group 5 (2013-2017) with 95 recipients received rATG/rituximab. Basiliximab was additionally added to subset of group 5 who received either an isolated intestine or modified MV. Maintenance therapy consisted of TAC and corticosteroids except in patients received alemtuzumab with only TAC planned.
- First ACR during the first 60 months posttransplant was observed in 61.3% of recipients. Among the first episode of ACR, 22.2% of recipients was classified as having severe ACR. Alemtuzumab and rATG/rituximab induction showed protective effects on both ACR and severe ACR during the first 24 days posttransplant, lower hazard rate of graft loss-due-to-rejection during first 6 months, and lower hazard rate of graft loss-due-to-infection.

Vianna R, et al. (2020). Association of alemtuzumab induction with a significantly lower incidence of GVHD following intestinal transplantation: Results of 445 consecutive cases from a single center. Transplantation, 104(10), 2179-2188. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31929428/

- Retrospective review of 445 adult or pediatric intestinal transplant recipients in a single center from 1994-2017 followed prospectively through March 2019. Patients were divided into 5 induction groups; Group 1(1994-1997) with 44 recipients received no/old induction (high-dose corticosteroids in 34), group 2 (1998-2011) with 159 recipients received anti-CD25 monoclonal antibody (daclizumab in 156), group 3 (2001-2011) with 113 recipients received alemtuzumab, group 4 (2006-2012) with 34 recipients received rATG, and group 5 (2013-2017) with 95 recipients received rATG/rituximab. Basiliximab was additionally added to subset of group 5 who received either an isolated intestine or modified MV. Maintenance therapy consisted of TAC and corticosteroids except in patients receiving alemtuzumab with only TAC planned.
- GVHD was observed in 8.8% of recipients during the first 60 months posttransplant with median time to onset of 1.5 months (range 0.5-17.3 months). Alemtuzumab induction shows a significantly lower hazard rate of developing GVHD, 2.7% vs. 10.8% for those receiving versus not receiving alemtuzumab induction, respectively.

Santeusanio AD, et al. (2019). Is there a role for desensitization in intestinal transplantation? Prog Transplant. 29(3):275-278. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31170898/

- Literatures supporting the role of desensitization therapy in intestinal transplant and a single center experience with a risk-stratified desensitization protocol and clinical practice issues with desensitization were discussed in this review article.
- Single center experience described 8 adult patients underwent desensitization based on cPRA risk. Desensitization therapy was well tolerated with only 1 case of infusion-related reaction to IVIG and 1 case of neuropathy with bortezomib.

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 47 year old 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.

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 (14 adults and 28 pediatrics) 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 group were 59% and 51%, respectively, compared to 52% and 50% in the high risk group.

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 (10 adults and 5 pediatrics) 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.

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 (adults and pediatrics) 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.

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 (adults and pediatrics) 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.

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.

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.

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.

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.

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.

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 adult 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 ($p=0.04$).

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%).

Lauro A, et al. (2007). Twenty-five consecutive isolated intestinal transplants in adult patients: a five-yr clinical experience. Clinical Transplantation, 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.

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.

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.

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.

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 adult 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% (11/13) of patients were alive at the time of publication. One patient died of pulmonary embolism 9 days after isolated intestinal transplantation and one patient died of multiorgan failure secondary to severe graft pancreatitis 7 days post-multivisceral transplantation.

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 adult and pediatric intestinal transplant recipients 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.

4.1.2 Induction/maintenance therapy - Pediatrics

Devine K, et al. (2020). Induction regimens and post-transplantation lymphoproliferative disorder after pediatric intestinal transplantation: Single-center experience. Pediatr Transplant, 24(5):e13723. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/petr.13723

- A single center retrospective review from 2000 to 2017 describe the incidence, characteristics, and outcomes of PTLD after induction with either rATG (n=135), alemtuzumab (n=22), or anti-IL-2R (n=14) after intestinal transplantation in children. Maintenance immunosuppression consisted of tacrolimus and steroids. The PTLD incidence in recipients was 16.2% (28/173) with 30 episodes of PTLD developed. Median time of onset was 129.5 days. The incidence of PTLD with alemtuzumab induction was 27.3% compared to 13.3% with rATG induction, though not significant. However, alemtuzumab induction was associated with fewer deaths after PTLD compared to rATG.

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.

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).

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.

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.

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.

4.1.3. Operational Tolerance

Kroemer A et al (2021). Operational tolerance in intestinal transplantation. Am J Transplant. Feb;21(2):876-882.

- First single case report of operational tolerance in a patient that became non-compliant to immunosuppressants.
- 14-year-old male with Berdon's Syndrome who received jejunoileum and R colon allograft transplant who received basiliximab induction followed by tacrolimus, rapamycin, and steroids. History of GVHD 5 months post-transplant treated with immunosuppression reduction and thymoglobulin 10.5 mg/kg. Course unremarkable otherwise except de-novo DSA at DQ4 approximately 3 years, 7 months post-transplant. Refused IVIG treatment and stopped taking immunosuppressants. Good allograft function was seen at 6, 7, and 8 years post-transplant. DSA at DQ4 remained stable and C4d staining remained negative.

4.2. Management of rejection

4.2.1. Cellular rejection

Venick RS. (2021). Grant monitoring after intestinal transplantation. Curr Opin Organ Transplant, 26(2), 234-239. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33410638/

- Review article discussing graft monitoring post-transplant including the use of endoscopy, histological scheme for cellular rejection, noninvasive biomarker potential to assist with predicting rejection, immunoreactivity tests measuring CD4+ T cells, and use of DSA post-transplant.

Kroemer A, et al (2021). Rejection of intestinal allotransplants is driven by memory T helper type 17 immunity and responds to infliximab. Am J Transplant, 21(3), 1238-1254. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32882110/

- Retrospective study comprised of patients receiving intestinal transplant from 2004-2019 who were diagnosed with moderate or severe rejection based upon clinical and pathological signs who had biospecimens available to analyze. Blood and tissue samples were analyzed with multiple tests to determine similarities and differences amongst patients with refractory rejection who did or did not respond to thymoglobulin.
- Fifty-one moderate to severe rejecting intestinal transplant patients were included and stratified into thymoglobulin responders (18) and non-responders (33). Blood samples showed an increased frequency of effector memory CD4+ T cells and less naïve T cells in rejecting patients compared to non-rejecting which suggested that this response of activated memory T-cells is resistant to thymoglobulin. Amount of CD3+ T cells present in responders and non-responders to thymoglobulin were similar amongst blood samples, suggesting concern in only monitoring CD3 counts during intestinal transplant rejection. When looking at immunohistochemistry of tissue samples, the presence of CD3+ cells was less in the thymoglobulin responders group compared to the non-responders. Predominate cells types in non-responders were CD4+ T-cells, CD8+ T-cells, and CD45RO+ effector memory cells. T-cells expressed chemokine CCR6 in the non-responders which is seen with T-cell h17 and many proinflammatory cytokines were released such as IL-17 and TNF-α. Infliximab was given to the 14 non-responders due to the expression of TNF-α and all patients recovered from rejection.

Varkey J (2021). Graft assessment for acute rejection after intestinal transplantation: current status and future perspective. Scand J Gastroenterol, 56(1), 13-19. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33202155/

- Review of biomarkers for use in predicting intestinal transplant rejection such as citrulline, calprotectin, and granzyme B/perforin. Citrulline, an amino acid from enterocytes in the small bowel shows varying data for use in predicting rejection and multiple patient factors must be considered if biomarker used such as time from transplant and renal function. Some studies reported a sensitivity of 96% and specificity of 68% when using citrulline biomarker in adults and children. Calprotectin, a protein in the neutrophilic cytosol may be considered for use to determine that no intestinal pathology is occurring. Specificity differs from study to study (47-83%), but sensitivity ranges from 77-100%. Granzyme B and perforin, cytotoxic mediators use for prediction in rejection has not yet been established. Sensitivity and specificity range from 70-80%. Endoscopy remains the gold standard for determining rejection.

Chung CS (2021). Surveillance of rejection after intestinal transplantation using an image enhanced endoscopy "VENCH" scoring system. Transplant Proc. 53(1), 364-370. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33309060/

- Prospective study analyzing the use of a scoring tool from visual appearance of intestinal allograft during image-enhance endoscopy to assist in predicting acute cellular rejection alongside biopsy histology.
- 4 patients were enrolled (3 females, 1 male) and 99 endoscopic biopsies were obtained. The VENCH scoring system was used evaluating villi appearance, mucosal erythema, capillary network, crypt widening and heterogeneity of mucosal changes on a grade of 0 to 2 (2 being the most concerning visual changes). Sensitivity and specificity increased as visual grade increased. VENCH scoring was correlated well with worse severity histological rejection ($p < 0.001$) suggesting potential use of the tool to assist in predicting acute cellular rejection.

Crismale JF, et al. (2020). The role of endoscopy in the small intestinal transplant recipient: a review. American Journal of Transplantation,21(5), 1705-1712.. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33043624/

- Review of the most common pathologies found on endoscopy following intestinal transplant, such as rejection, ischemia, gastrointestinal bleeding and fistula, post-transplant lymphoproliferative disorder, identical twins, gastroparesis, duodenal stasis, and intestinal inflammation.

Moon JI, et al. (2019). Routine surveillance endoscopy and biopsy after isolated intestinal transplantation-Revisiting the gold standard. Clin Transplant, 33(10), e13684. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31374126/

- Single center study comparing rejection surveillance triggered by clinical cause with historical cohort of routine endoscopy and biopsy.
- Incidence of acute rejection, graft salvage rate after acute rejection treatment, patient survival, and graft survival were similar between the two groups.

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.

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.

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.

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.

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.

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.

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.

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.

4.2.2. Cellular rejection - Pediatrics

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.

4.2.3. Antibody-mediated rejection

Matsumoto CS et al (2021). Donor-specific antibody and sensitized patients in intestinal transplantation. Curr Opin Organ Transplant. Apr 1;26(2):245-249.

- Review article on approach to DSA in intestinal transplant that describes pre-transplant and post-transplant strategies for handling DSA.
- Includes recommendations and data on monitoring patients pre-transplant, approaches to sensitization, monitoring and treatment approaches to DSA post-transplant, and data on the diagnosis of antibody mediated rejection.

Amin A, Farmer DG. (2019). Current outcomes after pediatric and adult intestinal transplantation, Curr Opin Organ Transplant. 24(2):193-198. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30676400/

- Review of factors affecting patient and allograft survival following intestinal transplantation.

Hawksworth JS, et al. (2019). Donor-specific antibody management in intestine transplantation: hope for improving the long-term durability of the intestine allograft?, Curr Opin Organ Transplant. 24(2):212-218. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30694995/

- Review of DSA monitoring and treatment and discussion of the current challenges in DSA management in intestinal transplantation.

Carroll RE. (2018). Endoscopic Follow-up of Intestinal Transplant Recipients. Gastroenterol Clin North Am. 47(2):381-391. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29735031/

- Review of endoscopic management following intestinal transplant for complications, such as rejection, infections, post-transplant lymphoproliferative disorder, graft versus host disease, dysmotility, anastomotic ulcers, recurrence of Crohn's Disease, and familial adenomatous polyposis.

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.

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.

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%) CD19positive B-lymphocytes in peripheral blood.

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. (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.

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.

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.

4.2.4 Antibody mediated rejection – Pediatrics

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.

4.3. Graft failure/retransplant

Garcia J et al (2021). Intestinal transplantation. Curr Opin Organ Transplant, 6(2), 229-233. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33651002/

- Review of current tendencies/practices in intestinal transplant discussing the use of intestinal rehabilitation programs, outcomes over time for intestinal transplantation such as cost effectiveness and quality of life, and a call to the future for transplant centers to unite on determining appropriate candidates for intestinal transplantation versus intestinal rehabilitation programs.

Hind JM (2021). Long-term outcomes of intestinal transplantation. Curr Opin Organ Transplant, 26(2),192-199. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33651001/

- Review article on long-term outcomes after intestinal transplantation that discusses current data on morbidity, mortality, and graft loss after intestinal transplant along with potential complications or benefits post-transplant.

- Includes center specific as well as database driven data on morbidity, mortality, and graft loss, briefly discusses complications with medications, rejection, PTLD, psychiatric disturbances, and provides evidence on nutrition and quality of life benefits post-transplant.

Kaenkumchorn T, et al (2021). Late graft loss after intestinal transplantation. Curr Opin Organ Transplant, 26(2):220-228. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33528223/

- Review article on late graft loss after intestinal transplantation that discusses the current data available on percentage of graft survival overtime and potential causes of late graft loss such as chronic rejection, PTLD, GVHD, and surgical complications.
- Includes data on approaches, incidence, and potential genetic component of chronic rejection, describes incidence of PTLD, discussing types and incidence of GVHD, and mentions potential surgical complications that may lead to rejection.

Chen AM, et al. (2020). Complex abdominal wound healing after multivisceral retransplant: A Case report on the importance of nutrition. Transplant Proc, 52(9), 2839-2843. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32576477/

- A case presentation of a 25-year-old man with multivisceral re-transplantation developed loss of abdominal wall domain. In this case, wound healing complications were improved with treatment of his malnutrition.

Ekser B, et al. (2018) Comparable outcomes in intestinal retransplantation: Single-center cohort study. Clin Transplant, 32(7), e13290. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29782661/

- Retrospective review all intestinal transplant from 2003 to 2014 at a single center. Among 218 intestinal transplants, 18 (8.3%) were retransplantation. The average time between primary and retransplantation was 616 ± 815 days (median 421 days). The cause of graft low were rejection (78%), pancreatitis (11%) and severe intestine dysmotility (11%). Survival rates at 1-year, 3-year, and 5-year were comparable between primary and retransplants, but there was a limited number of patients in the follow-up in retransplantation group after year 3.

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 (adults and pediatrics) 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.

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 adults and pediatric 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.

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

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 adult and pediatric 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.

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.

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.

4.4. Other post-transplant complications

4.4.1. Infectious

Cheung D, et al (2021). Re-evaluating blood markers as predictors of outcome in multivisceral and intestinal transplantation. Transplant Proc, 53(2), 696-704. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33558087/

- Single center, prospective cohort study evaluating blood markers from complete blood cell count immediate post-transplantation for correlation to infections, rejection, acute kidney injury, and graft failure after multivisceral/intestinal transplant. These markers may be difficult to utilize due to the proinflammatory state immediate post-transplant. Blood markers were measured at baseline, day 1, day 3, day 5, day 7, week 2 week 3, and week 4.
- 29 patients were enrolled and 1,160 data points were collected. Neutrophil lymphocyte count ratio (NLCR) and white blood cell (WBC) were found to be the most useful biomarkers to identify infected patients for multiple time points to initiate antibiotics. Eosinophil percentage was higher in majority of patients with rejection and may also be useful as a biomarker.

Simkins JJ, et al (2019). Bloodstream infection caused by enteric organisms during the first 6 months after intestinal transplant. Transpl Infect Dis, 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%).

Silva JT, et al (2016). Infectious complications following small bowel transplantation. American Journal of Transplantation, 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, 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.

Avsar Y, et al. (2014). Small bowel transplantation complicated by cytomegalovirus tissue invasive disease without viremia. Journal of Clinical Virology, 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.

Timpone JG, et al. (2013). Infections in intestinal and multivisceral transplant recipients. Infectious Diseases Clinics of North America, 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.

Akhter K, et al. (2012). Six-month incidence of bloodstream infections in intestinal transplant patients. Transplant Infectious Diseases, 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).

Ziring D, et al. (2005). Infectious enteritis after intestinal transplantation: incidence, timing, and outcome. Transplantation, 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.

Guaraldi G, et al. (2005). Outcome, incidence, and timing of infectious complications in small bowel and multivisceral organ transplantation patients. Transplantation, 80, 1742-1748. Retrieved 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.

4.4.2. Non-infectious

Venick, R (2018). Long-term results of intestinal transplantation in children: survival after 10 years, intestinal function, quality of life. Current Opinion in Organ Transplant, 23(2), 219-223. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29461274/

- Review highlighting post-intestinal transplant complications in children greater than 10 years post-transplant, including renal and metabolic outcomes, infections, rejection, PTLD, and psychosocial outcomes.

4.4.3. PTLD

Devine K, Ranganathan S, Mazariegos G, et al (2020). Induction regimens and post-transplantation lymphoproliferative disorder after pediatric intestinal transplantation: Single-center experience. Pediatr Transplant. 2020; 24(5):e13723. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32424963/

- Single-center, retrospective review of PTLD following intestinal transplantation in children.
- PTLD was not statistically different following anti-IL-2R antibody and alemtuzumab compared to rATG (28.6% and 27.3% vs 13.3%, p=0.076).

Stanley K, Friehling E, Ranganathan S, et al (2018). Post-transplant lymphoproliferative disorder in pediatric intestinal transplant recipients: A literature review. Pediatr Transplant. 2018;22(5):e13211. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29745058/

- This review article discusses the clinical presentation, risk factors, pathogenesis, management, and future directions of PTLD in pediatric intestinal transplant recipients.

Lauro A, Arpinati M, Pinna AD (2015). Managing the challenge of PTLD in liver and bowel transplant recipients. Br J Haematol, 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.

Berney T, et al (2002). Successful treatment of posttransplant lymphoproliferative disease with prolonged rituximab treatment in intestinal transplant recipients. Transplantation, 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.

Nalesnik M, et al (2000). Posttransplant lymphoproliferative disorders in small bowel allograft recipients. Transplant Proceedings, 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.

4.4.4. Renal Dysfunction

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.

Huard G, et al (2017). The high incidence of severe chronic kidney disease after intestinal transplantation and its impact on patient and graft survival. Clin Transplant, 31(5):doi:10.1111/ctr.12942. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/28241392/

- Report of the incidence of severe CKD post-intestinal transplantation and assessment of risk factors for developing CKD.

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

Ueno T, et al (2006). Renal dysfunction following adult intestinal transplant under tacrolimus-based immunosuppression. Transplantation Proceedings, 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.

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4.4.5 Hypogammaglobulinemia

Poole JA, et al (2016). Impact of immunoglobulin therapy in intestinal transplant recipients with posttransplantation hypogammaglobulinemia. Transplantation Proceedings, 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.

Farmer DG, et al. (2013). Incidence, timing, and significance of early hypogammaglobulinemia after intestinal transplantation. Transplantation, 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.

Quiros-Tejeira, RE. (2012). Immunological complications beyond rejection after intestinal transplantation. Current Opinion in Organ Transplantation, 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.

4.4.6 Graft-versus-host disease (GVHD)

Vianna R, et al (2020). Association of alemtuzumab induction with a significantly lower incidence of GVHD following intestinal transplantation: Results of 445 consecutive cases from a single center. Transplantation, 104(10), 2179-2188. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31929428/

- Single-center report of GVHD prevalence and risk factors.
- Authors reported 2.7% vs 10.8% incidence of GVHD in patients receiving alemtuzumab compared to those not receiving alemtuzumab (no induction or rabbit ant-thymocyte).

Ganoza A, Mazariegos GV, Khanna A (2019). Current status of graft-versus-host disease after intestinal transplantation. Curr Opin Organ Transplant. 2019; 24(2):199-206. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30762668/

- Review of the pathophysiology, clinical manifestations, diagnosis, incidence, outcome, and treatment of GVHD following intestinal 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, 48, 185-190. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/26915866/

- 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.

Wu G, et al (2011). Graft-versus-host disease after intestinal and multivisceral transplantation. Transplantation, 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.

Mazariegos GV, et al (2004). Graft versus host disease in intestinal transplantation. American Journal of Transplantation, 4, 1459-1465.

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

4.5. Intestinal disorders

4.5.1. Functional bowel problem

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.

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 on adults and pediatrics 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.

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 in adults and pediatrics.

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.

4.5.2. Short gut syndrome

Massironi S, et al. (2020). Understanding short bowel syndrome: Current status and future perspectives. Dig Liver Dis, 52(3), 253-261. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31892505/

- Review article on short bowel syndrome. Includes updated short bowel therapeutic approach.
- Therapeutic management and some clinical trials are included for the following agents: glutamine oral solution, growth hormone (somatropin), glucagon-like-peptitde-2 analog (tedglutide).

Pironi L. (2020) Translation of evidence into practice with teduglutide in the management of adults with intestinal failure due to short-bowel syndrome: A review of recent literature. JPEN J Parenter Enteral Nutr, 44(6), 968-978. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31802516/

- Review summary of recent studies regarding the use of teduglutide in short bowel syndrome associated with chronic intestinal failure.
- Discuss teduglutide expected treatment duration, effects after treatment cessation, adverse effects, quality of life improvement, and monitoring.

Goulet O, et al. (2019) Short Bowel Syndrome as the Leading Cause of Intestinal Failure in Early Life: Some Insights into the Management. *Pediatr Gastroenterol Hepatol Nutr*; 22(4):303-329. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31338307/

- Review article on short bowel syndrome (SBS). Includes etiology, outcomes of SBS and long term growth, and long term management of SBS intestinal failure in pediatric population.

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.

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.

4.5.3 Chronic intestinal pseudoobstruction

Sogawa H (2021). Twenty years of gut transplantation for chronic intestinal pseudo-obstruction: technical innovation, long-term outcome, quality of life, and disease recurrence. Ann Surg, 273(2):325-333. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31274659/.

- Retrospective cohort study evaluating long-term outcomes and quality of life for multi-visceral transplant patients who were transplanted due to chronic intestinal pseudo-obstruction (CIPO).
- 55 patients underwent multivisceral transplant for CIPO at the University of Pittsburgh Medical Center over the last 20 years, 23 patient were age < 18 years at time of transplant. Fifteen patients

underwent intestinal allograft only and 40 patients underwent stomach, intestinal, and pancreas transplant. Increased quality of life was reported for patients that had a median follow up of 4 years. Fourteen of the 40 patients additionally required a liver transplant. Over 20 years, mean follow up time for patients was 61 ± 41 months and 33 patients (60%) were alive, 23 of these patients were able to be maintained on enteral nutrition after transplant. Thirty-two patients (52%) had graft loss, 7 patients underwent re-transplant. Mortality occurred in 22 patients mostly due to infection, PTLD, or rejection. Acute rejection occurred within first 90 days post-transplant for 37 patients (67%). CIPO recurrence occurred in 4 patients (7%). Long-term survival is achievable with multivisceral transplant for CIPO with few recurrences of disease