Title

Non-HLA AT1R antibodies are highly prevalent after pediatric intestinal transplantation

Journal

Pediatric Transplantation, 25(3)

ISSN

1397-3142

Authors

Chan, Alvin P
Guerra, Marjorie-Anne R
Rossetti, Maura
et al.

Publication Date

2021-05-01

DOI

10.1111/petr.13987

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Transplant. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

Pediatr Transplant. ; : e13987. doi:10.1111/petr.13987.

Non-HLA AT1R antibodies are highly prevalent after pediatric intestinal transplantation

Alvin P Chan, MD[1], **Marjorie-Anne R Guerra, MD**[1], **Maura Rossetti, PhD**[2], **Michelle J Hickey, PhD**[2], **Robert S Venick, MD**[1], **Elizabeth A Marcus, MD**[1,4], **Suzanne V McDiarmid, MD**[1], **Douglas G Farmer, MD**[3], **Elaine F Reed, PhD**[2], **Laura J Wozniak, MD**[1]

[1]Pediatric Gastroenterology, Hepatology, and Nutrition, UCLA Mattel Children's Hospital and David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

[2]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

[3]Division of Liver and Pancreas Transplantation, Department of Surgery, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

[4]VA Greater Los Angeles Health Care System, Los Angeles, CA, USA

Abstract

Background: The role of angiotensin II type-1 receptor (AT1R) antibodies in intestinal transplantation (ITx) is unclear. The aims were 1) to identify the prevalence of AT1R antibodies in pediatric ITx, compared to pediatric intestinal failure (IF), and 2) to determine whether AT1R antibodies were associated with graft dysfunction.

Methods: 46 serum samples from 25 ITx patients (3 isolated ITx, 22 liver-inclusive ITx) were collected during routine visits >6 months apart and during episodes of graft dysfunction as a result of infectious enteritis or rejection. For comparison, samples were collected from 7 IF control patients. AT1R antibodies were considered positive for levels >17 U/mL.

Results: The median (range) AT1R antibody level for ITx patients was 40.0 U/mL (7.2–40.0), compared to 7.0 U/mL (5.7–40.0) for IF patients (p=0.02). There was a trend towards higher prevalence of AT1R antibodies in ITx compared to IF patients (68% versus 29%, p=0.09). Among ITx patients, the prevalence of AT1R antibodies was not different between periods of active graft dysfunction and normal health (83% versus 67%, p=0.31). For 16 patients with >2 samples, AT1R antibodies remained positive in 67% cases, developed in 14% cases, disappeared in 10% cases, and remained negative in 10% cases. The changes in AT1R antibodies did not correlate with de/sensitizing events.

Correspondence: Alvin P. Chan, Department of Pediatric Gastroenterology, Hepatology, and Nutrition, UCLA Mattel Children's Hospital and David Geffen School of Medicine, 10833 Le Conte Ave, MDCC 12-383, Los Angeles, CA 90095-1752, Telephone: 310-206-6134, alvinchan@mednet.ucla.edu.

Author Roles: APC, MRG, MR, MJH, RSV, EAM, SVM, DGF, EFR, and LJW contributed to research design and performance of the research and data analysis. APC drafted the manuscript. MRG, MR, MJH, RSV, EAM, SVM, DGF, EFR, and LJW participated in the critical evaluation of the paper. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Conclusion: This is the first study of AT1R antibodies in pediatric ITx. AT1R antibodies are highly prevalent after ITx and may be triggered by immune activation associated with the transplant. However, their pathogenicity and clinical utility remains in question.

Keywords

Angiotensin II type-1 receptor antibody; non-HLA antibody; antibody-mediated rejection; intestinal transplantation; liver/intestine transplant; pediatric

Background

Intestinal transplantation (ITx) has become a life-saving option for children with irreversible intestinal failure (IF). Advances over the past three decades have led to dramatic improvements in early pediatric ITx outcomes, but long-term success has lagged behind, with 5- and 10-year graft survival rates at only 50% and 41%, respectively.[1] Rejection remains a major barrier because of the profound immunogenicity of the transplanted intestine. Although ITx rejection is generally considered a T cell–mediated process, there is now also growing acceptance of an antibody-mediated component, with emerging evidence pointing towards the importance of auto- and alloantibody biomarkers as predictors of graft injury.[2, 3] Over the last several years, preformed and de novo human leukocyte antigen (HLA) donor-specific antibodies (DSA) have been associated with intestinal graft rejection, specifically antibody-mediated rejection (AMR).[4–6] Non-HLA antibodies are also likely to play a role in the long-term fate of the intestinal graft.[7]

Angiotensin II type-1 receptor (AT1R) antibodies are non-HLA antibodies that have gained widespread interest as potential contributors to graft injury and rejection. Described first in adult kidney transplants,[8] AT1R antibodies have now been linked to adverse outcomes in a number of other solid organ transplants, including the heart,[9] lung,[10] and liver.[11–14] More recently, AT1R antibodies have also been implicated in intestinal graft rejection. In a study of 29 adult ITx patients, Gerlach et al. screened for AT1R and anti-endothelin type A receptor antibodies and found a trend towards a higher risk of overall graft rejection (T-cell mediated rejection (TCMR) and AMR) in the presence of non-HLA antibodies compared to antibody-negative controls (80% versus 55%).[15] Particularly, AMR was more common with non-HLA antibodies than controls (55% versus 11%, $p<0.01$).

The impact of AT1R antibodies in pediatric ITx has not been investigated previously. Given differences between adults and children in nearly all aspects of ITx,[1, 2, 16] understanding the role of AT1R antibodies in pediatric ITx may help tailor immunosuppressive strategies for TCMR and AMR. Therefore, the aims of this study were 1) to identify the prevalence of AT1R antibodies in pediatric ITx, compared to pediatric IF, and 2) to determine whether AT1R antibodies were associated with graft dysfunction.

Materials and Methods

Study population

This was a sub-study of our previously performed, prospective, cross-sectional study on the characterization of T-cell immunophenotypes associated with graft dysfunction after ITx,

which showed an increase in markers of T-cell activation in graft rejection compared to infectious enteritis.[17] This current study retrospectively tested for the presence of AT1R antibodies in a subset of pediatric ITx recipients who had previously undergone HLA DSA testing as part of routine clinical care. This study was approved by the UCLA Institutional Review Board, IRB #12–001231.

All patients ≤18 years old followed by the UCLA Intestinal Transplant Program who received an ITx between 2000 and 2016 were eligible. All ITx recipients received an induction immunosuppression protocol consisting of corticosteroids and an interleukin-2 receptor antagonist for 6–8 weeks post-transplant in normal-risk recipients, or rabbit anti-thymocyte globulin or alemtuzumab in high-risk recipients for induction therapy; and a maintenance regimen consisting of corticosteroids, tacrolimus, mycophenolate mofetil, and/or sirolimus.[4, 17] Patients were included if AT1R antibody and HLA DSA testing were performed <100 days from one another. Patients were excluded if they received alemtuzumab in the past, received anti-thymocyte globin or rituximab within the past 6 months, or were diagnosed or treated with post-transplant lymphoproliferative disease (PTLD) within the past 3 months, due to their confounding effects on leukocyte and antibody depletion.

As a basis for comparison, patients with IF seen for ITx evaluation and/or management of home parenteral nutrition served as control patients. The rationale for using IF patients rather than healthy controls was to account for any differences in AT1R antibody sensitization that may have been affected by past abdominal surgeries, blood transfusions, and/or infectious complications, including episodes of sepsis, catheter-related bloodstream infections, and nosocomial infections.

Definition of graft dysfunction and data collection

Blood samples were collected from ITx recipients between November 2012 and September 2017 at clinical visits and/or during hospitalizations at any time point after transplant and classified into one of two categories: normal baseline health (n=31 samples) and graft dysfunction (n=15 samples). Samples designated as normal baseline health were collected during periods of stable intestinal graft function on baseline immunosuppression during routine clinical visits. Follow up samples were collected at subsequent clinical visits at least 6 months later. Samples designated as graft dysfunction were collected during periods of active graft dysfunction, defined as the presence of nausea/vomiting, ileus/obstruction, gastrointestinal bleeding, and/or high fecal outputs of >30 mL/kg/day. Viral and bacterial stool studies and/or endoscopy were performed for graft dysfunction at the discretion of the clinical team. The criteria for TCMR was biopsy-proven rejection based on the standardized grading scheme or indeterminate histopathology with high clinical suspicion.[18] The criteria for AMR was diagnosed based on clinical suspicion combined with endoscopic findings of mucosal congestion and focal hemorrhage in the setting of circulating immunoglobulins.[19] C4d deposition, while a diagnostic criterion for AMR in kidney grafts, shows inconsistent clinical relevance in ITx.[20]

Control samples were collected from IF patients during a period of clinical stability, defined by normal baseline state of health without active infection, hospitalization, or surgery.

Data was collected for each patient and included demographic information (age, sex, race), clinical characteristics (primary etiology of IF, type of intestinal graft, age at time of ITx, age at time of sample collection, immunosuppression regimen), laboratory results (complete blood cell count, comprehensive metabolic panel, HLA DSA tested as part of routine clinical care), and biopsy findings (if available).

Detection of ATIR antibody and HLA DSA

AT1R antibody was detected with an enzyme-linked immunosorbent assay test.[21] An AT1R antibody result >10 U/mL indicates an increased risk of endothelial cell dysfunction at a serum dilution of 1:100 at our laboratory, but cutoff levels may vary across other laboratories. Statistics were performed using different cutoff levels of 10 U/mL, 17 U/mL, and 40 U/mL. The lowest and highest cutoff values did not yield additional clinically significant results. For that reason, a cutoff level of >17 U/mL was defined as positive in this study to remain consistent with other published transplant studies on AT1R antibodies.[9, 12, 22] AT1R antibody level of 40 U/mL was the upper limit, and an AT1R antibody level >40 U/mL was coded as 40 U/mL for analysis purposes. HLA DSA, which had been measured as part of routine clinical care using a single-antigen bead Luminex test (LABScreen; One Lambda, Canoga Park, CA), were extracted from medical records. HLA DSA was defined as positive for a normalized mean fluorescence intensity value >1000.

Statistical analysis

Descriptive statistical analyses were used to summarize the collected data: continuous variables with medians (ranges) and categorical variables with observation counts and percentages. Relationships between clinical data and AT1R antibodies were analyzed using chi-square, Fisher's exact, and Kruskal-Wallis tests, with statistical significance defined by p-value <0.05. All statistical analyses were performed with Stata version 11 (StataCorp LP, College Station, TX).

Results

Thirty-two pediatric patients were included in the study: 25 ITx recipients (3 isolated intestine; 22 liver-inclusive transplant) and 7 IF control patients. A total of 46 serum samples were analyzed for the 25 ITx patients. The median (range) number of samples per patient was 2 (1–4). Table 1 compares the demographic and clinical characteristics and AT1R antibody results between the ITx and IF patients. Notably, the prevalence of AT1R antibodies (>17 U/mL) at study entry trended higher in the ITx patients compared to the IF patients (68% versus 29%, p=0.09). The median (range) AT1R antibody level for ITx patients was 40.0 U/mL (7.2–40.0), significantly greater than that for IF patients who had a median (range) of 7.0 U/mL (5.7–40.0) (p=0.02).

Table 2 summarizes the baseline characteristics of the ITx recipients at time of study enrollment, stratified by AT1R positive (n=17 patients) and AT1R negative (n=8). Age, sex, race, and etiology of IF were not significantly different between the two groups. Median (range) age of the AT1R positive patients was 12.0 years (3.1–19.8), while the median (range) age of the AT1R negative patients was 11.7 years (10.2–20.3). Median (range) time

of AT1R antibody collection from transplant were 6.9 years (0.7–14) and 9.5 years (1.3–14), respectively. A past history of graft dysfunction was common in all patients, regardless of AT1R antibody status. Number of immunosuppressive medications and history of PTLD also did not correlate with AT1R status. The presence of HLA-DSA was not associated with AT1R antibody status. However, there was a trend towards HLA-DSA, particularly HLA-DSA class II, among the AT1R negative patients.

The prevalence of AT1R antibodies were compared between periods of active intestinal graft dysfunction (n=15 samples) and normal baseline health (n=31 samples). From this, samples were excluded if there was no change in AT1R antibody status between serial samples to avoid redundancy in analysis (n=7 samples). In the end, there were no statistically significant differences in AT1R antibody prevalence between periods of active graft dysfunction (n=12 samples) and normal health (n=27 samples) (83% versus 67%, p=0.31). The median (range) AT1R antibody levels during graft dysfunction and normal baseline health were 40.0 U/mL (7.5–40.0) and 40.0 U/mL (7.2–40.0) (p=0.6), respectively. Graft dysfunction was caused by either infectious enteritis or rejection. Interestingly, AT1R antibodies were present in all 8 of the 8 episodes of infectious enteritis and 2 of the 4 episodes of rejection.

Serial AT1R antibody samples were collected for 16 of the 25 ITx patients: AT1R antibodies remained positive in 67% of cases, developed in 14% of cases, disappeared in 10% of cases, and remained negative in 10% of cases. The persistently positive AT1R antibodies were not associated with graft dysfunction. Also, the formation of AT1R antibodies in the 2 patients did not correlate with rejection or infection. The clearance of AT1R antibodies in the 1 patient did not occur with antibody-directed therapies, such as intravenous immunoglobulin, rituximab, or plasmapheresis.

Discussion

This represents the first study of the prevalence and clinical associations of AT1R antibodies in pediatric ITx recipients and IF controls. This study found AT1R antibodies >17 U/mL to be very common following ITx with a prevalence of 68%. The prevalence of AT1R antibodies was not different between periods of active graft dysfunction and normal health (83% versus 67%). Between AT1R antibody positive and AT1R antibody negative patients, there were no significant differences in the past history of graft dysfunction, PTLD, or amount of maintenance immunosuppression. The persistence, appearance and disappearance of AT1R antibodies could not be linked to any specific de/sensitizing events after transplantation, such as infection, rejection, or immunosuppression changes.

The prevalence of AT1R antibodies in this study was high. The development of AT1R antibodies is likely triggered in response to foreign or self-antigens as a result of ischemia-reperfusion injury, surgical trauma, alloimmunity, chronic inflammation, and infection.[7] These events are all very common after ITx. The intestine is also one of the most immunogenic solid organ transplants, carrying a significant burden of lymphoid cells.[23] Our post-transplant AT1R antibody prevalence was similar to that reported in the only other AT1R antibody ITx study on adults (68% versus 55%).[15] While the percentage of patients

with positive AT1R in the Gerlach et al. study was less than ours, children are known to be more susceptible to AT1R antibody formation because of surgical and hemodynamic challenges related to their size and higher risk of post-transplant infections.[22, 24] Although not statistically significant, the median age at time of transplant in this study was younger in patients with AT1R antibodies compared to those without antibodies, an observation also shown in pediatric liver transplantation.[12] The development of infectious enteritis was also more commonly seen in those with AT1R antibodies here.

Mechanistically, AT1R antibodies are agonistic antibodies that target the AT1R on the vascular endothelium throughout most tissues, causing microvascular damage, vasoconstriction and inflammation.[8, 25, 26] The major sites expressing AT1R are the vascular smooth muscle, kidney, lung, liver, and brain.[27] The direct effect of AT1R antibodies on the vascular disease pathology of hypertension and preeclampsia has been shown previously.[28] The negative effects of AT1R antibodies on heart, lung, kidney, and liver transplants have also been suggested.[9–13] However, the role of AT1R antibodies in ITx is unclear. Since AT1R is not distributed in the intestinal epithelium, the postulated mechanisms of AT1R antibody-mediated injury in ITx are damage to the vascular endothelium within the intestinal vasculature or heightened immune reactivity in response to high circulating antibodies. According to our study, AT1R antibodies did not appear to have a clinically significant impact on intestinal graft dysfunction or survival. The prevalence of AT1R antibodies did not differ significantly between times of active graft dysfunction and periods of normal baseline health. The dis/appearance of AT1R antibodies also did not seem to temporally correlate with specific de/sensitizing events, such as infection, rejection, or alterations in immunosuppressive medications. The high persistence of positive AT1R antibodies seen in this study was likely the result of an immunogenic event that occurred at an earlier time point with lack of antibody clearance over time.

In contrast to our study, Gerlach et al. found that AT1R antibodies actually accelerated immune responses following ITx. Among the 29 adult ITx patients, the rates of overall graft rejection were higher in the presence of non-HLA AT1R antibodies and/or anti-endothelin type A receptor antibodies than in negative-antibody controls (80% versus 55%)—but important to note is that the increased risk was not statistically significant.[15] The discrepancy between the Gerlach et al. study and ours may be due to differences in AT1R antibody detection methods, study population (adult versus pediatric), and frequency of liver-inclusive ITx (50% versus 88%). One of the most notable differences between adult ITx and pediatric ITx is the type of graft used, owing to the differing underlying etiologies for ITx. Liver-inclusive grafts comprise approximately 50% of all ITx in adults,[29] whereas they make up 70% in children.[1] Since the liver is thought to be immunoprotective,[5, 30] it is possible that less antibody-mediated injury was seen with the higher proportion of liver-inclusive transplants in our pediatric study.

Limitations

The results in this study should be interpreted in light of several limitations. Our inability to generate statistically significant results may be the result of small sample size and cross-sectional study design. As AT1R antibodies were not screened before transplant, this study

also does not differentiate between preformed and de novo antibodies, which may have different clinical implications. In addition, AT1R antibody levels >40 U/mL were not further diluted to determine the titer of the antibody. As more than half of all sera had levels >40 U/mL, the clinical effect of very high AT1R antibody levels may not have been fully captured. Next, the IF patients served as the control group in this study, but future research may also compare AT1R antibody prevalence with an isolated liver transplant control group given the high frequency of liver-inclusive ITx in pediatrics. In the few pediatric liver transplantation studies of non-HLA antibodies, AT1R antibody prevalence has ranged from 29% to 68% in stable liver transplant recipients.[12, 14] Finally, analyses from this study were limited to only AT1R antibodies. The significance of HLA-DSA, specifically HLA-DSA class II, has been shown previously to contribute to intestinal graft injury and loss. Cheng et al. demonstrated an increased risk of graft loss with preformed and de novo HLA-DSA, with a failure rate of 28% within 2 years.[4] Abu-Elmagd et al. reported a higher risk of acute rejection with preformed HLA-DSA and increased risk of chronic rejection and subsequent graft loss with persistent de novo HLA-DSA.[5] Future research can further investigate the combined roles of AT1R antibodies and HLA-DSA on graft dysfunction, especially as emerging data from the kidney and liver transplant literature suggests their synergistic impact on graft outcomes.[4, 11]

Future Directions

Given the limitations of this study, additional research is needed to determine how AT1R antibody testing can be best utilized in clinical practice in pediatric ITx. Future studies should explore 1) the differences in AT1R antibodies between isolated ITx and liver-inclusive ITx, 2) the implications of liver dysfunction on AT1R antibodies in liver-inclusive ITx, 3) the differential effects of higher AT1R antibody level thresholds, 4) the clinical impact of preformed and de novo AT1R antibodies, 5) the interaction between AT1R antibodies and HLA DSA, and 6) the role of angiotensin II receptor blockers when AT1R antibodies are present.

Conclusion

In summary, this was the first study evaluating the role of AT1R antibodies in pediatric ITx. AT1R antibodies were found to be highly prevalent after ITx, likely triggered by intensive immune activation associated with the inherent immunogenicity of the intestinal graft, complex surgical procedure, ischemia-reperfusion injury, blood transfusions, infection, and rejection. However, the pathogenicity and clinical utility of AT1R antibodies remain unclear.

Acknowledgments

Funding: This work was supported by the National Center for Advancing Translational Sciences UCLA CTSI Grant UL1TR001881. APC was supported by the UCLA Children's Discovery and Innovation Institute Resident Research Grant Award and NIH NIDDK T32DK007180. MRG was supported by the Children's Discovery and Innovation Institute Harry Winston Fellowship Award. EAM was supported by NIH R03DK110579 and R01DK105156. LJW was supported by the UCLA Children's Discovery and Innovation Institute Today's and Tomorrow's Children Fund and the UCLA Children's Discovery and Innovation Institute Seed Grant Award CDI-SGA-01012017. EFR was supported in part by NIH RO1 AI135201, PO1 AI120944, U19128913.

Data Availability

Data available on request from the authors.

ABBREVIATIONS

AMR	antibody-mediated rejection
AT1R	angiotensin II type-1 receptor
DSA	donor-specific antibody
HLA	human leukocyte antigen
IF	intestinal failure
ITx	intestinal transplant
TCMR	T-cell mediated rejection

References

1. Venick RS, Duggan E, Whatley J. Current status of pediatric intestinal transplantation in the United States. Curr Opin Organ Transplant. 4 2020;25(2):201–207. doi:10.1097/MOT.0000000000000744 [PubMed: 32073484]
2. Sudan D The current state of intestine transplantation: indications, techniques, outcomes and challenges. Am J Transplant. 9 2014;14(9):1976–84. doi:10.1111/ajt.12812 [PubMed: 25307033]
3. Wu GS, Cruz RJ, Cai JC. Acute antibody-mediated rejection after intestinal transplantation. World J Transplant. 12 2016;6(4):719–728. doi:10.5500/wjt.v6.i4.719 [PubMed: 28058223]
4. Cheng EY, Everly MJ, Kaneku H, et al. Prevalence and Clinical Impact of Donor-Specific Alloantibody Among Intestinal Transplant Recipients. Transplantation. 04 2017;101(4):873–882. doi:10.1097/TP.0000000000001391 [PubMed: 27490417]
5. Abu-Elmagd KM, Wu G, Costa G, et al. Preformed and de novo donor specific antibodies in visceral transplantation: long-term outcome with special reference to the liver. Am J Transplant. 11 2012;12(11):3047–60. doi:10.1111/j.1600-6143.2012.04237.x [PubMed: 22947059]
6. Gerlach UA, Lachmann N, Sawitzki B, et al. Clinical relevance of the de novo production of anti-HLA antibodies following intestinal and multivisceral transplantation. Transpl Int. 3 2014;27(3):280–9. doi:10.1111/tri.12250 [PubMed: 24279605]
7. Zhang Q, Reed EF. The importance of non-HLA antibodies in transplantation. Nat Rev Nephrol. 08 2016;12(8):484–95. doi:10.1038/nrneph.2016.88 [PubMed: 27345243]
8. Dragun D The role of angiotensin II type 1 receptor-activating antibodies in renal allograft vascular rejection. Pediatr Nephrol. 7 2007;22(7):911–4. doi:10.1007/s00467-007-0452-z [PubMed: 17340146]
9. Reinsmoen NL, Lai CH, Mirocha J, et al. Increased negative impact of donor HLA-specific together with non-HLA-specific antibodies on graft outcome. Transplantation. 3 2014;97(5):595–601. doi:10.1097/01.TP.0000436927.08026.a8 [PubMed: 24162250]
10. Reinsmoen NL, Mirocha J, Ensor CR, et al. A 3-Center Study Reveals New Insights Into the Impact of Non-HLA Antibodies on Lung Transplantation Outcome. Transplantation. 06 2017;101(6):1215–1221. doi:10.1097/TP.0000000000001389 [PubMed: 27973391]
11. Ohe H, Uchida Y, Yoshizawa A, et al. Association of anti-human leukocyte antigen and anti-angiotensin II type 1 receptor antibodies with liver allograft fibrosis after immunosuppression withdrawal. Transplantation. 11 2014;98(10):1105–11. doi:10.1097/TP.0000000000000185 [PubMed: 24914568]

12. Wozniak LJ, Hickey MJ, Chan AP, et al. Angiotensin II Type-1 Receptor Antibodies Are Associated With Active Allograft Dysfunction Following Pediatric Liver Transplantation. Transplantation. 2 2020;doi:10.1097/TP.0000000000003206

13. O'Leary JG, Demetris AJ, Philippe A, et al. Non-HLA Antibodies Impact on C4d Staining, Stellate Cell Activation and Fibrosis in Liver Allografts. Transplantation. 10 2017;101(10):2399–2409. doi:10.1097/TP.0000000000001853 [PubMed: 28665894]

14. Feng S, Bucuvalas JC, Demetris AJ, et al. Evidence of Chronic Allograft Injury in Liver Biopsies From Long-term Pediatric Recipients of Liver Transplants. Gastroenterology. 12 2018;155(6):1838–1851.e7. doi:10.1053/j.gastro.2018.08.023 [PubMed: 30144432]

15. Gerlach UA, Lachmann N, Ranucci G, et al. Non-HLA Antibodies May Accelerate Immune Responses After Intestinal and Multivisceral Transplantation. Transplantation. 1 2017;101(1):141–149. doi:10.1097/TP.0000000000001439 [PubMed: 27495766]

16. Matsumoto CS, Subramanian S, Fishbein TM. Adult Intestinal Transplantation. Gastroenterol Clin North Am. 6 2018;47(2):341–354. doi:10.1016/j.gtc.2018.01.011 [PubMed: 29735028]

17. Guerra MR, Rossetti M, Zhang Z, et al. Characterization of T cell immunophenotypes in intestinal transplantation: A pilot study. Transpl Immunol. 12 2018;51:50–57. doi:10.1016/j.trim.2018.09.003 [PubMed: 30243797]

18. Ruiz P, Bagni A, Brown R, et al. 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. Transplant Proc. 3 2004;36(2):335–7. doi:10.1016/j.transproceed.2004.01.079 [PubMed: 15050150]

19. Wu T, Abu-Elmagd K, Bond G, Demetris AJ. A clinicopathologic study of isolated intestinal allografts with preformed IgG lymphocytotoxic antibodies. Hum Pathol. 11 2004;35(11):1332–9. doi:10.1016/j.humpath.2004.07.001 [PubMed: 15668889]

20. de Serre NP, Canioni D, Lacaille F, et al. Evaluation of c4d deposition and circulating antibody in small bowel transplantation. Am J Transplant. 6 2008;8(6):1290–6. doi:10.1111/j.1600-6143.2008.02221.x [PubMed: 18444932]

21. Reinsmoen NL, Lai CH, Heidecke H, et al. Anti-angiotensin type 1 receptor antibodies associated with antibody mediated rejection in donor HLA antibody negative patients. Transplantation. 12 2010;90(12):1473–7. doi:10.1097/TP.0b013e3181fd97f1 [PubMed: 21030904]

22. Pearl MH, Zhang Q, Palma Diaz MF, et al. Angiotensin II Type 1 receptor antibodies are associated with inflammatory cytokines and poor clinical outcomes in pediatric kidney transplantation. Kidney Int. 01 2018;93(1):260–269. doi:10.1016/j.kint.2017.06.034 [PubMed: 28927645]

23. Berger M, Zeevi A, Farmer DG, Abu-Elmagd KM. Immunologic challenges in small bowel transplantation. Am J Transplant. 12 2012;12 Suppl 4:S2–8. doi:10.1111/j.1600-6143.2012.04332.x [PubMed: 23181675]

24. Dharnidharka VR, Agodoa LY, Abbott KC. Risk factors for hospitalization for bacterial or viral infection in renal transplant recipients--an analysis of USRDS data. Am J Transplant. 3 2007;7(3):653–61. doi:10.1111/j.1600-6143.2006.01674.x [PubMed: 17250559]

25. Dragun D, Catar R, Philippe A. Non-HLA antibodies against endothelial targets bridging allo- and autoimmunity. Kidney Int. 08 2016;90(2):280–288. doi:10.1016/j.kint.2016.03.019 [PubMed: 27188505]

26. Dragun D, Catar R, Kusch A, Heidecke H, Philippe A. Non-HLA-antibodies targeting Angiotensin type 1 receptor and antibody mediated rejection. Hum Immunol. 12 2012;73(12):1282–6. doi:10.1016/j.humimm.2012.07.010 [PubMed: 22819838]

27. Allen AM, Zhuo J, Mendelsohn FA. Localization and function of angiotensin AT1 receptors. Am J Hypertens. 1 2000;13(1 Pt 2):31S–38S. doi:10.1016/s0895-7061(99)00249-6 [PubMed: 10678286]

28. Xia Y, Kellems RE. Receptor-activating autoantibodies and disease: preeclampsia and beyond. Expert Rev Clin Immunol. 9 2011;7(5):659–74. doi:10.1586/eci.11.56 [PubMed: 21895478]

29. Grant D, Abu-Elmagd K, Mazariegos G, et al. Intestinal transplant registry report: global activity and trends. Am J Transplant. 1 2015;15(1):210–9. doi:10.1111/ajt.12979 [PubMed: 25438622]

30. Farmer DG, Venick RS, Colangelo J, et al. Pretransplant predictors of survival after intestinal transplantation: analysis of a single-center experience of more than 100 transplants.

Transplantation. 12 2010;90(12):1574–80. doi:10.1097/TP.0b013e31820000a1 [PubMed: 21107306]

Table 1.

Clinical summary of all pediatric patients at study entry (intestinal transplant patients versus intestinal failure control patients) (n=32)

	ITx (n=25)	IF (n=7)	p-value
Age in years, median (range)	12.0 (4.3–20.3)	9.9 (2.6–19.2)	0.11
Male	60%	71%	0.68
Race			
Hispanic	68%	86%	
White	20%	0%	0.65
Other	12%	14%	
Primary diagnosis			
Short bowel syndrome	84%	14%	
Motility disorder	4%	71%	<0.01 *
Mucosal defect	8%	0%	
Other	4%	14%	
AT1R antibody			
U/mL, median (range)	40.0 (7.2–40.0)	7.0 (5.7–40.0)	0.02 *
>10 U/mL	88%	29%	0.01 *
>17 U/mL	68%	29%	0.09
>40 U/mL	60%	29%	0.21

* Statistical significance defined by p-value <0.05

Table 2.

Baseline characteristics of pediatric intestinal transplant recipients (AT1R- versus AT1R+) (n=25)

	AT1R+ (n=17)	AT1R- (n=8)	p-value
Male	53%	75%	0.40
Race			
Hispanic	65%	75%	
White	18%	25%	0.66
Other	18%	0%	
Primary diagnosis			
Short gut syndrome	82%	88%	
Motility disorder	0%	12%	0.60
Mucosal defect	12%	0%	
Other	6%	0%	
Liver-inclusive graft	94%	75%	0.18
Re-transplant	12%	38%	0.28
Age in years, median (range)	12.0 (3.1–19.8)	11.7 (10.2–20.3)	0.38
Age at transplant in years, median (range)	2.4 (0.9–16.4)	4.1 (0.9–8.9)	0.91
Time since transplant in years, median (range)	6.9 (0.7–14)	9.5 (1.3–14)	0.48
Maintenance immunosuppression ≥ 2 agents (%)	94%	75%	0.23
History of anti-thymocyte globulin use	12%	25%	0.57
History of post-transplant lymphoproliferative disease	29%	25%	1.0
History of graft dysfunction	94%	100%	1.0
Donor specific HLA antibody	18%	50%	0.16
DSA Class I	6%	0%	1.0
DSA Class II	12%	50%	0.06