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Immunologic Complications and Graft Survival in Crohn's Disease and NOD2 Mutant Non-Crohn's Disease Adult Recipients Following Intestine Transplantation

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Background. Despite improved outcomes in the modern era of targeted immunotherapy, intestinal failure and chronic parenteral nutrition remains a significant burden for patients with Crohn's disease (CD) worldwide. Transplantation is a key component of management when a patient with CD suffers from life-threatening complications of parenteral nutrition. Nucleotide-binding oligomerization domain 2 (NOD2) mutation is a risk factor for both development of CD and intestinal allograft rejection. **Methods.** A retrospective review of a prospectively maintained database of intestinal transplants at a single center from 2003 to 2015 was conducted. Eleven adult patients with CD were identified and were compared with 103 adult control recipients. A sub-analysis was performed comparing the 11 CD recipients to the 13 NOD2 mutant non-CD recipients. **Results.** Patient and allograft characteristics were similar between the CD and control recipients. Although overall rejection-free survival was not significantly different, patients with CD suffered from more frequent, earlier, and more severe rejection compared with control patients. The onset, severity, and frequency of rejection was comparable between patients with CD and NOD2 mutant non-CD patients. There was a trend toward lower 5-year allograft survival for CD compared with control recipients (33% versus 63.3%; $P = 0.19$) and NOD2 mutant non-CD recipients (33% versus 57.14%; $P = 0.41$). **Conclusions.** Patients with CD remain a challenging population in intestine transplantation, and NOD2 mutant non-CD patients appear to have a similar immunologic phenotype. These high-risk recipients may require specialized immunosuppression protocols and management at experienced transplant centers.

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Crohn's disease (CD) is a multifactorial disease occurring in genetically predisposed individuals under the duress of environmental, microbiome, and autoimmune factors. Up to 80% of patients with CD will develop a stricturing or penetrating complication over the span of 20 years of disease, frequently necessitating a surgical intervention. Patients with CD are also more prone to postoperative complications following intestinal surgery, most radically including significant enterocutaneous and enteroenteric fistulae that can quickly

lead to inordinate amounts of small bowel being resected. Home parenteral nutrition (PN) is required for patients either unable to tolerate enteral intake or unable to maintain an adequate amount of hydration and calories. However, when patients develop life-threatening complications of PN, intestine transplantation is the preferred therapy. Catheter-related blood stream infections and loss of central venous access are the most common reasons for patients with CD to require for intestinal transplantation.^{1,2} Alternatively, transplantation becomes necessary with development of progressive liver disease, termed intestinal failure-associated liver disease.^{3,4}

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Intestinal transplantation involves augmentation of the native gastrointestinal tract with typically either a combination of jejunoleum, jejunoleum with colon, or in conjunction with additional organs including liver, pancreas, stomach, or duodenum.⁵ Outcomes in intestinal transplantation have steadily improved over the last 2 decades because of a variety of factors, which include innovation in immunosuppressive regimens that have helped counteract the high rate of cellular rejection seen in this solid organ transplant group, improved immunomonitoring with endoscopy protocols, and donor-specific antibody testing, as well as establishment of highly specialized centers with intestinal failure programs leading to earlier referral for evaluation and⁶⁻⁸ five-year survival now approaches 66%,⁹ which is a modest improvement from around 50% in the previous era.

Patients with CD present a unique population when it comes to intestinal transplantation because of the pathogenesis of their disease and the critical impact the innate immune system has on their morbidity. A recent retrospective review of the United Network for Organ Sharing registry revealed comparable outcomes in intestinal transplantations performed after the year 2000, with roughly 60% patient survival rates at 5 years.¹⁰

Immunologically, patients with CD possess a dysregulated immune system with T helper 17-mediated infiltration reminiscent of intestinal allograft rejection.¹¹ Furthermore, nucleotide-binding oligomerization domain-containing protein 2 (NOD2) mutations are a significant risk factor for both the development of CD in healthy individuals and for cellular rejection in intestinal transplantation.¹²⁻¹⁴ To our knowledge, an analysis of outcomes in non-CD NOD2 mutants compared with CD patients has not been performed. Mechanistically, NOD2 is involved in the intracellular sensing of bacterial cell wall products at the mucosal interface, with mutation leading to a breakdown of the mucosal barrier allowing unrestricted bacterial stimulation and an inappropriate immunologic response.¹⁵ This parallel and its implications for transplantation have been described but not fully elucidated. The aim of our study is to evaluate intestine transplant outcomes in our patients with CD, as well as in non-CD patients with the NOD2 mutation status.

MATERIALS AND METHODS

We identified patients enrolled in our longitudinal clinical and immune monitoring studies (IRB studies No. 2004-008 and No. 2017-0365) from 2003 up until 2015, giving at least 3 years of follow up. In this cohort, we had 222 patients who received either isolated intestinal transplantation or a multivisceral or modified multivisceral transplant with or without a liver allograft. Eleven adult patients received 12 intestinal transplants for complications related to CD. Pediatric patients were excluded, and 103 adult patients were selected. Data were obtained through historical chart review, as well as through records kept at the MedStar Georgetown Transplant Institute.

Study end points included freedom from rejection, onset, frequency and severity of rejection, and graft loss. Freedom from rejection was defined as time until development of acute cellular rejection as diagnosed by intestinal biopsy and expert histologic and clinical evaluation as is routine at our center. Rejection episodes were considered discrete if separated by a

normal biopsy. Graft loss included both explantation, which primarily occurred in the setting of severe or chronic rejection, as well as graft loss due to death. Chronic rejection was diagnosed when biopsies featured arteriosclerosis and progressive vascular narrowing; CD recurrence was not definitively diagnosed in our patient cohort.

Transplant definitions included either isolated intestinal graft without liver, which was defined as either a small bowel transplant or small bowel with inclusion of colon regardless of length or a multivisceral transplant, which we defined as the inclusion of a liver graft or other components of the foregut to include the stomach, duodenum, or pancreas.

Induction was performed using either interleukin 2 blockade (basiliximab) or thymocyte depletion (thymoglobulin) and varied depending on transplant (Tables 1 and 2). Our protocol for postoperative immunosuppression includes a combination of tacrolimus, sirolimus, and prednisone. Briefly, tacrolimus is titrated by trough levels daily for the first 30 days posttransplant with goal levels of 20–25 ng/mL. The acceptable trough levels are decreased to 15–20 ng/mL for postoperative month 2, 12–15 ng/mL for postoperative month 3, 8–12 ng/mL for months 4–6, and kept at 5–8 ng/mL beyond postoperative month 6. Sirolimus is similarly titrated on a daily basis with goal blood levels of 9–11 ng/mL for postoperative month 1, 6–8 ng/mL for months 2 and 3, and 4–6 ng/mL for >4 months postoperatively.

Postoperative care includes regular scheduled ileoscopy, which is performed through an ileostomy created during every intestinal transplantation to survey the graft clinically and histologically. Ileoscopy is performed twice weekly up until 1.5 months posttransplant, then weekly until 3 months, biweekly until 5 months, and then monthly up until 1 year posttransplant or their ileostomy closure. After which point the patients usually return for ileoscopy annually or as symptoms or clinical concern arises.

Statistical analysis was performed using Prism 8 software (GraphPad). Survival analysis was plotted using a Kaplan-Meier curve and analyzed using a log-rank (Mantel-Cox) test. All *P* values were displayed regardless of significance. Table statistical analysis was performed in a similar fashion with either 2-tailed Mann-Whitney *U* test for nominal data or χ^2 analysis for proportions.

The study did not require ethics board evaluation due to its retrospective manner and absence of patient contact.

RESULTS

We identified 11 CD patients who received 12 intestinal transplants. The indication in all cases was intestinal failure because of short gut syndrome from voluminous intestinal resections and life-threatening PN complications. All of the patients were adults, with a 75%/25% male to female predominance, and the majority (84%) received an isolated intestinal transplant with 16% multivisceral grafts (Tables 1 and 2). A comparable cohort of adult patients was identified from the same registry. Demographics and graft characteristics did not significantly vary between the 2 groups. Induction method was similar with 35.9% receiving thymoglobulin and 64.1% receiving simulect in the control as compared with 41.7% and 58.3% in the CD cohort, respectively (Table 2).

Patients with CD were significantly more likely to need more biopsies (38 ± 17 versus 28 ± 13, respectively; *P* = 0.02)

TABLE 1.**General characteristics of the Crohn's disease patient cohort**

Patient number	Type of transplant	Age	Sex	Donor NOD2 status	Recipient NOD2 status	Donor/recipient age ratio	Induction method	CMV status	Rejection	Survival
1	SB	35	M	Mutant	Mutant	0.23	Thymo		Grade 1 (d 26)	Dead, rejection/sepsis (d 260)
2	SB	53	M	WT	Mutant	0.25	Simulect	High Risk	Grade 1 (d 206)	Dead, rejection/sepsis (d 935)
3	SB	38	M	WT	Mutant	1.11	Simulect	High Risk	Grade 1 (d 153)	
4	SB/C	43	M	WT	Mutant	0.19	Simulect		Grade 1 (d 97)	Dead, rejection/sepsis (d 1117)
5	SB	27	F	WT	Mutant	0.48	Thymo		No	Dead, sepsis (d 602)
6	MVTx	31	F	WT	Mutant	1.13	Simulect	High Risk	No	Dead, sepsis (d 1641)
7	SB	48	M	Mutant	Mutant	0.33	Thymo		No	Alive
8	SB	49	M	WT	Mutant	0.22	Thymo		Grade 3 (d 58)	Dead, liver failure (d 947)
9	SB/C	53	M	WT	Mutant	0.13	Simulect	High Risk	Grade 3 (d 20)	Dead, sepsis (d 143)
10	SB	33	F	Mutant	Mutant	0.7	Simulect		Grade 1	Alive
11	SB	43	M	Mutant	WT	0.49	Simulect		No	Alive
12	MVTx	48	M	ND	Mutant	0.38	Thymo		No	Alive

Note the total number of patients is 11, with 1 patient receiving 2 isolated intestinal grafts. Rejection grade listed was the initial episode of rejection (not withstanding subsequent episodes). CMV, cytomegalovirus; MVTx, multivisceral transplant; NOD2, nucleotide-binding oligomerization domain 2; SB/C, small bowel/colon; WT, wild type.

TABLE 2.**Perioperative characteristics and demographics for the CD and adult cohorts**

	Adult ITx patients (n = 103)	CD patients (n = 12)	P
Recipient gender (M/F)	55/48 (53.4%/46.6%)	9/3 (75%/25%)	0.15
Primary pathology			
Short gut	67	12	
Motility/malabsorption	20		
Neoplasia	9		
Other	7		
Retransplant	6		
Isolated intestinal graft without liver	79	10	0.6
Multivisceral transplant	24	2	
Surgery case time	7:36 (H:M)	7:09 (H:M)	0.67
Donor/recipient age ratio	0.52 (mean)	0.47 (mean)	0.34
Donor/recipient weight ratio	0.9 (mean)	0.72 (mean)	0.23
Recipient NOD2 status			<0.0001
Wild type	83	1	
Mutant	13	11	
Induction method	(35.92%/64.08%)	(41.67%/58.33%)	0.7
Thymoglobulin	37	5	
Simulect	66	7	
Follow up (d)	1903 (Mean)	1451 (Mean)	0.41

Statistical significance assessed by χ^2 testing.

CD, Crohn's disease; ITx, intestinal transplant; NOD2, nucleotide-binding oligomerization domain 2.

and had a greater median number of rejection episodes (3 versus 1; $P = 0.01$). These rejection episodes were more likely to be severe ($P = 0.04$), with 50% of CD patients experiencing grade 3 rejection versus 27.2% of controls. They also tended to occur earlier although this did not reach statistical significance (mean 271 ± 474 versus 421 ± 772 d; $P = 0.95$) in CD patients as compared to adult controls (Table 3). Chronic rejection developed in 16.7% of patients with CD versus 12.8% ($P = 0.7$), and ultimately 25% of the patients with CD required explantation versus 13.6% for controls ($P = 0.29$). Graft survival (Figure 1) was 75%, 41.6%, and 33% for 1, 3, and 5 years for patients with CD and 85%, 65.8%, and 60.7% for adult controls (log rank $P = 0.45$ $P = 0.12$, $P = 0.08$).

NOD2 recipient status, however, was vastly different in our CD cohort, with 91.7% of patients having a recipient NOD2

mutation as compared with 13.5% in the control cohort ($P < 0.0001$). 1-, 3-, and 5-year freedom from rejection was 50%, 50%, and 50% for the CD cohort, with all instances of rejection occurring within the first year as compared with 62.2%, 56.9%, and 53.5% for the control cohort, respectively (Figure 2).

Given the significant role of NOD2 mutations in epithelial barrier dysfunction and previous works demonstrating the risk of rejection and other complications,¹³ we identified a subset of non-CD recipients with NOD2 mutations. This included 13 patients who received 11 (78.6%) isolated intestinal transplants and 3 (21.4%) multivisceral grafts ($P = 0.76$). Demographics, graft characteristics, and induction protocols were not significantly different between these 2 cohorts (Table 4).

TABLE 3.
Rejection characteristics of adult ITx patient cohorts vs CD

	Adult ITx patients (n = 103)	CD patients (n = 12)	P
Number of Bx	28 ± 13	38 ± 17	0.02
Overall rejection (% of total population)	49 (47.57%)	7 (58.3%)	0.48
Median number of rejection episodes	1	3	0.009
Grade 1	21	8	0.02
Grade 2	18	0	0.21
Grade 3	30	10	0.04
Time to first rejection from transplant (d)	421 ± 772 (mean)	271 ± 474 (mean)	0.95
Duration of rejection (d)	37 ± 31.8 (mean)	28 ± 13.2 (mean)	0.99
Development of chronic rejection	13 (12.75%)	2 (16.67%)	0.7
Explantation	14 (13.59%)	3 (25%)	0.29

Overall rejection entailed the rate of rejection in that cohort as a percent of the total group. Grade 1–3 categories denote number of episodes total in the cohort, not averaged per patient. Bx, biopsy; CD, Crohn's disease; ITx, intestinal transplant; NOD2, nucleotide-binding oligomerization domain 2.

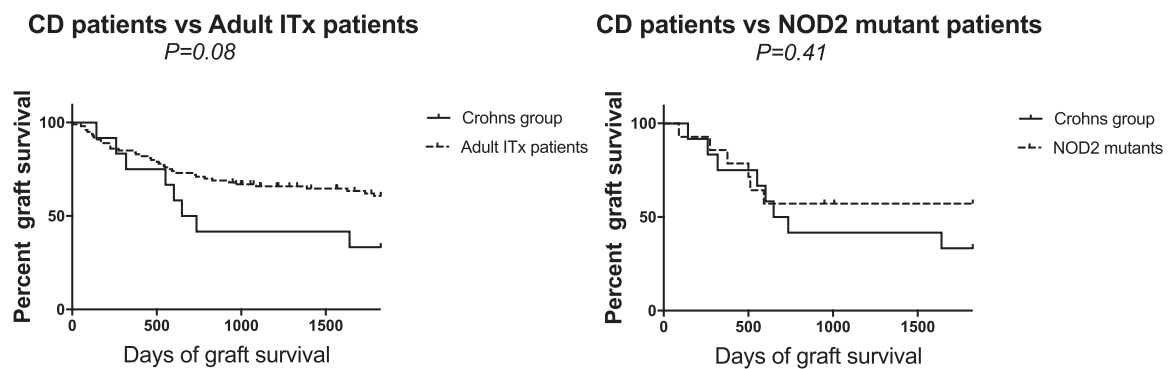


FIGURE 1. Patient graft survival rates for Crohn's disease (CD) vs adult (left) and adult patients with nucleotide-binding oligomerization domain 2 (NOD2) mutation (right) cohorts. CD patients had a trend toward higher rates of explantation as compared with healthy controls and surpassed even NOD2 mutants. ITx, intestinal transplant.

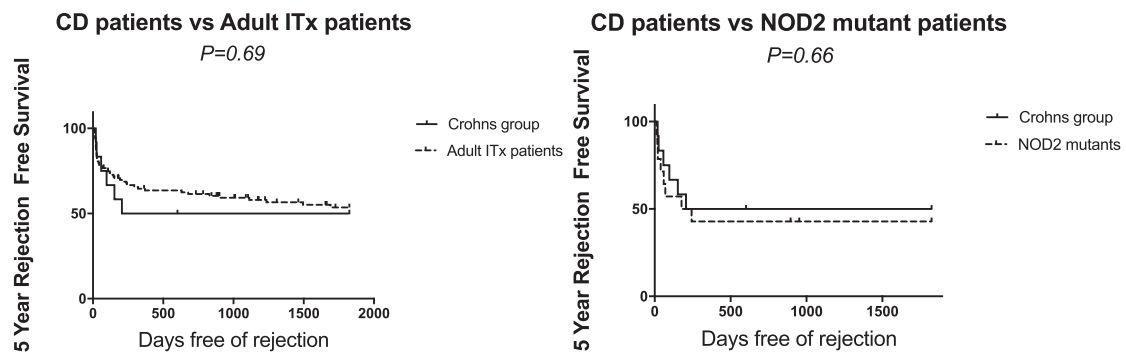


FIGURE 2. Rates of freedom from rejection in patients with Crohn's disease (CD) as compared with adult control patients (left) and nucleotide-binding oligomerization domain 2 (NOD2)-mutant adult patients (right) for 5 y from transplantation. Note while in the main adult cohort, the rate of rejection continues to increase over time, in our NOD2 mutant vs CD cohort, the patients were much more likely to experience at least one early episode of acute rejection. ITx, intestinal transplant.

Rejection was common with a rate of 69.2% for NOD2 mutants versus 58.3% for CD patients ($P = 0.57$), with similar median numbers of rejection episodes (2 versus 3; $P = 0.18$; Table 5). In our cohort 42.9% of NOD2 mutant patients and 50% of CD patients experienced grade 3 rejection ($P = 0.72$). Chronic rejection and explantation were rare in both groups. One-year freedom from rejection was 48.9%, with all instances of rejection occurring within the first year for the NOD2 mutant cohort. Graft survival was 85%, 57.14%, 57.14% for 1, 3, and 5 years, respectively, in NOD2 mutants versus 75%, 41.6%, and 33% for CD cohort ($P = 0.52$, $P = 0.58$, $P = 0.41$ respectively).

DISCUSSION

Intestinal failure is a chronic disease fraught with a wide variety of complications,^{16,17} leading to significant morbidity and frequently loss of life. When it becomes impossible to reestablish enteral autonomy either through intensive intestinal rehabilitation¹⁸ or surgical lengthening,¹⁹ PN remains the only way of survival. While the vast majority of CD patients never progress to intestinal failure²⁰ and PN dependence, those who do will frequently over time develop complications necessitating discussion of transplantation. Despite having a higher rate of rejection and complications as compared with other solid

TABLE 4.**Perioperative characteristics and demographics for the adult NOD2 mutant cohorts**

	NOD2 mutants (n = 13)	CD patients (n = 12)	P
Recipient gender (M/F)	8/6	9/3	0.34
Primary pathology			
Short gut	7	12	
Motility/malabsorption	4		
Neoplasia	2		
Other	0		
Retransplant			
Isolated intestinal graft without liver	11	10	0.7587
Multivisceral transplant	3	2	
Surgery case time	7:54 (H:M)	7:09 (H:M)	0.6
Donor/recipient age ratio	0.52 (mean)	0.47 (mean)	0.63
Donor/recipient weight ratio	0.79 (mean)	0.72 (mean)	0.37
Recipient NOD2 status			0.2881
Wild type	0	1	
Mutant	13	11	
Induction method			0.5368
Thymoglobulin	6	5	
Simulect	8	7	
Follow up (d)	1638 (mean)	1451 (mean)	0.68

Statistical significance assessed by χ^2 testing.

CD, Crohn's disease; NOD2, nucleotide-binding oligomerization domain 2.

organ transplants, intestinal transplantation remains a lifesaving operation for these patients.

Previous studies of intestinal transplantation in CD have been relatively small in scale. Desai et al¹⁰ highlighted outcomes of patients with CD from the United Network for Organ Sharing registry from 1987 to 2009, reporting rates of patient and graft survival of 85%, 67%, 54% and 85%, 55%, 45% for patients and grafts at 1, 3, and 5 years respectively. The differences in outcomes reported in this study could be related to a smaller sample size in our cohort, as well as the natural tendency of having more challenging cases as a larger tertiary referral center. Similar to their observation of gradual improvement in outcomes over time, we have also noted improvements in outcomes due to changes to induction and immunosuppression strategies over the last decade, as again rejection and sepsis remain the most common causes of morbidity and patient mortality. Limketkai et al²¹ performed a

similar retrospective review, and their reported rates of rejection at 1 year was 36.9% versus 33.3% for CD patients versus controls. Risk of death was 50.3% and 59.7% at 5 and 10 years posttransplantation.²¹

The role of NOD2 mutations as a predictor of clinical course in nontransplant CD patients has been debated, as previous reports of associations between mutations and clinical phenotype^{22,23} have not been successfully replicated in all patient groups.²⁴ The worse outcomes observed in our cohorts as compared with NOD2 wild-type adults could be the result of several factors. The primary complications hampering intestinal transplant outcomes are either infectious or immunologic,⁶ and NOD2 is an intracellular microbial sensor that is integral to barrier function.

The function of NOD2 occurs through recognition of bacterial peptidoglycan conserved motifs in the cytosol, allowing it to recruit a targeted immune response through nuclear factor - kappa beta and mitogen activated protein kinase signaling.²⁵ Its expression is found on multiple cell types including lymphocytes, antigen presenting cells, as well as Paneth cells and enterocytes. A lack of such response can lead to changes in microbiota toward more pathogenic bacteria that otherwise would have been culled into smaller populations. NOD2 mutation also leads to reduced expression of specific antimicrobial peptides, namely the human defensin 5 and human beta defensin defensins by Paneth cells, which creates a larger opportunity for microbial penetration of the mucosal barrier. This primes those deficient in NOD2 expression, regardless of CD status as susceptible to both septic and immunologic complications.

Our group previously demonstrated this phenomenon in our intestinal transplant cohort along with the substantial risk of rejection linked to NOD2 polymorphism.¹⁵ This study, however, expands on this critical connection by separating NOD2 mutation recipients into both CD and non-CD groups. Comparing these 2 groups has not been previously studied, and further supports that barrier integrity as mediated by NOD2 is essential for graft protection from microbes and survival posttransplantation, regardless of underlying clinical phenotype. This is in line with evolving research in CD targeting the microbiome and barrier homeostasis as a key pillar of pathogenesis and disease propagation.²⁶

One promising area of future research for improving clinical outcomes of these cohorts is the application of CD-related therapies in the treatment of both CD and non-CD intestinal

TABLE 5.**Rejection characteristics of adult NOD2 mutant patient cohorts vs CD**

	NOD2 mutants (n = 13)	CD patients (n = 12)	P
Number of Bx	31.25 ± 7.6	37.58 ± 17	0.25
Overall rejection (% of total population)	9 (69.23%)	7 (58.3%)	0.5706
Median number of rejection episodes	2	3	0.18
Grade 1	3	8	0.17
Grade 2	6	0	0.02
Grade 3	7	10	0.33
Time to first rejection from transplant (d)	356 ± 832 (mean)	271 ± 474 (mean)	0.68
Duration of rejection (d)	46 ± 38.5 (mean)	28 ± 13.2 (mean)	0.84
Development of chronic rejection	2 (15.38%)	2 (16.67%)	0.9304
Explantation	1 (7.69%)	3 (25%)	0.2383

Overall rejection entailed the rate of rejection in that cohort as a percent of the total group. Grade 1–3 categories denote number of episodes total in the cohort, not averaged per patient. Bx, biopsy; CD, Crohn's disease; NOD2, nucleotide-binding oligomerization domain 2.

transplant recipients experiencing severe cellular rejection. Anti tumor necrosis factor- α therapies have been used in the treatment of CD for almost 2 decades²⁷⁻²⁹ and have been previously used as a rescue therapy for intestinal transplant rejection.³⁰ This is thought to be mediated by T lymphocyte apoptosis,²⁷ although the mechanism for their efficacy remains not fully elucidated. Our center has observed a high response rate to biologic treatment for severe cellular rejection, and given the bio similarities between CD and non-CD NOD2 mutants, future studies of effectiveness in this cohort may improve clinical treatment.

The main limitations of our study relate to underpowered sample size, as well as the retrospective nature of the study. At our center, we plan to address these challenges by continuing to expand our intestinal failure program and prospectively monitoring our CD patients if and when they transition to becoming transplant recipients.

Immunologic complications remain a significant burden of disease in the CD transplant population when compared with non-CD adult recipients. We also identify a novel sub-cohort of non-CD NOD2 mutant recipient patients as another group at high risk for immunologic complications. The early and severe nature of acute cellular rejection in our patients shows the importance of constant vigilance on the part of the transplant team. Our center routinely genotypes recipients for NOD2 status as an additional data point in prognosis and postoperative multidisciplinary monitoring. Further patient outcome improvement in this cohort of high-risk patient rests on implementing better treatments for intestinal rejection, including novel biologic targeted therapy and research in augmenting intestinal barrier integrity.

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