De novo IBD after solid organ transplant: Case series and risk factor analysis

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ABSTRACT:

Background: Diarrhea is a frequent complication of solid organ transplant (SOT) with significant morbidity. Potential causes include infections and medications, but there is increasing recognition of de novo inflammatory bowel disease (IBD) as a cause in this population. The aim of this study was to evaluate the incidence of de novo IBD in SOT recipients and identify any potential risk factors for its development.

Methods: We conducted a retrospective, single center study of all patients receiving a solid organ transplant between 1988 and 2007. A diagnosis of de novo IBD was made based on clinical symptoms, exclusion of all other causes, and endoscopic and histologic criteria. Risk factor analysis was performed using a case-control design for liver transplant recipients.

Results: During this time period 23 cases of de novo IBD were identified among 6270 transplant recipients: liver (16), kidney (5), lung (1) and pancreas (1). Of the 16 liver transplants, 8 were performed for PSC or AIH. De novo IBD type was UC in 12, Crohn's disease in 9 and indeterminate in 2.The mean lag time between transplant and IBD diagnosis was 63.7 (10.4-240.5) months. The annual incidence for this cohort was 18.5 per 100,000. Among liver recipients, the annual incidence was much higher at 100 per 100,000 vs. 5.8 per 100,000 in the non-liver organ recipients. Neither CMV mismatch OR 1.55 (0.43-5.58), acute CMV infection OR 0.87 (0.25-3.07) nor tacrolimus exposure OR 5.26(0.55-50.022) could be confirmed as modifiable risk factors for developing IBD. Novel risk factors of personal or family history of autoimmunity, lymphopenia, and rejection episodes were not statistically significant.

Conclusion: De novo IBD occurs in liver transplant recipients at a rate 5x higher than the general population and over 17x higher than other SOT recipients. Previously identified risk factors could not be confirmed. Since patients diagnosed with de novo IBD require additional medications beyond their transplant immunosuppression for treatment, recognition of this entity has important clinical implications.

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INTRODUCTION:

Gastrointestinal (GI) complications occur in up to 50% of solid-organ transplant recipients with diarrhea being one of the most common. Diarrhea is most often caused by infections, medication effects (direct and indirect), immune mediated, and malignant etiologies. Idiopathic inflammatory bowel disease (IBD) has also been reported as a significant cause of diarrhea in this population, arising at a higher rate than in the general population. IBD arises in the background of immunosuppression in solid organ transplant (SOT) recipients and can be a source of significant morbidity and even mortality when not recognized in a timely manner. This may seem counterintuitive when considering that the majority of current therapies for IBD are immunosuppressive. In this thesis, I will review the causes of diarrhea in transplant recipients, summarize the available literature on de novo IBD arising in SOT recipients and describe the cases of and analyze risk factors for de novo IBD arising in the University of Minnesota transplant population over a 20year time period.

1.1 DIARRHEA IN THE TRANSPLANT PATIENT

Gastrointestinal (GI) complications in SOT recipients range from nausea to diarrhea to GI bleeding and even colonic perforation (1). Among these, diarrhea is a common and serious source of morbidity in patients who have received a solid organ transplant, occurring in >70% of this population (2). Diarrhea can occur as a single acute episode or a chronic persistent or recurrent process. Acute Diarrhea can be defined as increased fluidity of the stool or 3 or more stools per day. Chronic diarrhea is defined as liquid stools for more than one month and may affect 5-14% of the transplant population any given year. Diarrhea has been reported in all major solid organ transplant groups, ranging from 29.4% in lung to 39.8% in liver to 51.5% in kidney and 58.6% in heart

transplant recipients (1) (3) (4). Approximately 2/3 of diarrhea occurs > 6months after solid organ transplant.

GI complications have an impact on care in regards to patient and graft survival, cost, hospitalizations, patient nutrition and potential for failure of other organs. The differential for diarrhea is broad in this patient population due to their multiple medications, prolonged hospitalizations, immune dysregulation, and propensity for post-transplant malignancy. Even after a thorough work-up for the etiology of diarrhea (e.g. exclusion of infection, medication side effects), up to 1/3 of chronic diarrhea cases in these patients remains unexplained

1.2 REVIEW OF POTENTIAL ETIOLOGIES FOR DIARRHEA AFTER TRANSPLANT

Infections play a major role in post-transplant diarrhea and can be viral, bacterial parasitic, or fungal in nature. The most common virus seen is cytomegalovirus (CMV), however rotavirus is one of the most common diarrheal causes worldwide and can affect this group as well. CMV infects 21-85% of orthotopic liver transplant (OLT) recipients and causes end organ disease in 7.5-40%, though it only affects the GI tract in 1-2% of cases (5). CMV infection usually occurs within the first 2-4 months after transplantation but can recur in 25-30%. Risk factors for CMV infection include CMV mismatch, use of calcineurin inhibitors, which impairs the cell mediated anti-CMV response, use of OKT3 and age at time of solid organ transplantation (> 55yo) (6).

The major bacterial etiologies of diarrhea in the transplant patient are *C difficile, Campylobacter jejuni, Salmonella species and Listeria monocytogenes*. *C difficile* has been a ubiquitous problem in the last decade, with *C difficile* associated diarrhea (CDAD) being described frequently in both solid organ transplantation (SOT) and bone marrow transplantation (BMT) populations. The incidence in the SOT population is 3% in liver, 5.5% in kidney and kidney-pancreas and 9% in intestinal transplant recipients. This is low when compared to the BMT population with an incidence of 12-13% (7). As in other populations, the incidence in the transplant population has increased from 1.1% in 1996-2001 to 5.8% in 2005with a reported mortality of 2.3%. Incidence varies by transplant

type with liver transplant patients most commonly infected, followed by pancreas, lung, heart and kidney. Timing is also of interest with 65% of these episodes occurring during the initial post-transplantation hospitalization (8).

Cryptosporidium and giardia are the most common fungal and parasitic etiologies respectively; however strongyloides, cryptococcus, aspergillus and candida have been reported.

The immunosuppression used to prevent rejection or even to treat acute rejection episodes can play a role in the etiology of diarrhea. The use of immunosuppressive medications can lead to infection, mucosal injury, biliary tract disease, pancreatitis and malignancy. Mycophenolate mofetil (MMF) is the most implicated, though diarrhea has also been reported with cyclosporine, tacrolimus and sirolimus. MMF selectively suppresses T- and B-lymphocytes and causes diarrhea in 14-51% of OLT patients, leading to medication discontinuation in 10%. There is a possible dose dependent effect of this drug on symptoms, but not on histologic changes (9) Histology of the GI tract with MMF toxicity may resemble an infectious enterocolitis, Graft vs. Host Disease (GVHD) or even IBD. Suggested mechanisms include direct anti-proliferative effects on the epithelium, antimicrobial effects on bowel flora and exacerbation of an underlying IBD.

Beyond infection and medication side effects, less common etiologies for diarrhea in the SOT recipient include GVHD, post-transplantation lymphoproliferative disease (PTLD), colon cancer, non-specific transplant associated changes and changes in T-regulatory cell function.

GVHD can occur when cellular blood products and solid organs for transplant contain immunologically competent cells, leading to an onset of symptoms within 2-6 weeks of transplant. Symptoms and signs include fever, rash, pancytopenia and diarrhea which can be difficult to distinguish from CMV or MMF toxicity (10) Mortality is high (30% or more) as is reported in two cases series of GVHD in SOT which included recipients of livers, lungs, hearts, kidneys, pancreas, and small bowel (10) (11).

PTLD is a lymphoid malignancy associated with chronic immunosuppression and EBV, complicating 3% of adult and 10% of pediatric liver transplants. The GI tract is involved in 25-30% of PTLD patients leading to symptoms of diarrhea, anemia, protein

losing enteropathy, abdominal pain, and even GI bleeding (12) (13). This can occur anytime and with any organ, but has a higher incidence within the first year post transplant and with heavier immunosuppression.

Colon cancer risk is increased in the transplant population, especially if the OLT was for primary sclerosing cholangitis (PSC). Colon cancer is sometimes a cause of diarrhea and should be considered if no recent screening has been performed. Diagnosis of colon cancer in the SOT patient is often made at an earlier age and the survival rates are lower (14) (15).

The relative frequency of potential causes of diarrhea in transplant patients can be found in **Table 1**.

Table 1: Common causes of diarrhea in transplant patients. Adapted from Ginsburg et al. (6)

Tier 1	CMV, *C difficile*, MMF toxicity
Tier 2	Calcineurin inhibitor toxicity
Tier 3	IBD
Tier 4	PTLD, colon cancer, GVHD, lactose intolerance, celiac sprue, SIBO and other infections (*campylobacter, adenovirus, astrovirus, rotavirus, salmonella, microsporidia, cryptosporidia, shigella, amoebiasis)*

2.1 IBD AS A CAUSE OF DIARRHEA AFTER TRANSPLANT

Up to 1/3 of chronic diarrhea cases in these patients remains unexplained, even after a thorough work-up for the etiology of diarrhea (e.g. exclusion of infection, medication side effects). In many of these unexplained cases, inflammatory bowel disease (IBD) may be the etiology. IBD is an idiopathic relapsing and remitting condition of the gastrointestinal tract caused by a combination of genetic, environmental and immunologic factors. Consideration of IBD as an etiology in a subset of patients with

unexplained, chronic diarrhea is important because therapy for IBD differs from any other therapy usually employed in treatment of diarrhea in the transplant patient.

Even when this diagnosis is pursued, making a definitive histologic diagnosis of IBD may be challenging in this population due to the effects of immunosuppression (17). As previously mentioned, enteric changes with use of MMF can mimic IBD. Endoscopically apparent changes may include erythema, erosion, ulceration and congestion with histology showing a chronic active colitis and/or enteritis picture. Even in normal appearing mucosa in transplant patients, the histology may still be abnormal and suggest altered immune function. One example is a decrease in mucosal Foxp3 mRNA, a sign of T-regulatory cell deficiency, which was seen in a study of asymptomatic SOT recipients on prednisone, azathioprine and calcineurin inhibitors (tacrolimus) (16). T-regulatory cells are natural suppressors of autoimmunity and have also been found to be deficient in IBD patients suggesting some connection between these findings.

2.2 EPIDEMIOLOGY & LITERATURE REVIEW OF IBD AFTER TRANSPLANT

IBD after transplant should be divided into pre-existing IBD and de novo IBD, which is initially diagnosed after transplant. The incidence of IBD in the general population ranges from 3-20 per 100,000 per year and prevalence ranges from 26 to 246 per 100, 000 persons in the US, currently thought to affect 1.4 million individuals (16). The prevalence is higher in patients with primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH), common indications for liver transplant. The reported risk for de novo IBD development after transplant in this particular group is also high, ranging from 0-5% the first year, 10% at 5 years and up to 20% at 10 years (17). De novo IBD after transplantation is not limited to liver transplant recipients but has been reported in other solid organ (e.g. kidney, heart) and bone marrow recipients whose pre-transplant disease did not carry an increased risk for IBD (18).

The reported prevalence of IBD in transplant recipients ranges from 0.2-10% (18). However, most series were small and focused primarily on liver transplant recipients. The largest of these studies included multiple transplant types and found that 14 of 6800 subjects developed de novo IBD over a 4-year period after transplant. From this, the investigators computed an incidence of 206 per 100,000 per year, or 10 times the upper limit of the general population (19).

A review of the current literature to date yields a total of 74 reported cases of de novo IBD among 7555 transplants that were reviewed (17,19,20,21,22,23,25,27,30-49). Of these cases, 58 were in liver transplant patients, 10 were in kidney, 5 in heart and 1 in BMT. Over 65% of cases after liver transplant occurred when the indication for transplant was PSC or autoimmune hepatitis (AIH). The de novo IBD cases were labeled as ulcerative colitis (UC) in 49 patients, Crohn's disease (CD) in 18 patients and indeterminate colitis in 7 patients. See **Table 2** for full details.

Table 2: De novo IBD after transplant cases reported in the literature

KEY: NA= not available, PSC=primary sclerosing cholangitis, AIH= autoimmune hepatitis, PBC= primary bilary cirrhosis, NANBNC= non hepatitis A, B or C hepatitis, HBV=Hepatitis B, EtOH= alcoholic liver diseasetac=tacrolimus, CsA= cyclosporine, AZA=azathioprine, MMF= mycophenylate mofetil, CS=corticosteroids, rapa=sirolimus, OKT3= antirejection drug, pred=prednisone,. Mes=mesalamine, metro=metronidazole, cipro= ciprofloxacin, budes=budesonide. Abx= antibiotics IFX= infliximab

Author	Year	Total	Age	Gender	Organ	Disease	IBD type	Lag time (yrs)	Transplant Medications	IBD Medications
Riley TR	1997	14	22-68	female(8)/male (6)	liver(12)/kidney (2)	PSC(2)/AIH(4);other(8)	UC(9);CD(6)	4	10 tac,pred; 4 CsAPred	mes, pred, colectomy (2)
VerdonkRC	2006	8	NA	NA	liver(8)	PSC(5)/AIH(3)	UC(7)/IC(1)	5.2	tacrolimus	mes,pred,aza
Haagsma EB	2003	6	various	NA	liver(6)	PSC(3)/AIH(3)	UC (3)/IC(2)/CD	3.9	5 tac,AZA; 1 CsA+CS	NA
Woerns M	2006	5	16-64	female(4)/male(1)	liver(5)	AIH(2)/crypto(1)/other(2)	UC (4)/IC(1)	0.17-7.5	tac,pred, CsA, MMF, rapa	pred,mes
Vu,F	2006	4	NA	NA	liver(4)	Hep C(2)/EtOH/AIH	UC(3)/CD	NA	CsA	NA
Shaked A	1992	3	NA	NA	liver(3)	PSC(3)	UC(3)	1to3	independent of type	NA
Papatheodoris GV	1998	3	NA	female(3)	liver(3)	PSC(3)	UC(3)	0.75-3.75	independent of type	pred or none
Khan S	1999	3	NA	NA	liver(3)	PSC(2)/AIH	UC(3)	0.5-5	FK506; CsA,Aza,CS; fk506,mmf,CS	NA
Wahbeh G	2003	3	NA	NA	heart(3)	NA	IC(3)	0.42-3	Tac,mmf,aza,cs; csa,aza,cs	NA
Barritt AS	2008	3	46-60	male(2)/female	liver(3)	AIH/PSC/PBC	CD(2)/UC	1.17	tac,mmf,pred; csa,mmf; tac/sirolimus	mes 4g,prednisone,budes
Chalasani N	1998	2	NA	NA	liver(2)	PSC(2)	UC(2)	NA	CsA,AZA,CS; fk506, CS	NA
Ramji A	2002	2	50-52	female/male	liver(2)	PBC/HBV	CD(2)	1.58-3.25	CsA,AZA; tac, AZA	mes
Passfall J	1992	1	NA	NA	kidney	??	UC	6	CsA +AZA	pred
Cuoco L	1997	1	29	female	liver	EBV	UC	8	Csa;pred	NA
Befeler AS	1998	1	NA	NA	liver	PSC	UC	NA	NA	NA
Teo M	2002	1	NA	NA	kidney	?	UC	NA	CsA +AZA	NA
van de Vrie W	2003	1	NA	NA	liver	PSC	UC	NA	independent of type	NA
Papadakis KA	2004	1	NA	NA	liver	HCV	CD	0.92	FK506 + Rapamune	NA
Harms B	2004	1	NA	NA	heart	NA	CD	10	CsA +AZA	NA
Juengling B	2005	1	53	male	heart	chf	UC	2	CsA, pred, AZA	prednisolone
Forman R	2006	1	54	male	kidney	interstitial nephritis	CD	3	pred,tacrolimus	pred,mes,abx
Halim MA	2007	1	40	male	kidney	Glomerulonephritis	CD	3	I:Pred,MMF,basiliximab; M: CsA; Tac	pred,mes, metro,cipro
Hamptom DD	2008	1	39	female	liver	AIH	CD	2	CSA,Pred;MMF,Tac	pred,cipro
Halim MA	2008	1	39	male	kidney	Glomerulonephritis	CD	0.75	Pred,MMF,tac--> siro for tac	pred,asa,metro,cipro
Dehghani SM	2009	1	13	male	liver	NANBNC	UC	0.42	tac,mmf	pred,mesalamine
Parameswaran,s	2011	1	46	female	kidney	unknown	UC	9.00	CsA, AZA, Pred	mesalamine

2.3 HYPOTHESES FOR IBD DEVELOPMENT

Hypotheses surrounding the link between transplant and development of de novo IBD include the following: (1) immunosuppressive drugs cause an imbalance in the mucosal immune system; (2) a predisposition to opportunistic infection triggers IBD; (3) B-cells and T-cells from the transplanted organ alter immunity; (4)transplantation accelerates the natural history for patients with an autoimmunity background.

Potent immunosuppressants, such as cyclosporine and tacrolimus, have been associated with a higher incidence of de novo IBD after transplantation, as well as a more aggressive course for those with known IBD before transplantation. These calcineurin inhibitors reduce the number of regulatory T-cells by inhibiting IL-2 production by T-cells, thus altering the balance of T-helper and T-suppressor cells (25).This imbalance is also thought to be an important etiologic factor in IBD (20). In a study of 6 cases of de novo IBD by Verdonk et al, IBD was more likely to develop in those receiving immunosuppression regimens containing tacrolimus and less likely in those containing azathioprine. Interestingly, this held true even when azathioprine was used in combination with cyclosporine (17) (21).

CMV is the most reported post-transplant infection that has been associated with de novo IBD after SOT, both in case reports and formal risk factory analyses. One group of investigators found that de novo IBD was more likely to occur in those transplant patients who had experienced a CMV infection or who had a CMV mismatch between donor and recipient (22). Caution must be taken in relying on CMV DNA PCR alone as compartmentalization of the CMV infection in the gastrointestinal tract can occur (5).

There is circumstantial evidence to suggest that the liver or the immune cells in it may play a role in determining IBD susceptibility in SOT recipients, as well as in stem cell transplanted patients. The majority of de novo IBD cases reported have been in liver recipients. In one recipient who received a living related liver donation from a donor with Crohn's disease, they subsequently developed de novo Crohn's disease after transplantation (42). Other studies suggest that the cellular dysfunction is likely outside the end organ and liver. This is exemplified by a report of recurrence of IBD after stem

cell transplantation and the high frequency of recurrence in small bowel transplant. (50, 51)

It has been suggested that pan-immunosuppression such as is used in organ transplant can reveal underlying autoimmunity tendencies (46). This tendency towards autoimmunity may explain why the majority of de novo IBD after transplant is seen in those receiving a liver due to PSC or autoimmune hepatitis. The exact immune dysregulation remains to be defined. Some posit that despite tolerance to the transplanted graft, which is achieved through immunosuppression, some patients may still not tolerate self or intestinal luminal antigens (23) (24). Lymphopenia is common during the induction phase after SOT, however lymphopenia can also be a trigger to autoimmunity. While most people experience some lymphopenia during their lifetime with normal recovery, impairment of the regulatory T-cell function through immunosuppression (i.e. calcineurin inhibitors) may lead to suboptimal reconstitution of the T cells and immunologic tolerance (52). Given this finding, I will also evaluate the risk factors of personal or family history of autoimmunity, prolonged lymphopenia in the immediate post-transplant period and episodes of rejection requiring additional immunosuppression beyond corticosteroids.

3. SPECIFIC AIMS

Hypothesis 1: There is a greater incidence of IBD after transplant as compared to the general population.

Hypothesis 2: When controlling for organ and indication for transplantation, there will be significant modifiable risk factors such as CMV mismatch/acute infections, immune suppressive medications used and early lymphopenia that may predict incidence of de novo IBD after transplant.

4. METHODS AND MATERIALS

This is a retrospective, single center study and review of the literature to examine the incidence of and risk factors for de novo IBD. The initial part of this study was a retrospective cohort study of solid organ transplant recipients, examining qualitatively the diagnosis of inflammatory bowel disease after transplant. The second portion of this study was a case-control study of only the liver transplant recipients with risk factor analysis in regards to development of de novo IBD after transplant.

Cases were identified from the University of Minnesota transplant registry, a complete record of all solid organ transplants performed at the university starting in 1988. The registry was queried for colitis, enteritis, regional enteritis, Crohn's disease, ulcerative colitis. Potential cases of IBD were ultimately confirmed by chart review. Data sources included Electronic Transplant Databases, OPTN (a de identified center report), various EMRs, OTTR, Provation (an endoscopic database) and paper shadow charts with associated outside hospital records. Data from identified cases were entered into a case report form assigned a unique study number and the key to this data was maintained separately. This study was approved by the University of Minnesota Institutional Review Board.

Inclusion criteria included all patients receiving a solid organ transplant at the University of Minnesota between 1988 and 2007. The diagnosis of IBD was based on endoscopic, histologic and/or radiologic criteria for IBD. Infection had to have been excluded and/or treated with proof of eradication. Mention of IBD and treatment plan had to be mentioned in subsequent clinical encounters.

Patients were excluded if they had a diagnosis of IBD prior to transplant, a history of colectomy, history of small bowel transplant or death within one year of transplant. Pre-transplant colonoscopy and pathology data was examined where available.

Definition of the severity of IBD at onset was based on elements of the UCDAI for ulcerative colitis and Harvey Bradshaw Index for Crohn's disease. Progression of disease was based on escalation of medications and frequent need for steroids, not related to rejection episodes. These data were abstracted from the medical chart and medication lists.

ANALYSIS

Incidence was calculated based on person-years at risk collectively. Incidence was calculated both per organ transplanted and per organ recipient as some had experienced organ rejection and underwent repeat transplants. Those with known IBD prior to transplant were excluded from the denominator in calculating the incidence.

Only liver transplant recipients' data were used for risk factor analysis due the majority of cases of de novo IBD in the literature being found in liver transplants. This approach also served to keep a homogenous population and transplant practice for comparison. For de novo IBD in liver transplant recipients, a 2:1 matched case control analysis was performed. Cases and controls were matched based on age, sex, pre-transplant disease and year of transplant (at least 3 of 4). Controls were initially identified from the same transplant registry used to identify cases.

Descriptive statistics were performed using MS Excel, 2003.

Risk factor analysis was performed using multivariate analysis, SAS version 9.2, North Carolina.

5. RESULTS

5.1 DESCRIPTIVE STATISTICS

The estimated number of transplants performed at the University of Minnesota between 1988 and 2007 was 7390 transplanted organs, 6270 of which were primary. Of the abdominal organs, 3701 were kidney, 1102 were pancreas, 633 were kidney-pancreas, 18 were small intestine and 850 were liver transplants. Of the liver transplants, 76 were for PSC (50 had identified IBD, 26 had no IBD), 23 for autoimmune hepatitis (AIH) and 22 for cryptogenic etiologies. The other liver transplants were for viral hepatitis, alcohol and other causes. Of the thoracic organs, 560 were lung, 483 were heart, and 43 were heart-lung transplants.

During this time period 23 cases of de novo IBD were identified: 16 in liver, 5 in kidney, 1 in lung and 1 in pancreas transplant recipients. Sixty five percent of recipients

were female with a mean age of 34.3 at transplant. Thirteen percent had undergone multiple transplants. Of those receiving livers, 3 were for PSC and 5 for autoimmune hepatitis. The other etiologies for remaining transplants are listed in **Table 3**.

Across all primary transplanted organ recipients, an incidence of 18.5 per 100,000 per year and a prevalence of 370 per 100,000 can be calculated for this cohort. If calculated per organ transplanted the annual incidence is 15.7 per 100,000 and prevalence is 313 per 100,000. Dividing the entire time period into 5 year time periods, the numbers of cases are equally distributed (5-6 per period). By dividing this into organ groups, the annual incidence among liver recipients is 100 per 100,000 vs. 5.8 per 100,000 in the non-liver organ recipients. When liver recipients were further subdivided by etiology of liver disease into a PSC+AIH group vs. non-PSC/AIH group, the incidences of de novo IBD were similar.

The mean lag time between organ transplantation and onset of de novo IBD was 63.7(10.4 -240.5) months. The inflammatory bowel disease was labeled ulcerative colitis (UC) in 12 patients, Crohn's disease in 9 and indeterminate in 2. The mean follow-up time after the diagnosis of de novo IBD was 106(16.6-251) months. The prevalence of previously reported risk factors for de novo IBD in this cohort included CMV infection in 32% and CMV mismatch in 39%, while tacrolimus was part of 55% of transplant immunosuppression regimens. An autoimmune etiology for transplant was present in 48%. The prevalence of novel risk factors studied were lymphopenia in 62% for an average of 2.8 days, an episode of rejection in 39% and a family history of IBD or autoimmune disease in 4% and 26% of cases respectively. See **Table 4**.

Of note only 5 of 23 cases had confirmed, normal colonoscopies with biopsies prior to their initial or subsequent organ transplants.

Table 3: De novo IBD case series demographics	
% female	65
mean age in years at transplant(range)	34.3
mean age in years at IBD diagnosis(range)	39.5
Organ transplanted	
liver	15/23
kidney	5/23
pancreas	1/23
lung	1/23
combined liver/kidney	1/23
% with repeat organ transplant	13
Etiology of organ transplant	
PSC	3
AIH	5
EtOH +/- HCV	2
Bilary atresia	2
pyleonephritis	2
other liver (AHN, Alpha 1 antitrypsin)	2
other (other organs): cystic fibrosis, PCKD, DM I, DM II, IgA nephropathy	7

Table 4: IBD characteristics and transplant related Risk factors	
% Ulcerative Colitis	61
Mean lag between 1st Transplant and IBD diagnosis (months)	63.7(10.4-240.5)
Mean follow-up after IBD (months)	106(16.6-251)
% with documented CMV infection (80% pre IBD diagnosis)	32
% with documented rejection episodes (5/7 pre IBD diagnosis)	39
% with post-op lymphopenia/mean duration	62%/2.93days
% undergoing transplant for an autoimmune disease	48
% with family history of IBD/other autoimmune disease	4%/26%
Transplant regimen containing azathioprine	65%
Transplant regimen containing MMF	54%
Transplant regimen containing Cyclosporine A	59%
Transplant regimen containing tacrolimus	55%

5.2 RISK FACTOR ANALYSIS AMONG LIVER TRANSPLANTS

In case-control analysis of the liver transplant recipients, matched in a 2:1 manner for gender, age, year of transplant and etiology of liver disease (where possible), known and novel risk factors were examined. Risk factors including immunosuppressant type, rejection episodes, CMV status, autoimmune disease other than their transplant etiology and family history of IBD or autoimmune disease were evaluated.

The previously reported risk factors of CMV mismatch OR 1.55 (0.43-5.58), acute CMV infection OR 0.87 (0.25-3.07) and tacrolimus exposure OR 5.26 (0.55-50.022) were not found to be statistically significant. Some other factors trended toward being significant for an increased risk including use of azathioprine and a personal or family history of autoimmunity. See **Table 5**.

Of note, lymphopenia was noted in 62.5% of cases for an average of 2.7 days (0-7) vs. 53% of controls for an average of 3.3 days.

Table 5: Risk factors analysis for de novo IBD after transplant

Risk factor	**Odds Ratio (95% CI)**
Azathioprine	8.34 (0.98-71.0)
MMF	0.61 (0.15-2.42)
Cyclosporine	1.00 (0.13-8.00)
Tacrolimus	5.26 (0.55-50.022)
Rejection episode	non-estimable
Lymphopenia	non-estimable
CMV infection in recipient	0.87 (0.25-3.07)
CMV mismatch	1.55 (0.43-5.58)
Autoimmune disease (AID)	2.10 (0.56-7.80)
Family history of AID	2.04 (0.44-9.48)
Family history of IBD	non-estimable

5.3 IBD RELATED COURSE AND TREATMENTS

In this cohort with de novo IBD, 71% of patients required IBD directed medications beyond their transplant immunosuppression. Some of these had an aggressive course of IBD, including 13.7% who required a biologic agent (a TNF antagonist) to attain remission and 22% that required a colectomy for refractory disease or development of colon cancer. The remainder requiring IBD directed therapy received a combination of mesalamine, steroids (prednisone, budesonide) and/or azathioprine.

Table 6: IBD related outcomes	
% UC	61
% UC with non-liver organ transplant	43
Mean severity of IBD at onset (scale 1→3)	1.59
% that required IBD specific medication beyond Transplant meds	71
% requiring colectomy due to IBD (disease or CRC)	22
% on IBD treatment by medication type	
mesalamine	68.2
antibiotics	9
prednisone	63.6
budesonide	45.5
azathioprine	36.4
methotrexate	0
TNF antagonist (infliximab,adalimumab)	13.7
% with positive IBD serology (7/23 tested)	31.8

*Some may be on multiple agents.

6. DISCUSSION

This series is unique in that it is the largest series of de novo IBD patients at a single transplant center reported to date. De novo IBD was found in all types of solid organ transplantation, not just liver recipients. Furthermore only one half of the de novo IBD cases in liver transplant recipients occurred in those with an autoimmune hepatitis or PSC etiology for transplant. This suggests that the development of de novo IBD is not unique to the liver or to an autoimmune etiology (PSC, AIH) for liver transplant, which comprised only 48% of the cases we report. Three other non-liver SOT recipients had concomitant autoimmune disease and in two cases the disease was associated with the failure of the organ originally (DM1, IgA nephropathy). Taken together, an underlying autoimmune disease process may have a role in development of post-transplant IBD, though it only trended towards significance in our analysis.

The overall incidence of 18.5 per 100,000 per year for de novo IBD after transplant among all solid organ recipients was similar to that reported in the general population, though at the upper end (reported 3-20/100,000 per year). This was less than the annual incidence of 206/100,000 reported by Riley et al. in their series of 14 patients with de novo IBD(21), however when looking just at the liver transplant recipients in our series, the annual incidence is 100/100,000 or 5 times the upper limits of the incidence in the general population. The annual incidence of de novo IBD in other organ groups taken as a whole was only 5.8 per 100,000 or the background incidence, suggesting that the increased risk of de novo IBD may be unique to liver transplantation.

This study did not confirm the previous reported risk factors for de novo IBD including CMV mismatch, CMV infection and a calcineurin inhibitor (tacrolimus or cyclosporine) use in immunosuppression regimen (25). One potential reason for this may lie in the case control method and the small numbers in the series. Other series have looked at the population as a whole or mixed in pre-existing and de novo IBD (25). Another potential reason is the time period of the study, during which transplantation practices in regards to immunosuppression may have changed significantly in degree of immunosuppression, agents used, role and duration of prednisone, and CMV prophylaxis. One finding that may discount this confounder is that the number of new cases per 5 year

periods was similar throughout the time of study. Also, given that there was on average a five year lag between transplant and diagnosis of de novo IBD after transplant, any changes made to transplant procedures would have a delayed effect on this outcome. Some data was missing in regards to the above risk factors and could not be found in multiple sources, thus some risk factors were not directly comparable in cases and controls.

It was hypothesized that prolonged post-transplant lymphopenia, rejection episodes and family or personal history of autoimmunity may play role. These only suggested risk, but did not reach statistical significance. Lymphopenia affected both cases and controls in a similar proportion and length of lymphopenia was short overall (average ~3 days). This period is much less than the 30days or more of lymphopenia required in animal models to induce autoimmunity. The impact of recurrent, intermittent lymphopenia over a longer post-transplant period of time in a recipient could not be assessed in this study. The numbers of patients experiencing rejection episodes was the same in the cases and controls, thus this temporary intensification in immunosuppression and/or adjustment of the regimen did not lead to increases or decreases in onset of de novo IBD. A personal history of autoimmunity can more easily be abstracted from the medical record than can family history and this risk factor trended towards a two fold increase in risk for de novo IBD after transplant, however the small numbers likely kept this was being significant. Family history, while attained for all subjects, is subject to recall bias and is often incomplete in the medical record.

Limitations to this study include the relative large numbers of PSC and AIH patients among the cases and relative paucity of pre-transplant colonoscopic screening of these higher risk individuals. The small sample size of cases and utilization of a case-control design may have limited identification of definitive risk factors for de novo IBD. While the electronic registry has been maintained since 1988, potential cases may have been missed and some reporting from outside hospitals may have been incomplete. Records of those who migrated out of this university of Minnesota's catchment area may not have been updated if they started following with a new transplant center. The chart review of those cases identified by the registry allowed for specificity but not adequate

sensitivity to detect all cases. The ability to track different doses of the immunosuppressants before and after diagnosis of de novo IBD was limited. Thus the ability to pinpoint some of the possible proximal cause and effect between onset of IBD and medications was not always possible.

The diagnosis of IBD is a clinical one that does rely on symptoms, imaging, endoscopy findings and histology. At this institution, patterns of chronic active inflammation have been described in absence of other etiology as a possible separate but related entity to IBD. It is thought to be "secondary to a persistent infection in an immunocompromised patient or caused by an abnormal immunologic dysregulation secondary to chronic immunosuppressive therapy. The latter possibility is suggested by similarities between the histologic pattern seen in these biopsies and those present with inflammatory bowel disease." (53). A group of researchers in Boston recently described "cord colitis syndrome" as a culture negative, yet antibiotic responsive diarrhea not attributable to any other cause. It was observed in over 10% their cord-blood stem-cell transplantation population (54). Histologically this entity resembles Crohn's disease, but does not require more than antibiotics for its treatment. Antibiotics are part of the armamentarium used to treat Crohn's disease, but their efficacy as a maintenance therapy or intermittent therapy in absence of immunosuppressants is low.

Within this case series, information on the course of de novo IBD was available for a mean of 106 months after diagnosis. This revealed that ~35% had an aggressive course ending in use of biologic agents or colectomy while the remaining approximately 2/3 had a mild to moderate course. A further 36% had additional or substituted immune modulation with azathioprine and 45-65% required additional steroids in the form of prednisone or budesonide. This mild to moderate course for the majority of de novo IBD after SOT is similar to what has been reported in the literature (46).

Despite this milder course, it still underscores that IBD arises in the background of immunosuppression and requires the use of additional medications to induce and maintain remission. At our institution as at others, we have found success with short term budesonide and substitution of azathioprine for other immunosuppressants (MMF or TAC) when possible (19, 36). As always, extreme caution must be exercised and

monitoring for leucopenia may need to be more frequent while dose titrating. One alternative agent that does not cause leucopenia with the frequency of other immunomodulators and anti-rejection medications are the TNF alpha inhibitors (e.g. infliximab, adalimumab, certolizumab). A recently reported case series suggested efficacy and safety without an increase in organ rejection. The series consisted of 3 transplant patients who had received livers or kidneys. The IBD flare occurred de novo in 2 and in the background of pre-existing IBD in 1, but both all responded well to the respective anti-TNF agents (26)

Further areas that need to be explored include the histological changes in de novo IBD vs. transplant recipients alone and if this can be altered through alternative immunosuppressive regimens (25). The make-up of the native flora or microbiota may prove to be an important modifiable risk factor. Studies in this area have bloomed in recent times for a number of disease processes, including inflammatory bowel disease. Standardizing prophylaxis against common infections after transplant (e.g. CMV) and decreasing the amount of some induction and maintenance immunosuppression regimens are changes already in place. As always in this population, the cost of decreasing immunosuppression can be rejection and this risk needs to be balanced carefully with the benefit of prevention of sequelae of immunosuppression. The increasing use of novel immunosuppressants, e.g. belatacept, in practice may alter the pattern of existing IBD and incidence of de novo IBD in the future, but given the mean time to development of de novo IBD being over 5 years, it is too early to tell.

In conclusion, diarrhea is a common occurrence in the post-transplant patient and a careful work-up to exclude infection, medication side effects and ultimately de novo IBD should be undertaken. Those receiving a liver transplant, especially due to disease with PSC or AIH are at highest risk for developing de novo IBD. In those listed for liver transplantation regardless of indication, colonoscopy prior to transplant should be performed with sufficient time to address subclinical IBD prior to transplant. Despite the mild to moderate course of de novo IBD after SOT, additional medications beyond the transplant immunosuppressants are often required. While some risk factors are being

addressed through changes in current practice, further modifiable risk factors have yet to be discovered and may change how we approach these patients.

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