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A Prospective Analysis of Clinical Variables, Serologic Factors and Outcome of Ileal Pouch-Anal Anastomosis in Patients with Backwash Ileitis

Evan White[*], **Gil Y Melmed**[+], **Eric A. Vasiliauskas**[+], **Marla Dubinsky**[#], **Dror Berel**[**], **Stephan R. Targan**[+], and **Phillip R. Fleshner**[*]

[*]Divisions of Colon and Rectal Surgery, Departments of Surgery, Medicine and Pediatrics, Inflammatory Bowel Disease Center, Cedars-Sinai Medical Center, Los Angeles, CA 90048

[+]Gastroenterology, Departments of Surgery, Medicine and Pediatrics, Inflammatory Bowel Disease Center, Cedars-Sinai Medical Center, Los Angeles, CA 90048

[#]Pediatric Gastroenterology, Departments of Surgery, Medicine and Pediatrics, Inflammatory Bowel Disease Center, Cedars-Sinai Medical Center, Los Angeles, CA 90048

[**]Biostatistics, Departments of Surgery, Medicine and Pediatrics, Inflammatory Bowel Disease Center, Cedars-Sinai Medical Center, Los Angeles, CA 90048

Abstract

Purpose—The outcome of ileal pouch-anal anastomosis (IPAA) in patients with backwash ileitis (BWI) is controversial. We prospectively compared the outcome of IPAA in colitis patients with BWI (BWI+) and without BWI (BWI-neg).

Methods—Consecutive colitis patients undergoing IPAA were reviewed. All patients were classified after surgery as being either BWI+ or BWI-neg. Serum drawn preoperatively was assayed for anti-Saccharomyces-cerevisiae (ASCA), anti-outer membrane porin-C (OmpC), anti-CBir1, anti-I2, and perinuclear antineutrophil cytoplasmic antibody (pANCA) using ELISA. Outcomes included acute pouchitis (antibiotic responsive), chronic pouchitis (antibiotic dependent or refractory), or *de novo* Crohn's disease (small inflammation above the pouch inlet or pouch fistula).

Results—Within 334 patients were 39 patients who were BWI+ (12%). Comparing the BWI+ and BWI-neg patients, there was a higher incidence of pancolitis (100% *vs* 74%; p=.0001), primary sclerosing cholangitis (15% *vs* 2%; p=.001) and high-level (>100 ELISA units/ml) pANCA expression (29% *vs* 9%; p=.001). After a median followup of 26 months, 53 patients

Editorial correspondence to: Phillip Fleshner, MD, 8737 Beverly Boulevard, Suite 101, Los Angeles, CA 90048. Tel (310) 289 9224. Fax (310) 289 8995. PFleshner@aol.com.

Author Contribution: White Data acquisition, data analysis
Melmed Data analysis, critical review
Vasiliauskas Critical review
Dubinsky Critical review
Dror Data analysis
Targan Critical review
Fleshner Conception and design, data acquisition, data analysis, critical review, final approval

(16%) developed acute pouchitis, 37 patients (11%) developed chronic pouchitis and 40 patients (12%) developed *de novo* Crohn's disease (CD). There was no significant difference in the incidence of acute pouchitis, chronic pouchitis or *de novo* CD between the BWI+ and BWI-neg patient groups.

Conclusion—There was a significantly higher incidence of pancolitis, primary sclerosing cholangitis, and high-level (>100 ELISA units/ml) pANCA expression in BWI+ patients versus BWI-neg patient groups. The incidence of acute pouchitis, chronic pouchitis and *de novo* CD after IPAA do not differ significantly between BWI+ and BWI-neg patients.

Keywords

Ileal pouch-anal anastomosis; backwash ileitis; serologic factors; ulcerative colitis; indeterminate colitis; inflammatory bowel disease-unclassified; pouchitis

Introduction

Abdominal colectomy and ileal pouch-anal anastomosis (IPAA) has become the standard operative approach for patients with ulcerative colitis (UC) requiring colectomy for dysplasia, cancer or medically refractory disease. Despite excellent functional results and high patient satisfaction (1,2), pouchitis remains a significant clinical problem. For example, objective measurement tools have shown that pouchitis patients have a poorer quality of life compared to patients who have not developed pouchitis (3,4)

The mucosal inflammation observed in UC usually starts in the rectum and over time extends into more proximal colonic segments, usually in a continuous fashion. UC does not typically involve other areas of the intestinal tract, although mucosal inflammation proximal to the ileocecal valve is occasionally seen and is termed backwash ileitis (BWI) (5). The association of BWI in patients undergoing IPAA and pouchitis remains controversial. Although some studies have found higher rates of pouchitis in BWI+ patients (6-8), other papers have suggested that BWI+ patients have outcomes comparable to BWI-neg patients (9-11). These conflicting results in part arise from a number of factors, including study design, small patient numbers, suboptimal patient followup and referral center bias typical of these studies.

In this prospective study, we investigated the outcome of IPAA in a longitudinally followed cohort of consecutive UC patients with BWI operated on by a single surgeon. In addition, we examined whether any clinical or serologic factors could predict outcome in patients with BWI.

Methods

Study Population

As part of a prospective study to examine clinical, serologic and genetic markers with clinical phenotypes, UC, inflammatory bowel disease unclassified (IBDU) or indeterminate colitis (IC) patients requiring colectomy for medically unresponsive disease or dysplasia over the eleven-year period ending June 2008 were studied. All research related activities

were approved by the Cedars-Sinai Medical Center Institutional Review Board (IRB # 3358). Complete mucosectomy was performed in all patients by one surgeon (PRF). In addition, all patients had a temporary diverting ileostomy constructed at the time of pouch creation.

Assessment of Clinical Characteristics

Detailed clinical profiles assessing demographic information and characteristics of the disease and its treatment were prospectively generated by one investigator (PRF) using chart review and patient interview. Although we practice in a tertiary referral center, all patients were closely followed by one investigator (PRF). Patients were seen for follow up examinations every three months for the first year after stoma closure and yearly afterwards. Only patients followed for minimum of 3 months were included in this analysis.

Demographic information assessed included patient age at surgery, gender and length of followup after surgery. Disease characteristics examined included disease duration, perianal disease, transmural disease, extraintestinal manifestations, family history of inflammatory bowel disease (IBD) and the diagnosis of UC, IBDU or IC. Extraintestinal manifestations noted before colectomy included primary sclerosing cholangitis (PSC), skin lesions (pyoderma gangrenosum, erythema nodosum), bone/joint disease (arthritis, ankylosing spondylitis, sacroileitis) or eye disease (uveitis, episcleritis) considered by the investigators and the patients' physicians to be manifestations of IBD. The diagnosis of PSC was based on clinical findings and confirmed in all cases using liver biopsy. Disease duration referred to the time interval between IBD diagnosis and the date of colectomy. Treatment characteristics tabulated included the nature of medical therapy before colectomy (steroids alone vs. the use of other immunomodulators) and indications for surgery (medically-refractory disease vs. dysplasia/cancer).

Diagnosis of Backwash Ileitis

Backwash ileitis was defined as neutrophilic inflammation in the lamina propria and/or epithelium of the distal 1 to 2 cm of the terminal ileum. Features suggestive of chronic ileitis (such as pyloric metaplasia or villous architectural distortion) were not considered within the pathologic spectrum of BWI and these cases were excluded. The macroscopic or histological evidence of acute inflammation restricted to the distal 3 cm of the extreme terminal ileum was not thought to be related to Crohn's disease (CD). Patients with ulcerations isolated to the ileocecal valve were not considered to have BWI.

Diagnosis of Ulcerative Colitis, IBDU and Indeterminate Colitis

Clinical, endoscopic and pathologic criteria were reviewed in all patients to determine if they had UC, IBDU or IC according to the Montreal Classification (12). Clinically, UC patients had no perianal disease, and endoscopic features included continuous macroscopic disease extending varying distances from the dentate line. Radiologic evaluation revealed the distinct absence of either a colonic stricture or small-bowel disease 3 cm proximal to the ileocecal valve. Histologic patterns of continuous microscopic inflammation and the absence of noncaseating granulomas were mandatory to rule out CD. Additionally, these features were also identified after review of intraoperative findings and pathologic evaluation of the

resected specimen. Patients were classified as having IBDU when they had *preoperative* clinical, endoscopic or pathologic criteria of UC with some features suggestive but not diagnostic of CD. Preoperative features included discontinuous inflammation possibly related to medical therapy, history of an anal fistula or ulcer which was inactive at the time of surgery, noncaseating granulomas thought to be related to crypt rupture, or small bowel inflammation not involving the terminal ileum. Patients were classified as having IC when they had *postoperative* clinical, endoscopic or pathologic criteria of UC with some features suggestive but not diagnostic of CD. Postoperative pathologic features of IC included gross or microscopic transmural colonic inflammation or discontinuous histopathologic involvement of the colon possible related to medical therapy, history of an anal fistula or ulcer which was inactive at the time of surgery, noncaseating granulomas thought to be related to crypt rupture, or small bowel inflammation not involving the terminal ileum. According to these criteria, all patients were classified before surgery as having either UC or IBDU. Immediately after histopathologic evaluation of the resected specimen, all patients were then reclassified as having either UC or IC. Patients with granulomatous inflammation on histopathologic examination not thought to be related to a ruptured crypt were deemed to have CD and were excluded from study analysis.

Diagnosis of Pouchitis and Crohn's Disease

Pouchitis was defined as a clinical syndrome characterized by the onset of increased stool frequency often with bloody diarrhea, pelvic discomfort, urgency, malaise, and fever. The diagnosis of pouchitis was confirmed in all cases by endoscopy with afferent ileal limb intubation. Endoscopic findings in cases of pouchitis included diffuse mucosal inflammation, typically involving the entire pouch, characterized by exudate, ulceration, erythema, and sparing of the afferent ileal segment. Histopathologic evaluation of the pouch was not routinely performed. Acute pouchitis (AP) was defined as flares treated favorably with antibiotics occurring at least four months apart during which time the patient was completely asymptomatic and had returned to his/her usual bowel pattern. Chronic pouchitis (CP) required continuous antibiotic treatment for symptom relief and also included those patients who were did not respond to antibiotic treatment. Stool studies were obtained when conventional antibiotic therapy was unsuccessful or in patients with CP. However, pouchoscopy with biopsies was performed in all CP patients looking for granulomatous inflammation or cytomegalovirus inclusion bodies (13). *De novo* CD after IPAA was diagnosed either when mucosal inflammation (5 or more ulcers) involved the small bowel mucosa proximal to the ileal pouch (14) anytime after surgery and/or when a pouch fistula or other perianal complication developed more than 3 months after ileostomy closure. For patients with persistent symptoms, studies were done to exclude mechanical complications of surgery such as an anal stricture or partial small bowel obstruction. Patients using nonsteroidal anti-inflammatory drugs were also excluded from analysis (15). Time to diagnosis of pouchitis or *de novo* CD was defined as the time period from ileostomy closure.

Serologic Analysis

Serum was drawn immediately before colectomy, coded, and stored for future analysis. All sera were analyzed in a blinded fashion by Prometheus Laboratories (San Diego, California, USA) or performed at Cedars-Sinai Medical Center.

Stored serum was analyzed for expression of IBD-associated antibodies, including ASCA, anti-OmpC, anti-CBir1, anti-I2 and pANCA in a blinded fashion by enzyme-linked immunosorbent assay (ELISA), as previously described (16-18). All assays for anti-I2 were performed at Cedars-Sinai Medical Center. Antibody levels were determined and results expressed as ELISA units (EU/ml) which are relative to a Cedars-Sinai laboratory (OmpC-IgA, anti-I2, and anti-CBir1) or a Prometheus Laboratory standard (San Diego, CA; pANCA, ASCA-IgA and IgG) derived from a pool of patient sera with well-characterized disease found to have reactivity to these antigens. Qualitative positivity to any antibody was defined as being greater than cut-off values greater than 2 standard deviations above mean control titers for each assay. All assays were performed blindly without knowledge of patient clinical characteristics. Similarly, clinical course after IPAA was assessed without knowledge of the patient's serologic profile.

Our group has previously reported that patients having sera with high pANCA levels (greater than 100 ELISA units per milliliter) are predisposed to the development of chronic pouchitis but not acute pouchitis (19). These data suggest that high-level pANCA expression may identify a subset of patients with UC who may have a distinct type of mucosal inflammation representing an exquisite sensitivity to the presence of bacterial antigens. This observation stimulated our analysis of patients not only on pANCA positivity or negativity but also on the magnitude of antibody expression, namely antibody level. pANCA+ patients were thus stratified into 2 groups based on antibody level. High-level pANCA+ patients had levels equal to and above 100 ELISA units per milliliter. Low-level pANCA+ patients had levels below 100 ELISA units per milliliter

Statistical Analysis

All data were entered into a standardized database computer program (Microsoft® Excel, Seattle, Washington). For continuous covariates, medians were compared with the use of Wilcoxon nonparametric tests. Categorical variables were compared with Chi-square or Fishers' exact test (if expected cell counts were less than 5). Univariate time-to-event analysis using Cox proportional hazards modelling was separately performed for each outcome variable (acute pouchitis, chronic pouchitis, or Crohn's disease outcomes relative to those with no pouch complications) based on the presence or absence of BWI (R, The R Project for Statistical Computing). In addition, univariate time-to-event analyses were performed on each potential predictor variable for each of the 3 outcomes, with the intent to include all variables with log-rank $p<0.15$ into a multivariate model. All hypothesis testing was two-sided with a p-value of less than 0.05 considered statistically significant (JMP 8.0 the SAS Institute, Carey, NC).

Results

Patient Demographics and Clinical Characteristics

Patient demographic and clinical characteristics of the 334 study patients are shown in Table I. A majority of the patients were male. Of the 281 patients with medically unresponsive disease, 47 (17%) were steroid-dependent and 234 (83%) were refractory to other immunomodulatory therapy, including thiopurines (n=205), cyclosporin (n=96) and/or

infliximab (n=51). Seventy-three patients (22%) had EIMs associated with their disease, including arthritis (n=50), PSC (n=12), skin disease (n=10) or uveitis (n=1). Although the majority of patients had surgery for medically-refractory disease, IPAA was performed in 38 patients for dysplasia and 15 patients for an established carcinoma. Before surgery, 237 patients (71%) had UC and the remaining 97 patients (29%) had IBDU. The diagnosis of IBDU was based on discontinuous inflammation (n=65), anal disease (n=14), involvement of the small bowel proximal to the terminal ileum (n=9) and crypt-associated granulomas (n=9). After histologic evaluation of the resected specimen, there were a total of 236 UC patients and 98 IC patients. The diagnosis of IC was based on transmural inflammation on the colectomy specimen (n=41), discontinuous inflammation (n=21), crypt associated granulomas (n=14), involvement of the small bowel proximal to the terminal ileum (n=11), and anal disease (n=11).

Clinical Characteristics and Seromarker Expression in Backwash Ileitis

Backwash ileitis was identified in 39 (12%) patients. There were a number of significant differences in clinical characteristics between patient groups with or without BWI (Table II). All patients with BWI had pancolitis. The incidence of pancolitis was significantly higher in the BWI+ patient group versus the BWI- patient group (p=0.0001). Although there was no significant difference in the overall incidence of EIM, PSC was significantly more common in BWI+ patients compared to BWI- patients. A majority of BWI+ patients had atypical features of UC both before surgery (IBDU) and after surgery (IC). The diagnosis of IBDU in BWI+ patients was based on discontinuous inflammation (n=10), involvement of the small bowel above the terminal ileum (n=5), anal disease (n=4), and crypt-associated granulomas (n=1). The diagnosis of IC in BWI+ patients was based on involvement of the small bowel above the terminal ileum (n=8), transmural inflammation on the colectomy specimen (n=5), discontinuous inflammation (n=4), anal disease (n=4) and crypt associated granulomas (n=2). The incidence of both IBDU and IC was much higher in BWI+ patients versus BWI- patients.

As complete serology data was not available in 7 study patients, serologic analysis was performed on the remaining 327 study patients (BWI+=38; BWI-neg=289). Serum pANCA, anti-I2, anti-OmpC, anti-CBir1 and ASCA were detected in 220 patients (67%), 88 patients (27%), 68 patients (21%), 61 patients (19%) and 42 patients (13%), respectively (Table III). Within the 42 ASCA-positive patients were 32 patients who were ASCA IgA+, 18 patients who were ASCA IgG+ and 8 patients who expressed both forms of ASCA. The frequency of high-level pANCA expression was significantly higher in BWI+ patients versus BWI- patients. No other significant differences in either frequency of serologic marker positivity or median antibody level were noted between the BWI+ and BWI- patient groups.

Pouchitis Development

After a median followup time after ileostomy closure of 26 months (range, 3 to 492 months), 90 patients developed pouchitis, representing an overall incidence of 27%. Median time to diagnosis of pouchitis was 9 months (range, 3 to 116 months). Acute pouchitis was seen in 53 patients (16%). Median time to the diagnosis of AP was 10 months (range, 3 to 166 months). The median number of acute pouchitis episodes per patient was 2 (range, 1 to 5).

Chronic pouchitis developed in 37 patients (11%). Twenty-nine patients with CP were maintained on long-term antibiotic therapy. Four patients required a diverting ileostomy to control symptoms, two patients required immunomodulator therapy, and two patients were controlled using probiotic therapy alone. The median time to CP development was 6 months (range, 3 to 53 months). There was no significant difference in median time to pouchitis diagnosis between patients with acute pouchitis or chronic pouchitis.

Forty-two patients (13%) developed *de novo* CD of the pouch after IPAA. Median time to CD diagnosis was 8 months (range, 1 to 53). One patient developed CD of the pouch and proximal limb of the ileostomy one month after IPAA creation. All of the remaining patients developed CD more than 3 months after ileostomy closure. CD was diagnosed on the basis of afferent ileal limb disease (n=32), pouch fistulizing disease (n=5) and new perianal disease (n=5). Twenty-six patients were maintained on immunosuppressive therapy, 11 patients required a diverting ileostomy to control persistent symptoms after failing aggressive immunosuppression, and 5 patients were controlled with antibiotics alone.

Relationship between Backwash Ileitis and Outcome after IPAA

The association between the BWI+ and BWI- patient groups and outcome after IPAA is shown in Table IV. There was no significant difference in the overall rate of development of AP, CP, or CD using Cox-proportional hazards modeling (log-rank p-values for AP, CP, and CD were 0.63, 0.05, 0.96, respectively). Although there was a higher incidence of CP in BWI+ patients (21%) compared to BWI- patients (10%), this trend did not reach statistical significance. Since PSC, a well described risk factor for CP (11,20), was more common in the BWI+ patient group, we evaluated the association of BWI in patients who did not have PSC (n=322). Within this subgroup, CP was observed in 5 of the 33 BWI+ patients (15%) versus 27 of the 289 BWI- patients (9%) (p=0.35). Median time to diagnosis of acute pouchitis, chronic pouchitis and *de novo* CD were similar between BWI+ and BWI- patient groups (data not shown).

Factors Associated with Outcome in Patients with Backwash Ileitis

Associations of clinical characteristics and individual serologic responses to microbial antigens and outcome after IPAA in the BWI+ patient group are shown in Tables V and VI. None of the clinical variables examined was associated with either a favorable or adverse outcome in the BWI+ patient group. From a serological point of view, both anti-I2 and pANCA expression were not associated with any adverse outcome after surgery. Anti-OmpC was significantly associated with the development of *denovo* CD after IPAA. Although anti-CBir1 was also associated with *denovo* CD after IPAA, this trend was of borderline significance. ASCA-IgA expression was associated with the onset of chronic pouchitis. These trends were not observed in BWI+ patients who did not have PSC. Furthermore, we were unable to demonstrate any significant association when combining individual serologic markers and outcome after IPAA (data not shown).

Discussion

As long as symptoms are controlled by medical measures and no dysplasia or cancer develops, UC patients with BWI are managed with medical therapy in a similar fashion to UC patients without BWI. However, when colectomy is indicated, the distinction between BWI+ and BWI- may become important. Surgical outcomes after IPAA in BWI patients are controversial, with some studies reporting adverse effects of BWI+ versus BWI- and other studies showing no difference (Table VII). Many of these studies are retrospective in design, include small patient numbers, have suboptimal patient followup and are plagued with referral center bias. These discrepant data may also be partly explained by problems in clinical definitions of both BWI and pouchitis. The overall incidence of BWI varies significantly across studies (6% to 22%), corresponding to inconsistent clinical and pathologic criteria used to reach a diagnosis of BWI. Some studies have considered BWI to include not only patients with acute inflammation (i.e., the presence of neutrophils) but also patients who have chronic inflammation (i.e., lymphocytes) or those with morphologic features of regenerative changes without inflammation. We defined patients to have BWI only when there was acute inflammation in the extreme terminal ileum, corresponding to other expert opinions on this issue (21). Some authors define pouchitis on clinical grounds alone, while others require endoscopic confirmation. Although we do not believe that histologic assessment, as defined in the Pouchitis Disease Activity Index (22), is necessary for the diagnosis of pouchitis, it is clear that symptoms alone are not sufficient to accurately diagnose this condition (23).

Our study revealed a number of clinical phenotypes associated with BWI. The incidence of pancolitis was much higher in BWI+ patients compared to BWI-negative patients, corroborating the data of others (7,10). In fact, all of the BWI patients in our study had pancolitis. These data suggest that the presence of terminal ileal inflammation in a left-sided colitis patient should seriously raise the possibility of CD and not UC. The incidence of PSC was significantly higher in BWI+ patients compared to BWI- patients, also confirming the results of prior studies (24,25). Since bile acids are absorbed in the terminal ileum, it is interesting to speculate that the defects in bile acid metabolism noted in PSC patients (26) might account for the relationship between BWI and PSC.

Our study has several limitations. As a referral center, our patient population may have more aggressive or advanced disease at the time of surgery. However, one might conceive that this would actually bias results toward worse postoperative outcomes among those with ileal inflammation suggestive of backwash ileitis. A second limitation is that while the median duration to developing pouch inflammation was 9 months, some patients in the cohort were followed for fewer than 9 months. Thus, the possibility exists that these patients may develop pouch complications as they are followed out for a longer duration. Finally, our results are reported from the database of a single surgeon, and may thus not be readily generalizable.

A unique aspect of the current study was the evaluation of subclinical markers in BWI patients. There was no significant difference in serologic marker expression between BWI+ and BWI-negative patients, except that BWI+ patients did have a significantly higher

incidence (29%) of high-level pANCA expression than BWI-negative patients (9%). Although the mechanism responsible for the relationship between high levels of the anti-microbial antibody pANCA (27) and BWI is not well understood, it supports the concept that luminal factors such as bacteria or their excreted products play an integral role. Our group has previously shown that ASCA positivity is a prominent feature of patients with well characterized small bowel CD (17,18). The low incidence of both ASCA-IgA (5 percent) and ASCA-IgG (3 percent) observed in BWI+ patients strongly suggests that the presence of BWI itself should dissuade clinicians from thinking these patients all have CD and not UC. Serologic differences noted between BWI+ and BWI-negative patients in the current study require validation from other centers.

From the surgical point of view, we observed in this study no significant differences in the development of acute pouchitis, chronic pouchitis or *de novo* CD after IPAA between patients with BWI and those without BWI. We also attempted to identify subgroups of BWI patients, based on clinical or subclinical features, with either a favorable or adverse outcome after IPAA. None of the clinical variables were significantly associated with outcome in BWI+ patients. Although anti-OmpC was significantly associated with the development of *denovo* CD and ASCA-IgA expression was associated with the onset of chronic pouchitis after IPAA, none of these trends were observed in BWI+ patients who did not have PSC. These data suggest that in the absence of PSC, the clinical outcome of IPAA in patients with BWI cannot be predicted. Colorectal surgeons should feel comfortable in performing an IPAA in patients with BWI, especially in the absence of PSC.

In summary, this prospective study has shown that BWI+ patients appear to have the same overall incidence of acute pouchitis, chronic pouchitis, and *de novo* CD after IPAA as do BWI-negative patients. Preoperative counseling of these patients should clearly include a discussion of these findings.

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Table I

Clinical Features of the Study Cohort

Sex (M/F)	186 / 148
Median age (range)	38 (8 - 81)
Median disease duration (range)	60 months (3 - 492)
Disease extent	
Pancolitis	258
Left-sided	73
Proctitis	3
Preoperative medication	
Steroids alone	47
Immunomodulators	234
Extraintestinal disease	73
Arthritis	50
PSC	12
Other	11
Backwash ileitis	39
Family history of IBD	89
Perianal disease	17
Preoperative type of colitis	
Ulcerative colitis	237
IBDU	97
Postoperative type of colitis	
Ulcerative colitis	236
IC	98
Indication for IPAA	
Medically unresponsive	281
Cancer / Dysplasia	53

PSC primary sclerosing cholangitis

IBD inflammatory bowel disease

IBDU inflammatory bowel disease unclassified

IC indeterminate colitis

IPAA ileal pouch-anal anastomosis

Table II
Clinical Variables in Patients With and Without Backwash Ileitis

	Backwash-Positive (n=39)	Backwash-Negative (n=295)	p value
Sex (M/F)	20/19	166/129	0.61
Median age (range)	36 (8-67)	38 (9-81)	0.32
Median disease duration (mo)	61	60	0.58
Disease Extent			
Pancolitis	39 (100)	219 (74)	0.0001
Left-sided	0 (0)	73 (25)	
Proctitis	0 (0)	3 (1)	
Preoperative medication			
Steroids	4 (10)	42 (14)	0.80
Immunomodulators	28 (72)	209 (71)	
Extraintestinal disease	13 (33)	62 (21)	0.10
Arthritis	5 (13)	21 (7)	0.20
PSC	6 (15)	6 (2)	0.001 *
Other	2 (5)	35 (12)	0.28
Family history of IBD	8 (21)	82 (28)	0.44
Ulcerative colitis	4 (10)	59 (20)	
Crohn's disease	5 (13)	29 (10)	
Perianal disease	5 (13)	12 (4)	0.04
Preoperative type of colitis			
Ulcerative colitis	19 (49)	218 (74)	0.002
IBDU	20 (51)	77 (26)	
Postoperative type of colitis			
Ulcerative colitis	16 (41)	220 (75)	0.0001
IC	23 (59)	75 (25)	
Indication for IPAA			
Medically unresponsive	32 (82)	249 (84)	0.65
Cancer / dysplasia	7 (18)	46 (16)	

* comparison of PSC between BWI+ and BWI-negative patient groups

PSC primary sclerosing cholangitis

IBD inflammatory bowel disease

IBDU inflammatory bowel disease unclassified

IC indeterminate colitis

IPAA ileal pouch-anal anastomosis

Table III
Serologic Expression in Patients With and Without Backwash Ileitis

	BWI + Patients* (n=38)	BWI- Patients* (n=289)	p value
pANCA			
Positive	30 (79)	190 (66)	.14
Median level	56	52	.07
High-level (>100 EU/ml)	11 (29)	26 (9)	0.001
ASCA			
IgA+	2 (5)	30 (10)	.56
IgG+	1 (3)	17 (6)	.71
Either IgA+ or IgG+	2 (5)	40 (14)	.20
Both IgA+ and IgG+	1 (3)	7 (2)	1
Median level IgA+	35	34	.78
Median level IgG+	52	65	.44
anti-OmpC			
Positive	6 (16)	62 (21)	.53
Median level	29	34	.34
anti-CBir1			
Positive	8 (21)	53 (18)	.66
Median level	42	56	.34
anti-I2			
Positive	14 (37)	74 (26)	.17
Median level	29	33	.72

* one BWI+ patient and 6 BWI- patients did not have serology BWI backwash ileitis

Table IV
Association Between Backwash Ileitis and Pouchitis / Crohn's Disease

Diagnosis	n	Median Followup (months)	Acute Pouchitis	Chronic Pouchitis
Backwash positive	39	22	4 (10)	8 (21)
Backwash negative	295	29	49 (17)	29 (10)

Values in parentheses denote percentage

Table V

Association of Clinical Characteristics and Outcome of IPAA in Patients With Backwash Ileitis

Clinical Variable	No Pouchitis	Acute Pouchitis	Chronic Pouchitis	Crohn's Disease
Male Gender	50	15	15	20
Median age ≥36	65	10	20	5
Median disease duration ≥ 61 mo	55	10	20	15
Preoperative medication				
Steroids	50	0	50	0
Immunomodulators	60	11	18	11
Extraintestinal disease				
Arthritis	80	20	0	0
PSC	33	0	50	17
Other	100	0	0	0
Family history of IBD		13	13	0
Ulcerative colitis	75	0	25	0
Crohn's disease	80	20	0	0
Perianal disease	40	20	0	40
Preoperative type of colitis				
Ulcerative colitis	68	11	21	0
IBDU	50	10	20	20
Postoperative type of colitis				
Ulcerative colitis	75	6	13	6
IC	48	13	26	13
Indication for IPAA				
Medically unresponsive	60	9	22	9
Cancer / dysplasia	43	14	14	29

Values represent % of patients with the clinical variable that had each particular outcome

No differences were significant at p value <.05 (hypothesis testing by Chi square analysis or Fisher's exact test, as appropriate)

Table VI

Associations of Seromarker Expression and Outcome of IPAA in Patients With Backwash Ileitis

Serology	Acute Pouchitis	Chronic Pouchitis	Crohn's Disease
pANCA	13	27	17
High-level pANCA	18	18	27
anti-I2	7	29	7
anti-OmpC	17	17	50 *
anti-Cbir1	13	25	38
ASCA			
IgA+	0	100 +	0
IgG+	0	100	0
IgA+ *and IgG*+	0	100 ++	0

Values represent % of patients with the positive serology that had each particular outcome

* p = 0.02

+ p = 0.04

++ p = 0.04 (hypothesis testing performed with Chi-square analysis or Fisher's exact test, as appropriate

Table VII

Studies of Backwash Ileitis and Outcome after Ileal Pouch-Anal Anastomosis

Author (ref)	Year	Study Design	N	BWI (%)	Diagnostic Criteria For		Outcome (BWI+ versus BWI-neg)
					BWI	Pouchitis	
Gustavsson (9)	1987	R	131	11	Radiographic, acute and chronic inflammation	Clinical	No difference
Schmidt (6)	1998	R	67	NR	Acute and chronic inflammation	Histologic	Increased risk of pouchitis
Abdelrazeq (7)	2005	P	100	22	Acute inflammation	Clinical, endoscopic, histologic	Increased risk of pouchitis
Haskell (10)	2005	R	200	17	Regenerative changes without inflammation; Acute and chronic inflammation	NR	No difference
Fleshner (11)	2007	P	200	17	Acute inflammation	Clinical, endoscopic	No difference
Ferrante (8)	2008	R	173	6	NR	Clinical, endoscopic	Increased risk of chronic pouchitis
Current study	-	P	334	12	Acute inflammation	Clinical, endoscopic	No difference