

Risk Factors for Diseases of Ileal Pouch–Anal Anastomosis After Restorative Proctocolectomy for Ulcerative Colitis

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Background & Aims: Although pouchitis is considered the most common adverse sequela of ileal pouch–anal anastomosis (IPAA), inflammatory and noninflammatory conditions other than pouchitis are increasingly being recognized. The risk factors for these non-pouchitis conditions, including Crohn's disease (CD) of the pouch, cuffitis, and irritable pouch syndrome (IPS), have not been studied. The aim of this study was to assess risk factors for inflammatory and noninflammatory diseases of IPAA in a tertiary care setting. **Methods:** The study consisted of 240 consecutive patients who were classified as having healthy pouches (N = 49), pouchitis (N = 61), CD of the pouch (N = 39), cuffitis (N = 41), or IPS (N = 50). Demographic and clinical features were assessed to determine risk factors for each of these conditions by using logistic regression analysis. **Results:** Risk factors remaining in the final logistic regression models were for pouchitis: IPAA indication for dysplasia (odds ratio [OR], 3.89; 95% confidence interval [CI], 1.69–8.98), never having smoked (OR, 5.09; 95% CI, 1.01–25.69), no use of anti-anxiety agents (OR, 5.19; 95% CI, 1.45–18.59), or use of NSAIDs (OR, 3.24; 95% CI, 1.71–6.13); for CD of the pouch: a long duration of IPAA (OR, 1.20; 95% CI, 1.12–1.30) and current smoking (OR, 4.77; 95% CI, 1.39–16.25); for cuffitis: arthralgias (OR, 4.13; 95% CI, 1.91–8.94) and younger age (OR, 1.16; 95% CI, 1.01–1.33); and for IPS: use of antidepressants (OR, 4.17, 95% CI, 1.95–8.92) or anti-anxiety agents (OR, 3.21; 95% CI, 1.34–7.47). **Conclusions:** The majority of risk factors for the 4 inflammatory and noninflammatory conditions of IPAA are different, suggesting that each of these diseases has a different etiology and pathogenesis. The identification and modification of these risk factors might help patients and clinicians to make a preoperative decision for IPAA, reduce IPAA-related morbidity, and improve response to treatment.

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is the surgical treatment of choice for patients with medically refractory ulcerative

colitis (UC), UC with dysplasia, or familial adenomatous polyposis.^{1,2} Inflammatory and noninflammatory diseases can develop after IPAA, which adversely affect the outcome of IPAA and compromise patients' quality of life.³ These disease conditions of IPAA include pouchitis, Crohn's disease (CD) of the pouch, cuffitis, and irritable pouch syndrome (IPS).

Pouchitis is the most common long-term adverse sequela after IPAA.^{1,2,4–7} Therefore it has been a major focus of research in patients with IPAA. Its purported risk factors include extensive UC,^{1,8} backwash ileitis,⁸ extraintestinal manifestations (especially primary sclerosing cholangitis [PSC]),^{6,9,10} perinuclear neutrophil cytoplasmic antibodies,¹¹ interleukin-1 receptor antagonist gene polymorphisms,¹² being a non-smoker,¹³ and regular use of NSAIDs.¹⁴

We have encountered many IPAA patients whose symptoms were caused by conditions other than pouchitis, including CD of the pouch,¹⁵ cuffitis,¹⁶ and IPS.¹⁷ Risk factors for these conditions have not been investigated. This study was designed to test our hypothesis that the development of these diseases of IPAA might be attributed to certain demographic and clinical factors. The identification of such risk factors could help predict the outcome of IPAA and improve the outcome by modifying the risk factors and directing appropriate treatment.

Abbreviations used in this paper: ASCA, anti-Saccharomyces cerevisiae antibodies; CD, Crohn's disease; CI, confidence interval; CMV, cytomegalovirus; IPAA, ileal pouch–anal anastomosis; IPS, irritable pouch syndrome; OR, odds ratio; PDAI, Pouchitis Disease Activity Index; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

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1542-3565/06/\$32.00

PII: 10.1053/S1542-3565(05)00996-1

Patients and Methods

Study Subjects

The Cleveland Clinic Foundation Institutional Review Board approved this study, and written informed consent was obtained from all participants. A total of 240 consecutive adult (>18 years old) patients who underwent IPAA for an original diagnosis of UC between March 2002 and October 2004 were identified from our Pouchitis Clinic. These patients were classified as having healthy pouches (N = 49), antibiotic-dependent or antibiotic-refractory pouchitis (N = 61), CD of the pouch (N = 39), cuffitis (N = 41), or IPS (N = 50). To properly assess potential risk factors and to minimize selection and recall biases, we conducted the study by using a standard protocol and questionnaires by combining (1) an outpatient evaluation with assessment of demographic, clinical, endoscopic, and histologic data and (2) additional review of the clinical course of these patients from the prospectively maintained Pouchitis Database. All patients were followed after IPAA completion and ileostomy closure for a minimum of 12 months.

Inclusion and Exclusion Criteria

Inclusion criteria were (1) age >18 years and ability to give informed consent, (2) IPAA for UC, and (3) a diagnosis of antibiotic-dependent or antibiotic-refractory pouchitis, CD of the pouch, cuffitis, or IPS. Patients were excluded from the study if they had the same degree of inflammation in the pouch and cuff on endoscopic and histologic examinations, which would have prevented us from clearly classifying the pouchitis or cuffitis. Patients with active pouch leaks, abscesses, sepsis, or efferent or afferent limb syndrome were excluded as well as patients with a pre-IPAA diagnosis of CD. Patients with pouchitis, CD of the pouch, or cuffitis and concurrent active cytomegalovirus (CMV) or *Clostridium difficile* infection were also excluded.

Clinical, Endoscopic, and Histologic Evaluations

During the outpatient evaluation, demographic, clinical, endoscopic, and histologic data were collected. A GIF-160 upper endoscope (Olympus Optical, Tokyo, Japan) was used for evaluation of the afferent limb, pouch, and cuff. The Pouchitis Disease Activity Index (PDAI) was used to quantify symptoms and inflammation on endoscopy and histology.¹⁸ The PDAI endoscopic scores were measured separately for each segment of the ileal pouch. Additional endoscopic features, such as fistulas and strictures, were documented. Biopsies from the afferent limb, pouch, and cuff were taken and separately labeled. Mucosal biopsies were taken from the areas with maximal inflammation in the afferent limb, pouch, and cuff or from the posterior wall of the pouch if the pouch had a normal endoscopic appearance. A gastrointestinal pathologist who was blinded to the demographic, clinical, and endoscopic data assessed and graded the inflammation of the biopsy specimens. Additional features of mucosal histopathology were docu-

mented, including dysplasia, granulomas, and CMV infection. For patients with antibiotic-refractory pouchitis and CD of the pouch, CMV DNA in the blood and *C difficile* toxin A and B in the stool were assayed.

Diagnostic Criteria

Pouchitis was defined as a total of PDAI score >7. Antibiotic-responsive pouchitis was defined as a condition in which patients had infrequent episodes (<4 episodes per year) of pouchitis, and each of the episodes responded to a 2-week course of a single antibiotic. Antibiotic-dependent pouchitis was defined as a condition in which a patient with frequent episodes (>4 episodes per year) of pouchitis or persistent symptoms required long-term, continuous antibiotic or probiotic therapy to keep disease in remission. Antibiotic-refractory pouchitis was defined as a condition in which a patient failed to respond to a 2- to 4-week course of a single antibiotic (metronidazole or ciprofloxacin), requiring prolonged therapy of >4 weeks consisting of 2 antibiotics, oral or topical 5-aminosalicylate, corticosteroid therapy, or oral immunomodulator therapy.³ Only patients with antibiotic-dependent or antibiotic-refractory pouchitis were included in the study.

CD of the pouch was diagnosed if there were non-surgery related perianal fistulas, granulomas on histology, or inflammation and ulcerations in the afferent limb or in the small bowel on endoscopy in the absence of NSAID use. A recent study indicated that afferent limb ulcers in the absence of NSAID use in patients with IPAA are specific for CD.¹⁹

Cuffitis was defined as endoscopic and histologic inflammation of the rectal columnar cuff. In cases of concurrent inflammation of the pouch and cuff, the patient was diagnosed with pouchitis or cuffitis depending on whether the inflammation was predominantly in the pouch or cuff.

IPS was defined as the presence of symptoms of abdominal pain, pelvic discomfort, and diarrhea with no inflammation of the afferent limb, pouch, or cuff on endoscopy (PDAI endoscopic score ≤ 1 point) and histology.¹⁷ Patients had a total of 12 weeks or more of symptoms during prior 12-month period. Patients were considered to have healthy pouches if they were asymptomatic when entering the study, with no endoscopic and histologic inflammation and fewer than 2 episodes of antibiotic-responsive pouchitis (symptoms responding to a 2-week, single-agent antibiotic) per year with the last episode occurring at least 6 months before entry in the study.

Definitions of Variables

Studied variables were classified as either (1) variables whose values were known or measured at time of restorative proctocolectomy and IPAA, including age, gender, time interval between UC diagnosis and IPAA with ileostomy closure, extent and severity of UC, indication for colectomy, type and stage of IPAA, and family history of IBD and (2) variables that were measured at the time of study enrollment and that might reflect post-IPAA information, including PSC, arthralgias, consumption of tobacco or alcohol, use of antidepressants or anti-anxiety agents, narcotics, or NSAIDs. The presence of

these 2 categories of variables preceding the diagnosis of the inflammatory and noninflammatory diseases of IPAA was ascertained at the time of study enrollment.

Demographic and clinical variables were defined as follows: interval from UC diagnosis to IPAA—the time interval from UC diagnosis to the completion of IPAA with ileostomy closure; duration of IPAA—the interval between IPAA completed with ileostomy closure and time when the patient was seen at the Pouchitis Clinic with diagnosis confirmed; pancolitis—endoscopic, macroscopic, or microscopic disease extending proximal to the splenic flexure; fulminant colitis—patients with continuous bloody diarrhea, fever, abdominal distention, tachycardia, anemia, or radiographic evidence of dilated colon despite use of oral or intravenous corticosteroids who required urgent surgical intervention; indication for proctocolectomy and IPAA—the primary reason for the surgery on the basis of clinical presentation and preoperative diagnostic studies; PSC—presence of intra- or extrahepatic bile duct abnormalities documented on endoscopic retrograde cholangiopancreatography and/or magnetic resonance cholangiopancreatography; arthralgias—presence of daily symptoms of peripheral or central joint pains with or without joint swelling or radiographic arthropathy; smoking—consumption of >7 cigarettes per week since the surgery; ex-smoker—cessation of smoking 6 months before the entry in the study; alcohol use—excessive consumption of alcohol >1 drink per day since the surgery; family history of IBD—CD or UC in first-degree relatives; use of antidepressants—daily use of antidepressants since the surgery, such as use of citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine; use of anti-anxiety agents—daily use of an anti-anxiety agent since the surgery, such as alprazolam, lorazepam, temazepam, and clonazepam; narcotic use—daily use of narcotic analgesics since the surgery; and use of NSAID—regular use of NSAID more often than weekly since the surgery.

Statistical Analysis

To evaluate the risk factors for the IPAA-related conditions, 5 separate analyses were performed. For each of the 4 diseases of IPAA, an analysis was performed in which the outcome of interest was “have the condition” or “do not have the condition.” This approach was designed to reflect the unconditional likelihood of having the specific disease as opposed to any other outcomes. The fifth analysis used healthy pouch, as opposed to having any of the 4 diseases of IPAA, as the outcome. Univariable Wilcoxon rank sum (continuous variables), χ^2 , and Fisher exact tests (categorical variables) were used to measure the statistical significance of observed associations between the risk factors and each condition as appropriate. For the multivariable assessment, logistic regression analysis was performed. For each condition, models were selected by using a stepwise selection method, which started with a model containing only one constant term, and assessed by adding or deleting factors from the model until no additional terms could enter the model on the basis of a P value >.05, and no factors could be eliminated from the model on

the basis of a P value <.05. A type I error rate of 0.05 was used for all analyses. SAS 9.1 software (SAS Institute Inc, Cary, NC) was used to carry out all analyses.

Results

During the 30-month study period, 289 consecutive patients were seen in the Pouchitis Clinic, of whom 240 patients met the inclusion criteria. Forty-nine patients did not meet inclusion criteria and were excluded from the study; 35 patients had antibiotic-responsive pouchitis, 5 patients had concurrent pouchitis and cuffitis, 1 patient had antibiotic-refractory pouchitis with CMV viremia and viral inclusion bodies in mucosal biopsy of the pouch, and 8 patients had surgery-related complications (pouch leak, sepsis, anastomotic sinus, misfired staples at the pouch–anal anastomosis). None of the patients with antibiotic-refractory pouchitis or CD of the pouch had positive *C difficile* toxins. The results of the univariable and multivariable analyses are summarized in Tables 1 and 2, respectively.

Univariable and multivariable analyses were performed to assess the risks of having any of the 4 disease conditions of IPAA as compared with having a healthy pouch; all 4 diseases of IPAA were analyzed together and versus the healthy pouch. Arthralgias and the use of antidepressants, narcotics, or NSAIDs were all inversely associated with having a diseased pouch. Patients who had arthralgias or used antidepressants, narcotics, or NSAIDs had 5.3 ($P < .001$), 2.6 ($P = .03$), 5.1 ($P = .02$), and 2.0 ($P = .04$) times the odds of having a diseased pouch, respectively, compared with those who did not have these factors (Table 1). NSAID use was not statistically associated with arthralgias ($P = .54$), and both factors were considered for inclusion in the final models. In the multivariable analysis, only arthralgias remained in the final model after adjusting for NSAID use. Patients who had arthralgias had 5.32 times the odds (95% CI, 2.45–11.59) of having pouchitis, CD of the pouch, cuffitis, or IPS as compared with those who did not have arthralgias (Table 2). Therefore, the only significant predictor remaining in the model was the one that showed up most often (3 times) among the analyses of the 4 individual diseases.

Antibiotic-Dependent and Antibiotic-Refractory Pouchitis

Patients who underwent IPAA because of dysplasia had 3.0 times the odds of having pouchitis compared with those who underwent IPAA as a result of medically refractory UC ($P = .003$). Patients who used anti-anxiety agents or NSAIDs had 0.20 and 2.86 times the odds of having pouchitis, respectively, compared with those who

Table 1. Demographic and Clinical Data

	Healthy pouch	Pouchitis	CD of the pouch	Cuffitis	IPS
N	49	61	39	41	50
Age, y, median (25th, 75th percentiles)	42 (33, 52)	45.0 (33, 56)	44 (35, 49)	41.0 (32, 46)	45 (33, 54)
Male gender, n (%)	25 (51.0)	32 (52.5)	13 (33.3)	20 (48.8)	20 (40.0)
Interval from UC diagnosis to IPAA, y, median (25th, 75th percentiles)	4.0 (2.0, 10.0)	5.0 (2.0, 13.0)	4.0 (1.0, 10.0)	3.0 (2.0, 13.5)	6.0 (1.0, 12.0)
Duration of IPAA, y, median (25th, 75th percentiles)	3 (2, 7)	3 (2, 9)	8 (4, 13) ^a	3 (2, 7)	4 (2, 8)
Pancolitis, n (%)	45 (91.8)	57 (93.4)	39 (100)	37 (90.2)	47 (94.0)
Fulminant colitis, n (%)	6 (12.2)	4 (6.6)	5 (12.8%)	4 (9.8)	5 (10.0)
Surgical indication, n (%)					
Refractory/steroid-dependent	44 (89.8)	45 (73.8)	37 (94.9)	37 (90.2)	42 (84.0)
Dysplasia or cancer	5 (10.2)	16 (26.2) ^b	2 (5.1)	4 (9.8)	8 (16.0)
Pouch type, n (%)					
J	45 (91.8)	57 (93.4)	36 (92.3)	40 (97.6)	49 (98.0)
S	4 (8.2)	2 (3.3)	2 (5.1)	1 (2.4)	1 (2.0)
Others	0	2 (3.3)	1 (2.6)	0	0
Stage of IPAA, n (%)					
1	0	3 (4.9)	1 (2.6)	3 (7.3)	1 (2.0)
2	44 (89.8)	49 (80.3)	32 (80.2)	30 (73.2)	41 (82.0)
3	4 (8.2)	5 (8.2)	5 (12.8)	6 (14.6)	7 (14.0)
Redo	1 (2.0)	3 (4.9)	1 (2.6)	2 (4.9)	1 (2.0)
PSC, n (%)	0	4 (6.6)	1 (2.6)	2 (4.9)	1 (2.0)
Arthralgias, n (%)	9 (18.4) ^a	28 (45.9)	19 (48.7)	29 (70.7) ^a	27 (54.0)
Smoking, n (%)					
Current	4 (8.2)	2 (3.3)	7 (18.0) ^c	2 (4.9)	2 (4.0)
Ex-smoker	5 (10.2)	3 (4.9)	3 (7.7)	1 (2.4)	7 (14.0)
Excessive alcohol use, n (%)	2 (4.1)	2 (3.3)	1 (2.6)	1 (2.5)	3 (6.0)
Family history of IBD, n (%)	6 (12.2)	7 (11.5)	9 (23.1)	8 (19.5)	13 (26.0)
Antidepressant use, n (%)	6 (12.2) ^c	9 (14.8)	5 (12.8)	10 (24.4)	27 (54.0) ^a
Anti-anxiety agent use, n (%)	4 (8.2)	3 (4.9) ^b	3 (7.7)	9 (22.0)	20 (40.0) ^a
Narcotic use, n (%)	2 (4.1) ^c	6 (9.8)	3 (7.7)	9 (22.0)	16 (32.0) ^a
NSAID use, n (%)	14 (28.6) ^c	37 (60.7) ^a	14 (35.9)	14 (34.2)	21 (42.0)

NOTE. For all tests the outcome of interest is having the specified condition versus not having it.

^a*P* < .001.

^b*P* < .01.

^c*P* < .05.

Table 2. Risk Factors for Common Adverse Sequelae of IPAA: Multivariable Logistic Regression Analysis

	N	Variable	OR (95% CI)	<i>P</i> value
Healthy pouch	39	No arthralgias	5.32 (2.45–11.59)	<.0001
Pouchitis	61	IPAA for dysplasia	3.89 (1.69–8.98)	.001
		NSAID use	3.24 (1.71–6.13)	.0003
		Never smoked	5.09 (1.01–25.69)	.049
		Ex-smoker	0.44 (0.11–1.80)	.25
		Arthralgias	1.01 (0.53–1.92)	.97
CD of the pouch	39	Non-use of anti-anxiety agents	5.19 (1.45–18.59)	.01
		Duration of IPAA	1.20 (1.12–1.30)	<.0001
		NSAID use	0.47 (0.21–1.06)	.068
		Current smoking	4.77 (1.39–16.25)	.01
Cuffitis	41	Ex-smoker	0.67 (0.16–2.80)	.58
		Young age	1.16 (1.01–1.33)	.04
IPS	50	Arthralgias	4.13 (1.91–8.94)	.0003
		Antidepressant use	4.17 (1.95–8.92)	.0002
		Anti-anxiety agent use	3.21 (1.34–7.47)	.007

did not use anti-anxiety agents or NSAIDs. In the multivariable analysis, surgical indication for dysplasia, smoking, and use of anti-anxiety agents or NSAIDs remained in the final model (Table 1). Arthralgia was considered a clinically relevant factor and thus was included in the model, even though its effect was found to be statistically insignificant ($P = .97$). Adjusting for the above factors, patients who underwent IPAA for dysplasia had 3.89 times the odds (95% CI, 1.69–8.98) of having pouchitis compared with those who underwent IPAA for medically refractory UC. Subjects who had never smoked had 5.09 (95% CI, 1.01–25.69) times the odds of having pouchitis compared with subjects who were current smokers. Patients not using anti-anxiety agents had 5.19 times the odds (95% CI, 1.45–18.59) of having pouchitis compared with those who did. Patients who used NSAIDs had 3.24 times the odds (95% CI, 1.71–6.13) of having pouchitis compared with those who did not.

Crohn's Disease of the Pouch

Compared with patients without CD, patients with the disease had a longer duration of IPAA ($P < .001$). Smoking was also a risk factor for CD of the pouch ($P = .02$). Current smokers and ex-smokers had 4.2 and 1.1 times the odds of having the disease, respectively, compared with those who had never smoked. In multivariable analysis, duration of IPAA and smoking as risk factors remained in the final model (Table 1). Arthralgias and NSAID use were considered clinically relevant factors and thus were included in the model, even though their association with the disease was statistically insignificant ($P = .56$ and $P = .069$, respectively). Adjusting for use of NSAIDs, arthralgias, and smoking, for every 1-year increase in the duration of IPAA, the odds of having CD increased 20% ($P < .001$). Current smokers had 4.77 times the odds (95% CI, 1.39–16.25) of having CD compared with those who reported never having smoked, when adjusted for duration of IPAA, arthralgias, and NSAID use.

Cuffitis

Patients with arthralgias had 3.33 times the odds of having cuffitis compared with those who did not ($P < .001$). In multivariable analysis, the odds of having cuffitis were 4.13 times greater for patients with arthralgias than for those without, when adjusted for age. Age was also found to be significantly associated with having cuffitis (OR, 1.16; 95% CI, 1.01–1.33) (Table 2). For every 5-year decrease in age, the odds of having cuffitis increased 16%.

Irritable Pouch Syndrome

In univariable analysis, the use of antidepressants, anti-anxiety agents, or narcotics was found to be risk factors for IPS ($P < .001$). Patients who used antidepressants, anti-anxiety agents, or narcotics had 6.25, 5.88, and 4.00 times the odds of having IPS, respectively, compared with those who did not. In multivariable analysis, use of antidepressants or anti-anxiety agents was found to be a significant risk factor for IPS (Table 2). The odds of having IPS were 4.17 times higher for patients with antidepressant use than for those without, when adjusted for use of anti-anxiety agents. After adjusting for antidepressant use, patients who used anti-anxiety agents had 3.21 times the odds of having IPS compared with those who did not use them.

Discussion

This study is the first of its kind to evaluate and compare risk factors between patients with pouchitis, CD of the pouch, cuffitis, and IPS. In this study, we combined outpatient comprehensive evaluation with database analysis by using a standard protocol in a consecutive patient population. Logistic regression analysis revealed risk factors for each of the 4 disease conditions: for pouchitis—IPAA for dysplasia, never having smoked, use of NSAIDs, and non-use of anti-anxiety agents; for CD of the pouch—longer duration of IPAA and smoking; for cuffitis—younger age and arthralgias; and for IPS—the use of antidepressants or anti-anxiety agents. Patients with arthralgias in general had a higher risk of having any of the 4 diseases of IPAA. The risk factors that remained in the final model were significantly associated with the presence of the disease, even after adjusting for associations with the other remaining risk factors. In this sense, such risk factors can be thought of as having a relationship with disease that is not explained by the other remaining risk factors. The results, therefore, verify our hypothesis that the development of these conditions might be related to certain demographic and clinical factors. The identification of these risk factors might help to predict the outcome of IPAA and therefore improve the outcome via the modification of these risk factors.

In each of the 4 analyses in which a specific disease of IPAA was studied as an outcome, the presence of a risk factor was more likely to be detected if it was a risk factor for only the disease being analyzed, as opposed to if it were a risk factor for 2 or more of the diseases. In other words, diseases were essentially in competition with one another for the assessment of risk factors. However, if a particular risk factor were to increase the likelihood of all

diseases, then it could be expected to be most detectable in the analysis in which the outcome was healthy pouch versus any of the 4 IPAA diseases. Therefore, a scenario in which the diseases share a common set of risk factors would intuitively yield that set of risk factors in the analysis of the healthy pouch outcome. Because that analysis yielded only one predictor in the final model, and differing and larger sets of risk factors resulted from the analyses of individual diseases, this suggests that the sets of risk factors for the 4 diseases are not identical.

Regular use of NSAID likely represents a true risk factor for antibiotic-dependent or antibiotic-refractory pouchitis (OR, 3.24). Similar results have been shown in our previous studies.^{3,14} We also found that never having smoked was a risk factor for pouchitis (OR, 5.09), which is consistent with what has been previously reported in the literature.¹³ Dysplasia as an indication for IPAA was associated with pouchitis (OR, 3.89), which, to some extent, is similar to the results we achieved in a previous study that consisted of a different group of patients. In that study, we found that a fulminant colitis indication for surgery decreased the risk for chronic pouchitis.¹⁴ We also found that not using anti-anxiety agents was associated with higher frequency of pouchitis (OR, 5.19). It is possible that patients using anti-anxiety agents might have milder symptoms with lower PDAI symptom scores, or that some anti-anxiety agents, such as benzodiazepines, might affect host immune response and inflammatory process.^{20,21}

Our current study did not show statistically significant evidence to demonstrate that severity and extent of UC and PSC were associated with pouchitis, which is different from the results reported from other groups.^{1,8–11,13} There was little agreement in the literature as to which factors increase a patient's risk for pouchitis, which could be due to (1) diagnostic criteria used—diagnosis based on symptom assessment alone versus diagnostic instruments with combined assessment of symptoms, endoscopy, and histology; (2) stratification of pouchitis—acute versus chronic pouchitis or grouping both entities together^{14,22}; (3) number of patients studied (type 2 errors in some studies); or (4) intensity and duration of follow-up.⁷ In this study, we included only patients with antibiotic-dependent and antibiotic-refractory pouchitis because these chronic forms of pouchitis are often difficult to manage. The diagnosis of pouchitis was based on combined assessment of symptom, endoscopy, and histology. Our current study showed the prevalence of PSC was 6.6% (4/61) in patients with antibiotic-dependent/refractory pouchitis as compared with 0% (0/49) in patients with

healthy pouches. However, both univariable and multivariable analyses did not show that the association was statistically significant. This might also be due to the sample size and possible “diluting effect” in our multivariable analysis in which we compared the frequency of PSC in patients with pouchitis with the frequency of PSC in patients with healthy pouch, CD of the pouch, cuffitis, or IPS as a group.

The true incidence of CD of the pouch in patients who initially underwent surgery for UC is not known. Our group reported 74 patients (3.8%) with CD; the disease was diagnosed by using preoperative and postoperative pathology of colon specimens or ileal pouches in 1965 patients with IPAA.²² CD of the pouch occurred under the following circumstances: (1) IPAA was intentionally performed in a selected group of patients with Crohn's colitis without ileal or perianal diseases²³; (2) CD was inadvertently found in colectomy specimens in postoperative histologic evaluation in patients with preoperative UC^{24,25}; or (3) de novo CD of the pouch developed weeks or years after IPAA and ileostomy closure.^{26–28} To reduce the risk for CD of the pouch, the identification of preoperative and postoperative risk factors is important. This has been difficult to achieve, however, mainly because of the small number of cases that are available.^{27,28} In the current multivariable analysis, longer duration of IPAA (OR, 1.20) and smoking (OR, 4.77) were found to be statistically significant risk factors for CD. With a 1-year increase in the duration of IPAA, the odds of having CD increase 20% ($P < .0001$). In our clinical practice, we did encounter patients who developed CD of the pouch many years after IPAA with an initial preoperative diagnosis of UC. However, lead-time bias for the diagnosis of CD is possible, because it was difficult to determine how long patients had had the disease. Current smokers had 4.77 times the odds of having CD compared with those who reported never having smoked. The contrasting effects of smoking on pouchitis and CD of the pouch suggest that the 2 diseases are separate entities, similar to the discrepant associations of smoking with UC and CD.^{29,30} Pouchitis is unlikely a form of CD of the pouch, as previously suggested by some investigators.^{31,32}

Cuffitis can be considered a remnant of UC.¹⁶ Therefore, it is not surprising that in multivariable analysis, the odds of having cuffitis were 4 times greater for patients with arthralgias, as a part of extraintestinal manifestations of UC, than for those without. Younger age was also found to be significantly associated with an increased risk for having cuffitis (OR, 1.16). For every 5-year increase in age, the odds of having cuffitis decrease

14%. A similar trend was also observed in patients with UC in whom younger age at diagnosis was associated with more extensive disease.³³

IPS is a newly described disease entity in patients with IPAA. Our recent study, which used an electronic barostat, showed that patients with IPS had visceral hypersensitivity of the pouch as compared with patients with healthy pouches, although the biomechanical properties of the pouch (pouch compliance and tone) in the 2 groups were similar.³⁴ This would suggest that other points along the ascending visceral pain pathway, such as the central nervous system, might be involved in the generation of symptoms in IPS.

In this study, we found that the use of antidepressants (OR, 4.17) or anti-anxiety agents (OR, 3.21) was a significant risk factor of IPS. These results suggest that underlying psychological disorders, such as depression or anxiety, might be part of the pathophysiology of the disease. It would be interesting to know whether patients have had depression or other psychiatric disorders before the diagnosis of UC or before IPAA. None of the patients on antidepressants were using the tricyclic-type agents, which are effective in treating patients with irritable bowel syndrome.^{35,36} We are currently conducting a randomized trial of amitriptyline in patients with IPS.

There are some limitations to our study. Not all identified variables in a statistical model defined in a stepwise fashion are necessarily causal risk factors. Variables in the final model could simply have non-causal associations with the outcome or other risk factors, and there is also the possibility of inclusion by chance alone.³⁷ To categorize a risk factor as a causal factor, we evaluated it in clinical context. For example, arthralgia symptom was a risk factor but an unlikely causal factor for the diseases of IPAA. This study might also have been subject to bias when the data were abstracted. The estimation of duration of IPAA could have been compromised by the fact that it was difficult to identify how long the patient had had the disease. Instead, we measured the likelihood of having a specific disease at the time the subject visited the Pouchitis Clinic with the diagnosis of a disease confirmed. Future prospective studies should be aimed at obtaining a well-defined onset time of the first disease to occur after IPAA. Although our study showed risk factors (such as NSAID use for pouchitis and smoking for CD of the pouch) with statistical strength and temporal precedence of associations, we were not able to assess dose-response relations because of the sample size for multiple comparisons.

Although we have studied a total of 18 variables, we have not studied others. We have not included some

potential variables associated with increased risk for diseases of IPAA because of following concerns: (1) Some of the histopathologic features of the colectomy specimens, such as backwash ileitis or indeterminate colitis, could not be accurately assessed as potential risk factors for pouchitis or CD of the pouch because of the lack of consistent established and validated criteria for backwash ileitis^{8,38,39} or indeterminate colitis^{39,40} and because of the fact that original colectomy specimens in some of the patients were not available for pathology re-review. (2) The IPAA without mucosectomy could be a potential risk factor for cuffitis. However, we did not list mucosectomy versus non-mucosectomy as a separate variable because this particular variable would have overlapped with the current variable of surgical indication. According to the standard care at our institution, IPAA with mucosectomy is reserved for patients with UC and dysplasia or familial adenomatous polyposis. IPAA without mucosectomy is performed in patients with medically refractory UC who require surgery. (3) Genetic and serologic tests, such as perinuclear antineutrophil cytoplasmic antibodies and anti-Saccharomyces cerevisiae antibodies (ASCA), were not performed because of high cost and inconsistency of their diagnostic value reported in the literature. In addition, the status of serologic markers for CD or UC, such as perinuclear antineutrophil cytoplasmic antibodies and ASCA, can change over time during the course of disease.⁴¹ (4) Patients with diseases of IPAA could present a variety of extraintestinal manifestations, with arthralgias being the most common symptoms and PSC being a unique entity possibly associated with pouchitis.^{6,9,10} Therefore, arthralgias and PSC were evaluated in this study.

There could have been potential referral or selection bias. The patients seen in our Pouchitis Clinic often had disease that was difficult to manage, which might not reflect the current situation in community gastroenterology practice. We included only patients with chronic diseases of IPAA (antibiotic-dependent/refractory pouchitis, CD of the pouch, cuffitis, and IPS), which pose the greatest challenge in the investigation of etiopathogenesis and clinical management. To minimize referral and selection biases, we consecutively enrolled the patients and stratified the diseases of IPAA into antibiotic-dependent/refractory pouchitis, CD of the pouch, cuffitis, and IPS. Patients with surgical complications or antibiotic-responsive pouchitis were excluded from the study. Because the diseases of IPAA are rarely seen in the general population, it is difficult to perform such a study in a community hospital setting. The practice pattern in our institution might largely reflect that in the major

tertiary US institutions. The findings can only apply to the chronic and challenging forms of diseases of IPAA and mainly apply to the tertiary care setting.

In conclusion, arthralgia symptom is a risk factor shared by all 4 diseases of IPAA. However, most of the other risk factors that we identified for the diseases of IPAA were different, suggesting that each of these disorders has a different etiology and pathogenesis. Smoking had contrasting effects on pouchitis and CD of the pouch. NSAID use was associated with an increased risk for pouchitis. Younger age was associated with cuffitis. The use of antidepressants or anti-anxiety agents was associated with IPS. These findings would directly impact on the clinical decision making for both patients and clinicians regarding whether, when, and what IPAA would be performed and on modifying or intervening for some risk factors, such as smoking, NSAID use, to improve surgical outcome and patients' quality of life.

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Supported by NIH R03 DK 067275 and an American College of Gastroenterology Junior Faculty Development Grant (to B.S.).