

## Differentiating Risk Factors for Acute and Chronic Pouchitis

JEAN-PAUL ACHKAR,\* MOHAMMAD AL-HADDAD,\* BRET LASHNER,\* FEZA H. REMZI,†  
AARON BRZEZINSKI,\* BO SHEN,\* FARAH KHANDWALA,§ and VICTOR FAZIO†

\*Department of Gastroenterology, †Department of Colorectal Surgery, and the §Department of Biostatistics, Center for Inflammatory Bowel Disease, Cleveland Clinic Foundation, Cleveland, Ohio

**Background & Aims:** Pouchitis is the most common complication of ileal pouch anal anastomosis in patients with ulcerative colitis. In some cases the inflammation becomes chronic and requires long-term medical therapy. The clinical course and medical therapy are different between acute pouchitis and chronic pouchitis. The aim of this study was to determine if there are predictors of risk for acute vs. chronic pouchitis. **Methods:** Patients with acute pouchitis (N = 40) and patients with chronic pouchitis (N = 40) were matched with a control group who never had pouchitis (N = 40). Data were collected for multiple pre-, peri-, and postoperative factors and follow-up telephone calls were performed. Case-control univariable analyses and multivariate logistic regression were used to measure the association between covariates and pouchitis. **Results:** Multivariate logistic regression showed that extensive colonic disease (odds ratio [OR], 2.99; P = .045 for acute pouchitis; and OR, 4.61; P = .010 for chronic pouchitis) and extraintestinal manifestations (OR, 2.88; P = .037 for acute pouchitis; and OR, 2.69; P = .047 for chronic pouchitis) were associated with both acute and chronic pouchitis. Postoperative nonsteroidal anti-inflammatory drug (NSAID) use was associated with chronic pouchitis, but less so with acute pouchitis. Patients with fulminant colitis as an indication for surgery had a decreased risk for developing chronic pouchitis (OR, 0.22; P = .036), but no such association was seen for acute pouchitis. **Conclusions:** Extensive colonic disease and preoperative extraintestinal manifestations are associated with increased risk for both acute and chronic pouchitis. Fulminant colitis leading to colectomy is protective from development of chronic pouchitis. Postoperative use of NSAIDs is a risk factor for chronic pouchitis and possibly for acute pouchitis, and thus should be discouraged for patients who undergo ileal pouch anal anastomosis.

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is the surgery of choice for the majority of patients with ulcerative colitis who require surgical intervention. The most common long-term complication of this surgery is pouchitis, a nonspecific inflammatory process of the ileoanal pouch.<sup>1</sup> The incidence of pouchitis varies with factors such as duration of

follow-up evaluation, the diagnostic criteria used to define pouchitis, and the intensity of evaluation for pouch inflammation.<sup>1,2</sup> The reported 10-year cumulative incidence rates in patients with underlying ulcerative colitis vary between 15% and 50%.<sup>1–4</sup> In most cases, pouchitis is an acute process that responds rapidly to a short course of antibiotics.<sup>1</sup> However, in approximately 5% of patients, pouchitis can develop into a chronic problem requiring repeated courses of antibiotics over short periods of time or even chronic therapy with antibiotics or other agents.<sup>1,2</sup> In addition, patients with chronic pouchitis may be at higher risk for requiring pouch excision.

The cause of pouchitis is unclear but the disease occurs much more frequently in patients with underlying ulcerative colitis than those with familial adenomatous polyposis.<sup>1,3</sup> Risk factors for the development of pouchitis in ulcerative colitis have been reported in several studies, although there have been some conflicting results as well. Reported risk factors include primary sclerosing cholangitis,<sup>4,5</sup> other extraintestinal manifestations of inflammatory bowel disease,<sup>5–7</sup> young age at diagnosis of ulcerative colitis,<sup>5</sup> extensive colonic disease,<sup>8,9</sup> preoperative terminal ileal inflammation,<sup>9</sup> and the presence of perinuclear antineutrophil cytoplasmic antibodies.<sup>10,11</sup> On the other hand, one study showed that smoking was protective against the development of pouchitis.<sup>12</sup> Most of these studies evaluated patients who predominantly had acute pouchitis. Only a few studies have focused specifically on chronic pouchitis.<sup>10,11</sup> It is not known whether acute and chronic pouchitis represent different spectrums of the same disease, or whether they have the same underlying cause and the same risk factors. Determining risk factors for chronic pouchitis may be relatively more important given the chronicity of symptoms and frequent need for long-term medical therapy. Therefore, the aim of this study was to evaluate patients with

**Abbreviations used in this paper:** CI, confidence interval; IPAA, ileal pouch–anal anastomosis; OR, odds ratio.

© 2005 by the American Gastroenterological Association  
1542-3565/05/\$30.00

PII: 10.1053/S1542-3565(04)00604-4

acute and chronic pouchitis to determine if there were different risk factors for these 2 groups.

## Methods

### Study Population

We performed 2 case-control studies evaluating a total of 120 patients with ulcerative colitis or indeterminate colitis who had undergone restorative proctocolectomy with IPAA. Patients with a course suggestive of Crohn's disease based on either colectomy pathology or postsurgical clinical course (development of perianal fistulas or inflammation in the small bowel proximal to the pouch detected by pouch endoscopy or radiographic studies) were excluded from the study.

Cases consisted of patients with acute pouchitis (N = 40) and chronic pouchitis (N = 40) as defined later. The control group consisted of asymptomatic IPAA patients who have never had pouchitis (N = 40). Patients were matched as closely as possible by date of surgery and by sex.

Patients were identified from 2 sources. The first source was the outpatient clinical practice at the Center for Inflammatory Bowel Disease at the Cleveland Clinic Foundation. The second source was the Cleveland Clinic Ileal Pouch Registry. This registry is a prospectively maintained database that includes information on over 2800 patients who have undergone IPAA at the Cleveland Clinic Foundation since 1987. Patients are evaluated with standardized yearly questionnaires and receive a screening pouch endoscopy every 1–2 years. Patients who met the definitions listed later were selected randomly from this registry.

The study was approved by the Cleveland Clinic Foundation Institutional Review Board.

### Definitions of Pouchitis

All patients classified as having either acute or chronic pouchitis were required to have typical symptoms of pouchitis and at least one abnormal pouch endoscopy during one of these symptomatic episodes. Typical symptoms were defined as increased number and looser consistency of bowel movements compared with baseline, rectal bleeding, urgency, incontinence, and/or abdominal or pelvic cramps.

Acute pouchitis was defined as: (1) 3 or fewer episodes of pouchitis per year, (2) symptoms lasting less than 4 weeks at a time with each episode, (3) symptoms responding to short courses ( $\leq 14$  days) of antibiotics, and (4) at least one pouch endoscopy showing endoscopic and histologic inflammation of the pouch during one of these episodes of pouchitis.

Chronic pouchitis was defined as the presence of 1 or more of the following criteria: (1) 4 or more episodes of pouchitis per year, (2) active symptoms lasting continuously for more than 4 weeks despite antibiotic therapy, or (3) chronic antibiotic or anti-inflammatory therapy to control symptoms of pouchitis. In addition, we required at least 1 pouch endoscopy showing endoscopic and histologic inflammation of the pouch during an episode of pouchitis.

### Data Collection

Detailed information regarding preoperative, perioperative, and postoperative factors was obtained by review of medical records. Telephone interviews then were conducted with all patients to confirm the number of episodes of pouchitis and to ascertain demographic data, smoking history, and use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Preoperative factors that we evaluated were as follows: (1) age at diagnosis of ulcerative colitis; (2) family history of inflammatory bowel disease; (3) use of immunomodulators (not including corticosteroids) to control disease; (4) presence of extraintestinal manifestations including arthralgias related to disease activity, peripheral arthritis, ankylosing spondylitis, ocular manifestations including scleritis, episcleritis, or uveitis, skin involvement including erythema nodosum and pyoderma gangrenosum, and primary sclerosing cholangitis; and (5) maximal extent of disease involvement. Because the overall numbers for each extraintestinal manifestation were relatively small, we combined all of these manifestations into one group and performed an analysis as to presence of any extraintestinal manifestation vs. no extraintestinal manifestation. The determination of extent of disease was based on maximal macroscopic extent and was classified as either extensive (disease extending proximal to the splenic flexure) or left sided (disease up to or distal to the splenic flexure).

Perioperative factors that we evaluated were as follows: (1) duration of disease before surgery; (2) indication for surgery; (3) terminal ileal inflammation (backwash ileitis) as determined by colectomy pathology; and (4) number of surgeries at time of ileostomy closure. Indication for surgery was classified as medically refractory disease (chronic disease failing to respond to standard outpatient therapy of ulcerative colitis including 5-aminosalicylic acid agents, corticosteroids, and immunomodulators), fulminant colitis (defined as severe colitis requiring hospitalization and failing to respond to intravenous corticosteroids), and dysplasia/cancer. The number of surgeries at time of ileostomy closure was classified as 1-, 2-, or 3-stage surgery. Of note, only 3 patients in all of the study groups had a 1-stage proctocolectomy with IPAA so we analyzed 1- or 2-stage vs 3-stage surgeries.

Postoperative factors that we evaluated were as follows: (1) use of NSAIDs after colectomy as assessed during the past 1 year before the telephone interview was conducted, (2) pouchitis course and response to treatment, and (3) smoking history at time of follow-up evaluation. The use of NSAIDs was classified if study patients used either over-the-counter or prescription NSAIDs including aspirin at least once per week for a period of at least 6 months. Smoking status was classified as current smoker, ex-smoker (quit for at least 6 months before the telephone interview), or never smoker.

### Statistical Analysis

Two case-control studies, one comparing acute pouchitis with the control group and one comparing chronic pouchitis

**Table 1.** Demographic Features of the 3 Groups

Factor	Controls	Acute pouchitis	Chronic pouchitis
Male/Female	27/13	23/17	25/15
Age at diagnosis (y)	31.3 ± 10.9	32.0 ± 13.0	30.9 ± 12.3
Age at colectomy (y)	42.7 ± 13.1	40.0 ± 13.4	40.5 ± 11.8
Duration of follow-up evaluation after ileostomy closure (y)	5.2 ± 3.7	6.6 ± 3.8	5.2 ± 3.5

tis with the control group, were conducted. Analyses were performed as unmatched comparisons.

Univariable comparisons were made via Wilcoxon rank-sum tests for continuous variables and  $\chi^2$  and Fisher exact tests for categorical variables. Variables significant at a .30 level or less then were placed in an initial logistic regression model and backward selection was used to eliminate nonsignificant factors. Interactions among significant factors also were tested.

A significance level of .05 was used for all analyses. Results were computed by using SAS 8.2 (SAS Institute Inc., Cary, NC).

## Results

As shown in Table 1, the 3 study groups were similar in terms of sex, age at diagnosis of ulcerative colitis, and age at colectomy. There was a slightly longer duration of follow-up evaluation after ileostomy closure for the acute pouchitis group, but this difference was not significant. The majority of patients were matched within a 2-year period to date of surgery.

### Univariable Analysis

Case-control analyses were performed for the acute pouchitis vs control groups and for the chronic pouchitis vs control groups. There were no differences for age at diagnosis, age at colectomy, and years of disease before colectomy between the acute pouchitis and control groups or between the chronic pouchitis and control groups. The results for the other factors analyzed in the univariable analyses are shown in Tables 2 (acute pouchitis) and 3 (chronic pouchitis). Because no patients in the control group had terminal ileal inflammation, odds ratios (ORs) could not be estimated for this factor. In comparison with the controls, 3 of 33 (9%) patients with chronic pouchitis ( $P = .1$  vs controls) and 6 of 33 (18%) patients with acute pouchitis ( $P = .009$  vs. controls) had evidence of terminal ileal inflammation at the time of colectomy.

As shown in Table 2, factors that either reached or were close to reaching statistical significance for an association with an increased risk for acute pouchitis were extensive disease ( $P = .04$ ), presence of preoperative extraintestinal manifestations ( $P = .04$ ), and postopera-

**Table 2.** Univariable Comparisons of Categorical Measures: Acute Pouchitis Versus Controls

		Acute		Control		<i>P</i> value
		N	%	N	%	
Family history of IBD	Negative	31	77.5	29	72.5	.61
	At least 2nd degree	9	22.5	11	27.5	
Disease extent	Rectosigmoid/left colon	8	20.5	17	42.5	.04
	Extensive	31	79.5	23	57.5	
Indication for surgery	MRD	24	60.0	23	59.0	.93
	Dysplasia or cancer	6	15.0	5	12.8	
	Fulminant colitis	10	25.0	11	28.2	
Immunosuppression before surgery	No	29	74.4	29	72.5	.85
	Yes	10	25.6	11	27.5	
Extraintestinal manifestations	No	21	52.5	30	75.0	.04
	Yes	19	47.5	10	25.0	
3-stage surgery	No	31	77.5	28	70.0	.45
	Yes	9	22.5	12	30.0	
NSAID	No	16	45.7	27	67.5	.06
	Yes	19	54.3	13	32.5	
Smoking	Never	24	60.0	19	48.7	.31
	Ex-smoker	16	40.0	20	51.3	

IBD, inflammatory bowel disease; MRD, medically refractory disease.

tive use of NSAIDs ( $P = .06$ ). Similarly, as shown in Table 3 for chronic pouchitis, the same factors were associated with an increased risk for pouchitis: extensive disease ( $P < .01$ ), presence of preoperative extraintestinal manifestations ( $P = .02$ ), and postoperative use of

**Table 3.** Univariable Comparisons of Categorical Measures: Chronic Pouchitis Versus Controls

		Chronic		Control		<i>P</i> value
		N	%	N	%	
Family history of IBD	Negative	31	77.5	29	72.5	.61
	At least 2nd degree	9	22.5	11	27.5	
Disease extent	Rectosigmoid/left colon	5	12.5	17	42.5	<.01
	Extensive	35	87.5	23	57.5	
Indication for surgery	MRD	29	74.4	23	59.0	.06
	Dysplasia or cancer	7	18.0	5	12.8	
	Fulminant colitis	3	7.7	11	28.2	
Immunosuppression before surgery	No	27	67.5	29	72.5	.63
	Yes	13	32.5	11	27.5	
Extraintestinal manifestations	No	20	50.0	30	75.0	.02
	Yes	20	50.0	10	25.0	
3-stage surgery	No	35	87.5	28	70.0	.06
	Yes	5	12.5	12	30.0	
NSAID	No	16	40.0	27	67.5	.01
	Yes	24	60.0	13	32.5	
Smoking	Never	18	46.2	19	48.7	.82
	Ex-smoker	21	53.9	20	51.3	

IBD, inflammatory bowel disease; MRD, medically refractory disease.

**Table 4.** Extraintestinal Manifestations by Study Group

Extraintestinal manifestation	Acute pouchitis <sup>a</sup>	Chronic pouchitis <sup>a</sup>	Controls
Primary sclerosing cholangitis	2	2	0
Ankylosing spondylitis	2	1	1
Uveitis	1	1	0
Peripheral arthritis	3	2	0
Arthralgias	13	16	9

<sup>a</sup>Two patients with acute pouchitis and 1 patient with chronic pouchitis had more than 1 extraintestinal manifestation.

NSAIDs ( $P = .01$ ). In addition, 2 factors appeared to be associated with a decreased risk for chronic pouchitis: a fulminant colitis indication for surgery ( $P = .06$ ) and a 3-stage surgery ( $P = .06$ ). Of note, however, these latter 2 factors appear to be related to each other as shown by the fact that 22 of 24 (92%) patients with fulminant colitis underwent a 3-stage surgery compared with only 3 of 96 (3%) patients with medically refractory disease or dysplasia/cancer ( $P < .001$ ). Because of this interaction between the 2 factors, only indication for surgery was included in the logistic regression model. We also noted that patients with a fulminant colitis indication for surgery had a significantly shorter disease duration before colectomy (median, 4.5 y; 25th, 75th quartiles, 2.3, 8.5, respectively) compared with patients with all other indications for colectomy (median, 8.0 y; 25th, 75th quartiles, 3.3, 16.0, respectively;  $P = .02$ ).

A more detailed breakdown of the different extraintestinal manifestations by group is shown in Table 4. Arthralgias associated with ulcerative colitis disease activity were the most common extraintestinal manifestation. Of note, there were only 4 patients in the study who had primary sclerosing cholangitis and all 4 developed pouchitis—2 had acute pouchitis and 2 had chronic pouchitis.

**Logistic Regression**

The risk factors identified on univariable analysis can interact with each other. For example, we showed that the number of surgeries is related to the indication for surgery, whereas other studies have shown that the extent of disease is related to the indication for surgery and to the presence of extraintestinal manifestations. We therefore constructed models looking at the extent of disease, extraintestinal manifestations, and indication for surgery separately while adjusting for NSAID use (Tables 5 and 6).

For acute pouchitis (Table 5), extensive disease (OR, 2.99; 95% confidence interval [CI], 1.02–8.71;  $P =$

**Table 5.** Logistic Regression Models for Acute Pouchitis

	OR (95% CI)	P value
<b>Model 1</b>		
Extraintestinal manifestations	2.88 (1.07–7.80)	.037
NSAID	2.18 (.83–5.75)	.116
<b>Model 2</b>		
Extensive disease	2.99 (1.02–8.71)	.045
NSAID	2.46 (.92–6.53)	.072
<b>Model 3</b>		
Fulminant colitis indication	.82 (.27–2.48)	.721
Dysplasia/cancer indication	1.09 (.28–4.30)	.900
NSAID	2.32 (.89–6.04)	.084

.045) and extraintestinal manifestations (OR, 2.88; 95% CI, 1.07–7.80;  $P = .037$ ) were associated with increased risk for pouchitis. Postoperative NSAID use bordered on statistical significance in 2 of the models.

For chronic pouchitis (Table 6), extensive disease (OR, 4.61; 95% CI, 1.45–14.63;  $P = .010$ ) and extraintestinal manifestations (OR, 2.69; 95% CI, 1.01–7.15;  $P = .047$ ) also were associated with increased risk for pouchitis, as was postoperative NSAID use (ORs ranged between 2.73 and 2.83 in the 3 models). A fulminant colitis indication for surgery was associated with a decreased risk for developing chronic pouchitis (OR, .22; 95% CI, .05–.92;  $P = .038$ ).

**Subgroup Analysis of Chronic Pouchitis**

Because the chronic pouchitis group consisted of a mixture of patients on intermittent but frequent antibiotics ( $N = 23$ ) and patients on chronic therapy with either antibiotics ( $N = 14$ ) or other agents ( $N = 3$ ), we compared these 2 groups to determine if they had similar characteristics. As shown in Table 7, there were no significant differences between the 2 groups in terms of sex, age at diagnosis, duration of ulcerative colitis before colectomy, extraintestinal manifestations, fulminant colitis, smoking, or NSAID use. The frequency of extensive disease bordered on being statistically different but was

**Table 6.** Logistic Regression Models for Chronic Pouchitis

	OR (95% CI)	P value
<b>Model 1</b>		
Extraintestinal manifestations	2.69 (1.01–7.15)	.047
NSAID	2.83 (1.10–7.24)	.030
<b>Model 2</b>		
Extensive disease	4.61 (1.45–14.63)	.010
NSAID	2.73 (1.04–7.14)	.041
<b>Model 3</b>		
Fulminant colitis indication	.22 (.05–.92)	.038
Dysplasia/cancer indication	.98 (.26–3.66)	.978
NSAID	2.78 (1.07–7.24)	.037

**Table 7.** Comparison of Chronic Versus Intermittent Therapy Groups of Chronic Pouchitis

	Chronic therapy (N = 17)	Intermittent therapy (N = 23)	P value
Sex	9 F/8 M	6 F/17 M	.16
Age at diagnosis <sup>a</sup>	50.0 (41.3, 57.8)	44.0 (33.8, 51.5)	.22
Years of disease <sup>a</sup>	9.0 (3.8, 17.3)	8.0 (3.0, 14.8)	.69
Extraintestinal manifestations	6 (35%)	14 (61%)	.20
Extensive disease	17 (100%)	18 (78%)	.06
Fulminant colitis indication for surgery	1 (6%)	2 (9%)	1.0
Ex-smokers	9 (53%)	12 (52%)	.79
NSAID use	12 (70%)	12 (52%)	.40

<sup>a</sup>Values reported as median (25th, 75th percentiles).

high in both groups (100% for chronic therapy vs. 78% for intermittent therapy).

## Discussion

Most studies to date that have evaluated risk factors for pouchitis have focused on groups consisting predominantly of patients with acute pouchitis or a mixture of patients with acute and chronic pouchitis. Our study analyzed risk factors for acute vs chronic pouchitis.

We used a priori definitions to ensure that we could distinguish between the 2 groups. The definitions we chose are somewhat arbitrary, which is owing to the fact that there currently are no standardized criteria to distinguish between acute and chronic pouchitis. However, several reports have been published on chronic pouchitis suggesting that this condition is a separate disease entity from acute pouchitis. Our definitions therefore were derived based on those prior studies, which used general categories relating to one or more of the following: (1) frequent relapses of pouchitis over a short period of time, (2) persistent or recurrent symptoms requiring chronic suppressive medical therapy, or (3) chronic symptoms refractory to medical therapy.<sup>4-8,10,11,13-16</sup> The fact that we did find differences in risk factors between the acute and chronic pouchitis groups would imply that these groups are different from each other and that the definitions we used can indeed distinguish between them. We also specifically looked at the chronic pouchitis group in more detail, comparing those on chronic therapy with those on intermittent therapy to determine if there was significant heterogeneity within the group. As shown in Table 7, there were no significant

differences found between these 2 subgroups in terms of sex, age at diagnosis, duration of ulcerative colitis before colectomy, extraintestinal manifestations, fulminant colitis indication for surgery, smoking, or NSAID use. The frequency of extensive disease bordered on being statistically different but was high in both groups. Furthermore, we were more stringent in our inclusion criteria than many prior studies because we required evidence of inflammation on at least one pouch endoscopy with biopsy examinations during an episode of typical symptoms for both the acute and chronic pouchitis groups. Our group has shown previously that symptoms suggestive of pouchitis do not always correlate with an objective diagnosis of pouchitis based on the pouchitis disease activity index,<sup>17</sup> and therefore we wanted to be sure that patients indeed had endoscopic and histologic confirmation of pouchitis. All these factors would suggest that the definitions we chose allowed us to distinguish between the acute and chronic pouchitis groups.

After selecting our patient groups, we performed case-control studies to analyze potential risk factors for acute and chronic pouchitis. Univariable analyses revealed the following factors that either achieved or were close to achieving statistical significance for increased risk for both acute and chronic pouchitis: extensive disease, presence of preoperative extraintestinal manifestations, and postoperative use of NSAIDs. In contrast, a fulminant colitis indication for surgery and a 3-stage surgical approach were associated with a decreased risk for chronic pouchitis, but these factors were not associated with acute pouchitis. On logistic regression, we confirmed that extensive disease and preoperative extraintestinal manifestations were associated with increased risks for developing both acute and chronic pouchitis and that patients with a fulminant colitis indication for surgery were less likely to develop chronic pouchitis.

Extensive disease, defined as maximal macroscopic extent of inflammation proximal to the splenic flexure, was associated with increased risk for developing both acute and chronic pouchitis, but was associated more strongly with risk for developing chronic pouchitis. ORs were 4.61 ( $P = .01$ ) for chronic pouchitis and 2.99 ( $P = .045$ ) for acute pouchitis. Two other studies have revealed similar results.<sup>8,9</sup> Luukkonen et al.<sup>8</sup> analyzed a mixed group of acute and chronic pouchitis and found that these patients had a significantly lower incidence of disease limited to the left colon compared with patients without pouchitis. Similarly, Schmidt et al.<sup>9</sup> found that extensive macroscopic and microscopic colonic disease both were associated with significantly higher pouch biopsy inflammation scores during subsequent follow-up

evaluation. These investigators also showed that macroscopic colonic disease extent exhibited a significant linear association with pouch inflammation.

The presence of preoperative extraintestinal manifestations was associated with equally increased risks for developing both acute and chronic pouchitis with ORs of 2.88 ( $P = .037$ ) for acute pouchitis and 2.69 ( $P = .047$ ) for chronic pouchitis. Other investigators have found similar results. Penna et al<sup>4</sup> found a strong correlation between primary sclerosing cholangitis and both acute and chronic pouchitis. Patients with primary sclerosing cholangitis had an estimated 10-year risk of 79% for the development of pouchitis compared with 46% for those without primary sclerosing cholangitis. There were only 4 patients with primary sclerosing cholangitis in our study groups, so we could not analyze this factor separately. Interestingly, however, all 4 of these patients developed pouchitis (2 patients developed acute pouchitis and 2 patients developed chronic pouchitis). Because patients with extraintestinal manifestations other than arthralgias were few, we combined all extraintestinal manifestations into one group for analysis. A limitation of this approach is that we cannot evaluate the effect or degree of risk conferred by any one particular extraintestinal manifestation. Two other studies used a similar approach of combining extraintestinal manifestations and found similar results.<sup>6,18</sup> Lohmuller et al<sup>6</sup> reported that the presence of both preoperative and postoperative extraintestinal manifestations were associated with increased risk for pouchitis. Hata et al<sup>18</sup> evaluated Japanese patients who underwent IPAA and reported a hazard ratio of 16.85 (95% CI, 3.12–91.00;  $P = .001$ ) for risk for pouchitis among patients with extraintestinal manifestations.

On univariable analysis, we found that indication for surgery and a 3-stage surgical approach impacted on the risk for developing chronic pouchitis but not acute pouchitis. We also showed that the indication for surgery was related directly to the number of surgical stages with 92% of patients with fulminant colitis having undergone a 3-stage surgery compared with only 3% of patients with other indications for surgery. Based on the fact that these factors were related directly, we only included indication for surgery in our logistic regression model for chronic pouchitis because we thought that this was more likely to represent an independent association. In this model, a fulminant colitis indication for surgery had a protective effect against the development of chronic pouchitis with an OR of .22. This finding is somewhat surprising because one would predict that patients with more aggressive preoperative disease would be more

likely to develop postoperative complications such as pouchitis.

Based on the finding that fulminant colitis is associated with a decreased risk for chronic pouchitis but is not associated with risk for acute pouchitis, we hypothesize that underlying causative factors such as genetic predisposition may impact on both the preoperative and postoperative course of patients with ulcerative colitis. Although acute and chronic pouchitis do share some risk factors, chronic pouchitis has a different clinical course and therefore may have a different underlying cause. Specifically, we propose that a factor such as a genetic mutation not only may predispose to the development of ulcerative colitis but also may lead to a fulminant course of disease and may be protective against the development of chronic pouchitis. For example, patients in our study with fulminant colitis had a shorter duration of disease before colectomy (median, 4.5 y) compared with patients with other indications for surgery (median, 8.0 y;  $P = .02$ ), suggesting a different phenotypic manifestation of disease. Support for this theory comes from a recently published study that found that certain cytokine gene polymorphisms were associated with a decreased risk for pouchitis.<sup>19</sup> Specifically, carriage of either interleukin-1–receptor antagonist allele 2 or of tumor necrosis factor allele 2 was associated with a decreased risk for developing pouchitis.<sup>19</sup> Of note, interleukin-1–receptor antagonist allele 2 has been reported previously to be associated with increased genetic susceptibility to the development of ulcerative colitis, especially among patients with extensive colitis.<sup>20,21</sup> Others have suggested that patients with chronic pouchitis may represent a genetically distinct subset of patients with ulcerative colitis.<sup>10,11,16</sup> An example of this has been the association of perinuclear antineutrophil cytoplasmic antibodies with chronic pouchitis in some studies.<sup>10,11</sup> One study found that the risk for developing chronic pouchitis increased with higher titers of preoperative perinuclear antineutrophil cytoplasmic antibody levels.<sup>11</sup> Patients who had high preoperative antibody titers had a relative risk of 8.47 (95% CI, 1.67–16.95) of developing chronic pouchitis.<sup>11</sup>

Finally, postoperative use of NSAIDs was associated with increased risk for chronic pouchitis and almost achieved statistical significance for association with risk for acute pouchitis. Some studies have suggested that the use of NSAIDs is associated with relapses of inflammatory bowel disease.<sup>22</sup> It is therefore reasonable to hypothesize that, in similar fashion, postoperative NSAID use may predispose to the development of pouchitis. In addition, we have shown that the use of postoperative NSAIDs is associated with the development of ulcers in the pouch and afferent limb in patients who have under-

gone IPAA.<sup>23</sup> Based on this information, we would recommend that patients be counseled to avoid NSAIDs after IPAA surgery.

In summary, we have shown that acute and chronic pouchitis share some similar risk factors: extensive disease and extraintestinal manifestations. In addition, other associations, which have not been described previously, and that appear unique for chronic pouchitis were found. Postoperative NSAID use is associated with increased risk for chronic pouchitis, whereas a fulminant colitis indication for surgery is associated with a decreased risk for chronic pouchitis. Future confirmation of these findings would be important given that the inverse association with fulminant colitis could suggest a unique underlying cause for chronic pouchitis and the fact that postoperative use of NSAIDs is a modifiable risk factor.

## References

- Mahadevan U, Sandborn WJ. Diagnosis and management of pouchitis. *Gastroenterology* 2003;124:1636–1650.
- Sandborn WJ. Pouchitis following ileal pouch-anal anastomosis. Definition, pathogenesis, and treatment. *Gastroenterology* 1994;107:1856–1860.
- Fazio VW, Ziv Y, Church JM, et al. Ileal pouch-anal anastomosis complications and function in 1005 patients. *Ann Surg* 1995;222:120–127.
- Penna C, Dozois R, Tremaine W, et al. Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. *Gut* 1996;38:234–239.
- Stahlberg D, Gullberg K, Liljeqvist L, et al. Pouchitis following pelvic pouch operation for ulcerative colitis: incidence, cumulative risk, and risk factors. *Dis Colon Rectum* 1996;39:1012–1018.
- Lohmuller JL, Pemberton JH, Dozois RR, et al. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. *Ann Surg* 1990;211:622–629.
- Aisenberg J, Wagreich J, Shim J, et al. Perinuclear anti-neutrophil cytoplasmic antibody and refractory pouchitis: a case-control study. *Dig Dis Sci* 1995;40:1866–1872.
- Luukkonen P, Jarvinen H, Tanskanen M, et al. Pouchitis—recurrence of the inflammatory bowel disease. *Gut* 1994;35:243–246.
- Schmidt CM, Lazenby AJ, Hendrickson RJ, et al. Preoperative terminal ileal and colonic resection histopathology predicts risk of pouchitis in patients after ileoanal pull-through procedure. *Ann Surg* 1998;227:654–662.
- Sandborn WJ, Landers CJ, Tremaine WJ, et al. Antineutrophil cytoplasmic antibody correlates with chronic pouchitis after ileal pouch-anal anastomosis. *Am J Gastroenterol* 1995;90:740–747.
- Fleshner PR, Vasiliauskas EA, Kam LY, et al. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. *Gut* 2001;49:671–677.
- Merrett MN, Mortensen N, Kettlewell M, et al. Smoking may prevent pouchitis in patients with restorative proctocolectomy for ulcerative colitis. *Gut* 1996;38:362–364.
- Hurst RD, Molinari M, Chung TP, et al. Prospective study of the incidence, timing, and treatment of pouchitis in 104 consecutive patients after restorative proctocolectomy. *Arch Surg* 1996;131:497–502.
- Perrault J, Berry R, Greseth J, et al. Pouchitis in young patients after the ileal pouch-anal anastomosis. *Inflamm Bowel Dis* 1997;3:181–185.
- Rauh SM, Schoetz DJ, Roberts PL, et al. Pouchitis—is it a wastebasket diagnosis? *Dis Colon Rectum* 1991;34:685–689.
- Schwartz DA, Sandborn WJ. Chronic pouchitis. In: Bayless TM, Hanauer SB, eds. *Advanced therapy of inflammatory bowel disease*. Hamilton, Ontario: B.C. Decker Inc, 2001:219–223.
- Shen B, Achkar JP, Lashner BA, et al. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. *Gastroenterology* 2001;121:261–267.
- Hata K, Watanabe T, Shinozaki M, et al. Patients with extraintestinal manifestations have a higher risk of developing pouchitis in ulcerative colitis: multivariate analysis. *Scand J Gastroenterol* 2003;38:1055–1058.
- Aisenberg J, Legnani PE, Nilubol N, et al. Are pANCA, ASCA, or cytokine gene polymorphisms associated with pouchitis? Long-term follow-up in 102 ulcerative colitis patients. *Am J Gastroenterol* 2004;99:432–441.
- Mansfield JC, Holden H, Tarlow JK, et al. Novel genetic associations between ulcerative colitis and the anti-inflammatory cytokine interleukin-1 receptor antagonist. *Gastroenterology* 1994;106:637–642.
- Tountas NA, Casini-Raggi V, Yang H, et al. Functional and ethnic association of allele 2 of interleukin-1 receptor antagonist gene in ulcerative colitis. *Gastroenterology* 1999;117:806–813.
- Felder JB, Korelitz BI, Rajapakse R, et al. Effects of nonsteroidal anti-inflammatory drugs on inflammatory bowel disease: a case-control study. *Am J Gastroenterol* 2000;95:1949–1954.
- Wolf JM, Achkar JP, Lashner BA, et al. Afferent limb ulcers predict Crohn's disease in patients with ileal pouch-anal anastomosis. *Gastroenterology* 2004;126:1686–1691.

---

Address requests for reprints to: Jean-Paul Achkar, MD, Department of Gastroenterology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk A30, Cleveland, Ohio 44195. e-mail: achkarj@ccf.org; fax: (216) 444-6305.