Transmural Inflammation, Ileitis, and Granulomas at the Time of Proctocolectomy in Patients with Ulcerative Colitis Do Not Predict Future Development of Pouchitis

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Abstract
Background: The most common complication following ileal pouch-anal anastomosis (IPAA) in patients with ulcerative colitis (UC) is pouchitis. Our study aimed to investigate the relationship between histopathologic findings of ileitis, granuloma, or transmural inflammation on the colectomy specimen of patients with clinically and endoscopically diagnosed UC and the development of pouchitis within the first 2 years after IPAA. Methods: We performed a retrospective cohort study evaluating patients undergoing colectomy with IPAA for UC between January 1, 2004 and December 31, 2016. Bi-variate analyses were conducted to evaluate the relationship between clinical factors and the development of pouchitis. We performed multivariate logistic regression to evaluate the relationship between histologic, clinical, and demographic factors at the time of colectomy and subsequent development of pouchitis. Results: Among 626 patients, pouchitis occurred in 246 (39%). Patients with primary sclerosing cholangitis were more likely to develop pouchitis (adjusted odds ratio [aOR] 2.81, 95% confidence interval [CI] 1.02–7.72), as were patients with a family history of inflammatory bowel disease (aOR 1.75, 95% CI 1.11–2.77). Histologic findings of ileitis, granuloma, or transmural inflammation were not associated with an increased odds of developing pouchitis (aOR 0.70, 95% CI 0.45–1.08). Discussion/Conclusion: Patients with ileitis, granulomas, or transmural inflammation at the time of colectomy were not at greater risk for development of pouchitis in the 2 years after IPAA. These pathologic findings should not preclude IPAA for UC.
Introduction

Although proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the most common restorative surgical procedure among patients with ulcerative colitis (UC) who require surgical therapy for refractory colitis or dysplasia-associated UC, the burden of inflammatory conditions after IPAA is well recognized [1, 2]. Up to 80% of patients will develop pouchitis at some point after IPAA is well recognized [3, 4], and 10% will develop Crohn’s-like disease of the pouch, despite a preoperative diagnosis of UC [5]. Despite their relatively high prevalence, there is a paucity of predictors of these complications.

Traditionally, the findings of transmural inflammation and a granuloma on gross pathology have been associated with a clinical diagnosis of Crohn's disease [6]. Thus, the identification of these findings at the time of total abdominal colectomy in a patient with UC might conceivably impact surgical planning, including the decision to pursue an IPAA or treatment strategies in the early postoperative setting. Prior studies have demonstrated an increased risk for pouchitis among patients with UC-associated ileitis (backwash ileitis) [7, 8] and ileitis on histopathology at the time of colectomy [9]. However, this relationship is not definitive as other studies have demonstrated no significant association [10–12]. Similarly, the relationship between histopathologic findings such as granuloma and subsequent pouch outcomes is not well defined [12]. Although end ileostomy in the setting of UC may also be associated with complications and variable effects on quality of life [13], we hypothesized that these histopathologic findings might increase the risk of early pouchitis. If such a relationship were demonstrated, we believed that the potential for worse pouch-related outcomes due to perioperative pathological findings could prompt a change in surgical planning, including the decision to pursue end ileostomy over IPAA. Given the lack of definitive data regarding the impact of histopathology at the time of colectomy and future outcomes after IPAA, we performed a retrospective cohort study to evaluate the relationship between the presence of ileitis, granuloma, or transmural inflammation on histopathology from colectomy specimens and the development of pouchitis within the first 2 years after IPAA among patients with UC.

Methods

Patient Selection

We identified 758 patients who underwent restorative proctocolectomy with IPAA for UC at the University of North Carolina at Chapel Hill (UNC) between January 1, 2004 and December 31, 2016. Of these, 626 (83%) met the inclusion criteria for the study. Patients were identified utilizing the Carolina Data Warehouse for Health (CDW-H), a central data repository that contains clinical and administrative data from electronic health records in the UNC Health system. Pertinent clinical, demographic, and laboratory data were extracted from the electronic medical record using a standardized case extraction form. Any patient older than 18 years who had undergone proctocolectomy with IPAA for clinically established UC at the UNC during the study period and had 2 years of complete follow-up after surgery was eligible for inclusion. The preoperative diagnosis of UC was based on available clinical, endoscopic, and pathological data prior to the time of colectomy and confirmed on the review of the medical record. Patients undergoing IPAA for UC during the study period without a full 2 years of follow-up after IPAA were excluded from the study. Additionally, patients with a preoperative diagnosis of Crohn’s disease or IBD-unclassified (IBD-U) at the time of colectomy were excluded.

Outcomes of Interest

The primary outcome of interest was the development of pouchitis within the first 2 years after the final stage of IPAA surgery. At least 2 of 3 expert gastroenterologists (E.L.B., B.K., or H.H.H.) reviewed the charts of all 626 included patients to determine if the patient had a diagnosis of pouchitis within the first 2 years of IPAA. This diagnosis was based on clinical symptoms including frequency, urgency, abdominal pain, and a sense of malaise, as well as response to therapy. Pouchoscopy and/or biopsies were not required for a diagnosis of pouchitis. Any cases where a discrepancy existed between the reviewers were automatically re-reviewed with the assistance of a third reviewer to resolve the differences and make the final determination on the clinical diagnosis of pouchitis. The inter- and intra-rater reliability of the assessment of pouchitis were assessed using kappa statistics and intra-class coefficients as directed by the Landis and Koch [14] benchmarks (<0.00 poor, 0–0.2 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.00 almost perfect). For inter-rater reliability, the kappa was 0.70 (95% confidence interval [CI] 0.64–0.76) indicating substantial agreement; for intra-rater reliability, the kappa was 0.86 (95% CI 0.76–0.96) indicating almost perfect agreement.

Covariates

The medical record of each patient was examined to extract demographic, clinical, and pathological factors that might be associated with the development of pouchitis, including preoperative factors such as disease extent and medications prior to colectomy and concomitant diagnoses such as primary sclerosing cholangitis (PSC). At our center, a modified 2-stage IPAA is defined as follows: a total abdominal colectomy with end ileostomy is completed in the first operation, and after a recovery interval, a second surgery is performed including completion proctectomy and IPAA (without a diverting loop ileostomy) [15]. A traditional 2-stage IPAA was defined as a total proctocolectomy IPAA with loop ileostomy followed by an ostomy takedown. We specifically evaluated the pathology report of each patient’s colectomy specimen to document the presence of ileitis, granulomas, or transmural inflammation on the examination of the gross specimen removed at the time of colectomy. All pathological findings were confirmed by documentation of the presence of specific findings in pathological reporting. The stated absence of findings in the

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pathological report (lack of granuloma, ileitis, or transmural inflammation) was not required.

**Statistical Analysis**

Continuous variables were summarized using means and standard deviations and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as proportions and compared using Fisher’s exact and χ² testing, as appropriate. Bivariate and multivariable logistic regression models were utilized to evaluate the relationship between specific pathological findings at the time of colectomy (ileitis, granulomas, or transmural inflammation) and the development of pouchitis within the first 2 years after IPAA, controlling for potential confounders. All covariates included in the multivariable analyses were identified a priori based on suspected association with disease activity in UC preoperatively or the subsequent development of pouchitis after IPAA. All statistical analyses were performed using SAS (version 9.4) statistical software (SAS Institute, Cary, NC, USA). The study protocol was approved by the Institutional Review Board at the UNC.

### Table 1. Demographics and clinical characteristics of patients undergoing proctocolectomy with IPAA between 2004 and 2016

| Patients undergoing IPAA (n = 626) | n | % |
|-----------------------------------|---|---|
| Age at surgery (median, IQR), years | 40.6 | 29.5–52.5 |
| Disease duration prior to surgery (median, IQR), years | 6.08 | 2.18–14.2 |
| Female sex | 302 | 48 |
| Race<sup>a</sup> | | |
| White | 545 | 11 |
| Non-white | 66 | 89 |
| Hispanic | 13 | 2 |
| Family history of IBD | 97 | 17 |
| Indication for surgery | | |
| Medically refractory colitis | 494 | 79 |
| Dysplasia or cancer | 83 | 13 |
| Other indication | 49 | 8 |
| Disease extent prior to surgery | | |
| Proctitis | 26 | 4 |
| Left-sided colitis | 173 | 29 |
| Extensive colitis | 388 | 66 |
| Type of IPAA surgery | | |
| 1-Stage | 116 | 19 |
| 2-Stage | 224 | 36 |
| Modified 2-stage<sup>b</sup> | 234 | 37 |
| 3-Stage | 51 | 8 |
| Ileitis on pathology | 105 | 17 |
| Granuloma on pathology | 26 | 4 |
| Transmural inflammation on pathology | 34 | 5 |
| Abscess or pelvic sepsis after IPAA surgery | 117 | 19 |
| Evidence of an IPAA leak immediately after surgery | 46 | 7 |
| PSC | 19 | 3 |
| Medications prior to colectomy | | |
| Systemic aminosalicylate | 495 | 79 |
| Topical aminosalicylate | 302 | 48 |
| Thiopurine | 390 | 62 |
| Methotrexate | 67 | 11 |
| Anti-TNF | 321 | 51 |
| Vedolizumab | 17 | 3 |
| Cyclosporine | 26 | 4 |

<sup>a</sup>Race was missing or not reported for 15 patients. <sup>b</sup>Modified 2-stage IPAA: a total abdominal colectomy with end ileostomy is completed in the first operation, and after a recovery interval, a second surgery is performed including completion proctectomy and IPAA.
### Results

Among 626 patients who underwent proctocolectomy with IPAA for UC, 246 (39%) developed pouchitis within the first 2 years after the final stage of IPAA surgery. Of the 626 patients, 302 (48%) were female, and the median age of patients at the time of IPAA was 40.6 years, interquartile range 29.5–52.5 years (shown in Table 1). The most common type of surgical procedure performed was a modified 2-stage IPAA (37%), although another 36% of patients underwent a traditional 2-stage IPAA. When evaluating the specific pathological findings of interest on the colectomy specimen, 17% of patients had ileitis, 4% had a granuloma or granulomas, and 5% had transmural inflammation.

Among patients developing pouchitis, the median time to development of pouchitis was 148 (interquartile range 75–320) days. When evaluating the clinical factors

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**Table 2. Univariate comparison of demographic and clinical characteristics of patients with and without pouchitis in the 2 years following an IPAA**

|                                | Patients without pouchitis (n = 380) | Patients with pouchitis (n = 246) | p value |
|--------------------------------|-------------------------------------|-----------------------------------|---------|
|                                | n        | %     | n        | %     |         |
| Age at surgery (median, IQR), years | 42.4 30.7–54.3 | 39.6 29.7–51.9 | 0.17    |
| Disease duration prior to surgery (median, IQR) | 5.73 2.18–15.3 | 6.21 2.21–13.1 | 0.93    |
| Female sex | 179 47 | 123 50 | 0.48    |
| Race | | | | |
| White | 327 88 | 218 91 | 0.30    |
| Non-white | 44 12 | 22 9 | |
| Hispanic | 6 2 | 7 3 | 0.56 |
| Family history of IBD | 49 14 | 48 21 | 0.02 |
| Indication for surgery | | | |
| Medically refractory colitis | 297 78 | 197 80 | 0.02 |
| Dysplasia or cancer | 55 15 | 28 11 | 0.50 |
| Other indication | 28 7 | 21 9 | |
| Disease extent prior to surgery | | | |
| Proctitis | 17 5 | 9 4 | 0.22 |
| Left-sided colitis | 95 27 | 78 34 | |
| Extensive colitis | 242 68 | 146 63 | |
| Type of IPAA surgery | | | |
| 1-Stage | 75 20 | 41 17 | 0.03 |
| 2-Stage | 119 31 | 105 43 | |
| Modified 2-stage | 155 41 | 79 32 | |
| 3-Stage | 30 8 | 21 9 | |
| Ileitis on pathology | 70 18 | 35 14 | 0.17 |
| Granuloma on pathology | 18 5 | 8 3 | 0.36 |
| Transmural inflammation on pathology | 27 7 | 7 3 | 0.02 |
| Abscess or pelvic sepsis after IPAA surgery | 71 19 | 46 19 | 0.10 |
| Evidence of an IPAA leak immediately after surgery | 28 7 | 18 7 | 0.98 |
| PSC | 8 2 | 11 5 | 0.09 |
| Medications prior to colectomy | | | |
| Systemic aminosalicylate | 291 77 | 204 83 | 0.06 |
| Topical aminosalicylate | 175 46 | 127 52 | 0.17 |
| Thiopurine | 225 59 | 165 67 | 0.05 |
| Methotrexate | 43 11 | 24 10 | 0.53 |
| Anti-TNF | 196 52 | 125 51 | 0.85 |
| Vedolizumab | 7 2 | 10 4 | 0.10 |
| Cyclosporine | 12 3 | 14 6 | 0.12 |

Anti-TNF, anti-tumor necrosis factor alpha; IPAA, ileal pouch-anal anastomosis; IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis.
associated with the development of pouchitis, patients with pouchitis were more likely to undergo a traditional 2-stage IPAA than patients without pouchitis (43% vs. 31%) and were less likely to undergo a modified 2-stage IPAA (32% vs. 41%, shown in Table 2). There were no significant associations between preoperative medication use and development of pouchitis, including the preoperative use of biologics.

In bivariate analysis, patients with pouchitis were less likely to demonstrate transmural inflammation alone on gross pathology of their resected colon and rectum than patients without pouchitis (3% vs. 7%, p = 0.02). There were no significant differences in the proportion of patients with granulomas or ileitis on pathology when comparing patients who developed pouchitis compared to patients who did not develop pouchitis (3% vs. 5% and 14% vs. 18% respectively).

In the unadjusted analysis, the combined findings of ileitis, granuloma, or transmural inflammation on pathology at the time of colectomy were not associated with the development of pouchitis within the first 2 years after IPAA. These findings have a clinical impact for gastroenterologists, surgeons, and patients, given the significant concern about the postoperative burden of inflammatory conditions of the pouch. Although almost 40% of patients developed pouchitis within the 2-year follow-up period, these pathological findings at the time of colectomy that might give providers pause in proceeding with restorative surgery were not predictive of future pouchitis. Despite a relatively small prevalence, well-recognized risk factors such as PSC [16, 17] were associated with future development of pouchitis.

When evaluating the surgical procedure used, patients who underwent a modified 2-stage procedure were less likely to develop pouchitis than those undergoing a 2-stage procedure (aOR 0.64, 95% CI 0.42–0.97).

### Discussion

In an analysis of 626 patients undergoing colectomy with IPAA for UC at our tertiary care referral center between 2004 and 2016, histopathologic findings of ileitis, granuloma, and transmural inflammation were not associated with the development of pouchitis within the first 2 years after IPAA. These findings have a clinical impact for gastroenterologists, surgeons, and patients, given the significant concern about the postoperative burden of inflammatory conditions of the pouch. Although almost 40% of patients developed pouchitis within the 2-year follow-up period, these pathological findings at the time of colectomy that might give providers pause in proceeding with restorative surgery were not predictive of future pouchitis. Despite a relatively small prevalence, well-recognized risk factors such as PSC [16, 17] were associated with future development of pouchitis.

Currently, a staged approach to restorative proctocolectomy with IPAA is preferred over a 1-stage operation in patients with active, therapy-refractory UC [1]. Although a 3-stage IPAA has several advantages including a decreased rate of pelvic sepsis and a decreased risk

### Table 3. Unadjusted and adjusted odds of developing pouchitis among patients undergoing proctocolectomy with IPAA as a treatment of UC

|                                | Unadjusted OR (95% CI) | aOR (95% CI) |
|--------------------------------|------------------------|-------------|
| Age at the time of surgery     | 1.01 (1.00–1.02)       | 1.01 (0.99–1.02) |
| PSC                            | 2.18 (0.86–5.49)       | 2.81 (1.02–7.72) |
| Family history of IBD          | 1.70 (1.09–2.63)       | 1.75 (1.11–2.77) |
| Disease extent prior to surgery|                        |             |
| Proctitis                      | 0.65 (0.27–1.53)       | 0.67 (0.28–1.64) |
| Left-sided colitis             | Reference              | Reference   |
| Extensive colitis              | 0.74 (0.51–1.06)       | 0.78 (0.53–1.16) |
| Type of IPAA surgery           |                        |             |
| 1-Stage                        | 0.62 (0.39–0.98)       | 0.61 (0.37–1.03) |
| 2-Stage                        | Reference              | Reference   |
| Modified 2-stage               | 0.58 (0.40–0.84)       | 0.64 (0.42–0.97) |
| 3-Stage                        | 0.79 (0.43–1.47)       | 0.85 (0.43–1.69) |
| Ileitis, granuloma, or transmural inflammation on pathology | 0.59 (0.40–0.89) | 0.70 (0.45–1.08) |

CI, confidence interval; OR, odds ratio; aOR, adjusted OR; IPAA, ileal pouch-anal anastomosis; IBD, inflammatory bowel disease; UC, ulcerative colitis; PSC, primary sclerosing cholangitis. a Pathological findings evaluated as combined variable, given that each pathological finding was underpowered to include as an individual variable.
for unplanned reoperations [1], the initial total abdomi-
nal colectomy also allows for the examination of the gross
pathology from the resected specimen, which could influ-
ence decision-making if there were concerns regarding
future inflammatory conditions of the pouch. Our study
extends the results of a prior study from Cedars-Sinai
Medical Center, which found that no single atypical his-
topathologic feature of UC (or combination of features)
was associated with worse outcomes after IPAA in multi-
variate analysis [12]. However, the study from Cedars-
Sinai Medical Center included only 153 patients, 22% of
whom carried a preoperative diagnosis of indeterminate
colitis. Although we attempted to identify those patients
with clinically diagnosed UC prior to colectomy, the find-
ings of transmural inflammation and (and more specifi-
cally granuloma) at the time of colectomy likely indicate
a spectrum of disease, given that no prior indication of
IBD-U existed in these patients. UC-associated or back-
wash ileitis, which was found in 17% of our patients at the
time of colectomy, has been associated an increased risk
of developing pouchitis or a higher incidence of pouchitis
after IPAA in a number of small studies [7–9]; however,
these results are not conclusive as a separate smaller study
showed no relationship [10], and in a prospective study,
backwash ileitis was not associated with the development
of acute or chronic pouchitis after IPAA [18].

Other preoperative factors have been identified with
an increased risk for pouchitis. PSC has been identified as
a significant risk factor for the later development of pou-
chitis [7, 19–25], and some authors have speculated that
PSC-related pouchitis may be a different phenotype from
other idiopathic forms of pouchitis that develop after
IPAA [26]. We also demonstrated a significantly in-
creased risk of pouchitis in the first 2 years after surgery
among patients with a positive family history of IBD, which
has also been associated with an increased risk for
development of Crohn’s-like disease of the pouch [27].
Due to the relatively short follow-up, we cannot rule out
that our positive association may result in an increased
incidence of a Crohn’s-like phenotype of pouch inflam-
mation with a longer follow-up. A recent publication
from the University of Chicago indicated that patients
with preoperative use of anti-tumor necrosis factor alpha
therapy were at an increased risk to develop pouchitis
during a median follow-up of 62 months [28]. In our
analysis, there was no relationship between preoperative
biologic exposure and subsequent development of pou-
chitis.

Taken together, these findings suggest that in patients
with clinically and endoscopically proven UC, the pres-
ence of ileitis, granulomas, or transmural inflammation
on the resected colectomy specimen is not associated with
increased risk for pouchitis. Thus, in patients with a
planned staged IPAA, these histopathologic findings
should not change the future plans for restorative surgery.
Given that the presence of UC-associated ileitis and gran-
uloma might be noted in the preoperative setting, includ-
ing on biopsies from colonoscopy, these specific findings
might also extend to pathological findings from preopera-
tive evaluations and not the gross colectomy specimen.
However, this remains a continued area of research.

Our study has multiple strengths including large sam-
ple size collected over a 13-year period of time from a
tertiary care IBD referral center. However, our study has
limitations. Our outcomes occurred in a single IBD cen-
ter. Given that this was a retrospective study, we did not
have accurate data regarding smoking or the presence of
extraintestinal manifestations of UC at the time of colec-
tomy, both of which have been evaluated as risk factors
for pouchitis [29, 30]. We also did not evaluate the use of
immunosuppressive or biologic therapies in the post-
IPAA period, which could have influenced the develop-
ment of pouch inflammation or other complications. Al-
though we had a complete 2-year follow-up for all includ-
ed patients, allowing us to evaluate the incidence of
pouchitis within the first 2 years after IPAA as it related
to specific clinical predictors, we do not have long-term
data on these patients. Thus, we could not evaluate the
relationship between these predictors and other poten-
tially important but longer term outcomes such as
Crohn’s-like disease of the pouch and pouch failure. Fi-
ally, the overall rate of the pathological findings of inter-
est was low, limiting the power to evaluate these patho-
logical features individually in a multivariable analysis.
However, no individual pathological factor was associ-
ated with an increased risk of pouchitis in bivariate com-
parison, and thus, by combining these high-risk factors,
we were aiming to amplify any signal not detected by the
small sample size of each individual factor.

In summary, among patients with UC undergoing re-
storative proctocolectomy with IPAA, histopathologic
findings at the time of colectomy including ileitis, granu-
loma, and transmural inflammation were not associated
with an increased risk for the development of pouchitis
within the first 2 years after IPAA. These data provide re-
assurance that gastroenterologists, colorectal surgeons,
and patients who encounter these findings on pathology
at the time of the initial colectomy should not prevent
further planned stages of restorative surgery in the form
of an IPAA. Future studies should evaluate the impact of
these findings on long-term outcomes such as Crohn’s-like disease of the pouch and pouch failure in the current biologic era.

Statement of Ethics

This study was a retrospective analysis and informed consent was not required on review of the study protocol by the Institutional Review Board at the UNC (18-1804). All study protocols and research were conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

Edward L. Barnes has served as a consultant for AbbVie, Gilead, Pfizer, Takeda, and Target RWE. Bharati Kochar has served as a consultant for Pfizer. Michael D. Kappelman has served as a consultant for AbbVie, Takeda, Janssen, and Eli Lilly and has received research support from Abbvie and Janssen. Millie D. Long has served as a consultant for AbbVie, UCB, Takeda, Janssen, Pfizer, Salix, Valeant, and Target Pharmasolutions and has received research support from Pfizer and Takeda. Hans H. Herfarth has served as a consultant for Alivio, AMAG, Finch, Gilead, Lycera, Merck, Otsuka, Pfizer, PureTech, and Seres and research support from Pfizer and Artizan Biosciences. Joshua Hudson, Scott Esckilsen, Mark Koruda, and Robert S. Sandler have no relevant disclosures or conflicts of interest.

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Author Contributions

E.L.B. was involved in the study concept and design, data acquisition, statistical analysis, interpretation of the data, drafting of the manuscript, and critical revision of the manuscript. J.H., S.E., R.K., M.K., and H.H.H. were involved in the study concept and design, data acquisition, interpretation of the data, and critical revision of the manuscript. M.D.K., M.D.L., and R.S.S. were involved in the study concept and design, interpretation of the data, and critical revision of the manuscript.

Data Availability Statement

Raw data and analytic methods may be available by contacting the corresponding author at edward_barnes@med.unc.edu.

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