

Chronic Antibiotic Dependent Pouchitis Is Associated With Older Age at the Time of Ileal Pouch Anal Anastomosis (J-pouch) Surgery

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Background: Risk factors for the development of chronic antibiotic dependent pouchitis (CADP) are not well understood.

Methods: Using multivariable logistic regression, we compared clinical factors between 194 patients with acute antibiotic responsive pouchitis or CADP.

Results: Individuals with CADP were significantly older (40.9 vs 30.8 years, $P < 0.001$) and demonstrated a longer disease duration before IPAA (10.3 vs 7.0 years, $P = 0.004$). Age ≥ 55 years at the time of IPAA was significantly associated with CADP (adjusted odds ratio = 4.35, 95% confidence interval = 1.01–18.7).

Conclusions: Although older age should not represent a barrier to IPAA, further studies evaluating etiologies of this association are warranted.

Key Words: age, chronic antibiotic dependent pouchitis, ileal pouch-anal anastomosis

INTRODUCTION

Although restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the preferred surgical treatment for the management of medically refractory ulcerative colitis (UC) and UC-related dysplasia,^{1,2} between 50% and 80% of those with an IPAA will experience pouchitis symptoms.^{3,4} While pouch function and durability are typically thought to be excellent,⁵ there were early concerns regarding outcomes of this surgical approach in older patients.^{6,7} Other studies have suggested no increased risk for adverse outcomes among older patients with UC undergoing colectomy with IPAA.^{8–11} Additionally, colorectal surgery societies have stated that age

alone should not be used as an exclusion criteria when considering IPAA in a patient with a history of UC.²

In addition to the burden of acute pouchitis, recurrent pouchitis is common, with up to 19% of patients developing a chronic antibiotic dependent pouchitis (CADP).¹² There is an overall paucity of predictors for the development of pouchitis, with the vast majority of cases being considered idiopathic.¹³ Modifiable factors such as NSAID use,¹⁴ body mass index (BMI),^{15, 16} and smoking status¹⁴ have been suggested as potential factors in acute and/or chronic pouchitis. Additionally, perioperative decision making can influence outcomes after IPAA, as delayed pouch creation has been associated with a decreased risk for unplanned reoperations and complications

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after surgery.¹⁷ Other factors such as disease extent at the time of colectomy¹⁸ and age at the time of surgery are not modifiable. Understanding the potential for any adverse outcomes among older patients with UC undergoing proctocolectomy with IPAA is critical, given that the aging population of patients with inflammatory bowel disease (IBD) is increasing. Approximately 10%–30% of patients with IBD are over the age of 60 years,^{19,20} and a recent meta-analysis suggested that patients with UC diagnosed at age 50 and older underwent surgery at a significantly higher rate as compared with patients with onset of disease at younger ages.²¹

We performed a retrospective cohort study of patients with pouch-related disorders to identify potential predictors of the development of CADP. Our primary objective was to analyze potential predictors of the development of CADP among patients treated for pouch-related disorders in our multidisciplinary IBD center, including age at the time of IPAA creation, the number of stages necessary for total proctocolectomy with IPAA, BMI, and comorbidities at the time of surgery.

METHODS

Patient Population

We performed a retrospective cohort study, examining data from patients who underwent a proctocolectomy with IPAA (J-pouch) as a treatment for refractory UC or UC-related dysplasia and later developed acute pouchitis or CADP. All patients were treated in the University of North Carolina (UNC) Multidisciplinary Inflammatory Bowel Diseases Center, and all data were previously entered into a central electronic database. Patients were identified for inclusion into the database using International Classification of Diseases 9th and 10th Clinical Modification (ICD-9-CM and ICD-10-CM) coding (569.71 and K91.850) and the Informatics for Integrating Biology and the Bedside (i2b2) platform through the Carolina Data Warehouse for Health. As previously described,^{22,23} i2b2 is the flagship tool developed by the i2b2 Center, a National Institutes of Health (NIH) funded National Center for Biomedical Computing based at Partners HealthCare System. Patients were eligible for inclusion if they met all of the following criteria: (i) age \geq 18 years, (ii) history of proctocolectomy with IPAA as a treatment for UC, (iii) treated for acute pouchitis or CADP between January 1, 2009 and December 1, 2016. Patients were eligible for inclusion if they were treated in any IBD clinic, including the gastroenterology or surgery clinics, as well as the specialized UNC Multidisciplinary Pouch clinic, which is largely a referral population. Patients were identified with ICD-9-CM and ICD-10-CM using the i2b2 platform, with confirmation of typical pouchitis symptoms required including frequency, urgency, incontinence, or abdominal pain/discomfort.¹⁴ Patients were evaluated from their first visit following proctocolectomy with IPAA, and all patients underwent pouchoscopy at UNC. Individuals with Crohn disease (CD) of

the pouch were excluded from this study. CD of the pouch was diagnosed based upon the Cleveland Clinic criteria including the presence of granulomas on histology, inflammation, or ulcerations in the afferent limb, development of fistula over 12 months after IPAA, or strictures in the mid-pouch, pouch inlet, or afferent limb in the absence of nonsteroidal anti-inflammatory drug use.^{24–26}

Definition of Cohorts

All patients with pouchitis were treated with antibiotics per the prescribing provider's decision, with no standard regimen enforced. Those patients with response to a course of antibiotics (14 days or less) were identified as having acute pouchitis, responsive to antibiotic therapy. Those patients who required antibiotics at least 3 times each year or continuously for more than 3 months to control pouchitis symptoms were identified as having CADP.²⁷ These 2 patient groups (acute pouchitis vs relapsing CADP) represented the 2 cohorts for comparison in this study.

Definition of Covariates

Our primary aim in this study was to identify predictors of the development of CADP. To identify potential predictors, we analyzed both demographic and clinical factors that could be related to the development of CADP, including age at the time of IPAA, sex, body mass index (BMI), the number of stages necessary for total proctocolectomy with IPAA, and concomitant therapies used to treat pouchitis. Given our interest in the relationship between age at the time of IPAA and risk for development of CADP, age was analyzed in both a continuous fashion and in categorical analysis. To account for comorbidities at the time of IPAA, we utilized the Deyo-modification of the Charlson comorbidity index, which has been validated for use as a marker of comorbid illness.²⁸

Statistical Analysis

Continuous variables are summarized using means and standard deviations, and compared using Student *t* tests and Wilcoxon-rank-sum testing. Proportions are used to express categorical variables, which were analyzed using Fisher exact and chi-square testing. Multivariable logistic regression was used to adjust for confounders in the evaluation of potential predictors of the development of CADP. All covariates were included in regression models due to their clinical relevance, and all factors included were identified *a priori*. Multicollinearity was assessed in the creation of multivariable models, given concerns regarding model fit.

Given our interest in evaluating age at the time of IPAA as a potential risk factor for development of CADP, we performed a series of secondary analyses to evaluate for any potential cohort effects. First, we eliminated any patients older than age 70 from the evaluation. In the second of these analyses, we

evaluated patients grouping the age at the time of surgery categorically. A 2-tailed P value of 0.05 was chosen as the threshold for statistical significance for all tests. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) are presented. All analyses were performed using SAS (version 9.4) statistical software (SAS Institute, Cary, NC). The study protocol was approved by the Institutional Review Board at UNC-Chapel Hill.

RESULTS

A total of 287 patients were evaluated for pouch-related disorders during the study period. From this initial population, 90 (31%) were excluded due to a diagnosis of CD of the pouch, and 3 were excluded due to a diagnosis of CD or indeterminate colitis at the time of proctocolectomy with IPAA. Of the remaining 194 patients, 123 (63%) met the criteria for a diagnosis of CADP (Fig. 1). Of all eligible patients, 139 (71%) were seen and treated in the UNC Multidisciplinary Pouch Clinic.

When compared to patients who demonstrated acute, antibiotic responsive pouchitis, patients with CADP were significantly older at the time of IPAA (40.9 years vs 30.8 years, $P < 0.001$, Table 1) and demonstrated a longer disease duration at the time of IPAA (10.3 years vs 7.0 years, $P = 0.004$). There were no significant differences in stage of IPAA ($P = 0.990$) or disease extent before colectomy ($P = 0.320$) when comparing patients with CADP to those with acute pouchitis. There was also no significant difference when comparing the indication for colectomy, with a significant majority of patients in both groups undergoing colectomy for medically refractory disease (89% vs 92%, $P = 0.453$).

In our planned secondary analysis, all patients older than age 70 at the time of IPAA creation were removed from the analyses ($n = 13$). In this analysis, patients with CADP continued to demonstrate a significant difference in age at the time of IPAA when compared with patients with antibiotic responsive pouchitis (38.2 years vs 31.2 years, $P < 0.001$). When age at the time of surgery was evaluated in 5 categories, a significant trend was noted, with increased frequency of CADP as the age at the time of surgery increased (chi-square test of trend, $P < 0.001$, Fig. 2). Additionally, in pairwise comparisons, significant differences in the development of CADP were noted when comparing patients aged 55 or older at the time of IPAA creation to patients aged 35–44 ($P = 0.006$), aged 25–34 ($P = 0.009$) and those patients < 25 years of age ($P < 0.001$) at the time of IPAA creation.

When examined in logistic regression, age ≥ 55 years at the time of IPAA creation remained a significant predictor for the development of CADP in the unadjusted analysis (OR $\&= 5.21$, 95% CI $\&= 1.51$ –18.1) and after adjusting for potential confounders (aOR $\&= 4.35$, 95% CI $\&= 1.01$ –18.7, Table 2). All other variables included in the multivariable analysis including male sex, disease duration at the time of IPAA, and the Charlson Comorbidity score at the time of IPAA were not significantly associated with the development of CADP.

DISCUSSION

Recent studies have demonstrated that older age at the time of IPAA is not associated with worse outcomes.^{7,29–32} In our retrospective analysis of individuals with history of IPAA for medically refractory UC or UC-related dysplasia and at least

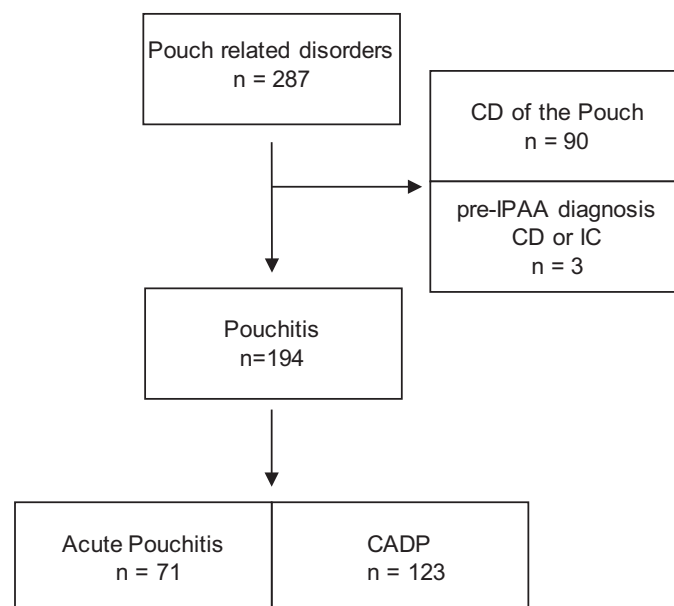


FIGURE 1. A flow chart of the included study population. CADP, chronic antibiotic dependent pouchitis; CD, Crohn disease; IC, indeterminate colitis; IPAA, ileal pouch-anal anastomosis.

TABLE 1. A Comparison of Baseline Clinical Factors Among Patients With Acute, Antibiotic Responsive Pouchitis and Patients With Chronic Antibiotic Dependent Pouchitis

| | Antibiotic Responsive Pouchitis, n &= 71 | | Chronic Antibiotic Dependent Pouchitis, n &= 123 | | P |
|---|--|----------|--|----------|--------|
| | Mean | SD | Mean | SD | |
| Age at time of IPAA | 30.8 | 12.3 | 40.9 | 14.9 | <0.001 |
| Disease duration at time of IPAA | 7.0 | 6.3 | 10.3 | 9.5 | 0.004 |
| Body mass index at time of IPAA | 25.2 | 5.2 | 26.0 | 5.3 | 0.330 |
| | n | % | n | % | |
| Male sex | 29 | 41 | 65 | 53 | 0.094 |
| Indication for proctocolectomy | | | | | 0.453 |
| Medically refractory disease | 66 | 92 | 109 | 89 | |
| Dysplasia | 5 | 7 | 14 | 11 | |
| Stages of IPAA ^a | | | | | 0.990 |
| 1 | 11 | 15 | 19 | 17 | |
| 2 | 43 | 61 | 76 | 69 | |
| 3 | 9 | 11 | 16 | 14 | |
| Disease extent before proctocolectomy | | | | | 0.320 |
| Proctitis | 10 | 14 | 11 | 9 | |
| Left-sided colitis | 7 | 10 | 19 | 15 | |
| Pancolitis | 42 | 59 | 82 | 67 | |
| Unknown | 12 | 17 | 11 | 9 | |
| Family history of IBD | 15 | 20 | 27 | 22 | 0.893 |
| Charlson comorbidity score at time of IPAA | | | | | 0.079 |
| 0 | 55 | 77 | 76 | 62 | |
| 1 | 9 | 13 | 25 | 20 | |
| 2 or more | 7 | 10 | 22 | 18 | |
| History of <i>Clostridium difficile</i> infection | 6 | 8 | 14 | 11 | 0.518 |
| History of anti-TNF therapy for pouchitis | 6 | 8 | 20 | 16 | 0.124 |
| Current chronic opioid use | 18 | 25 | 34 | 28 | 0.729 |

IBD, inflammatory bowel disease; IPAA, ileal pouch-anal anastomosis; TNF, tumor necrosis factor alpha.

^aStage of IPAA was missing for 21 patients.

one episode of pouchitis treated at the UNC Multidisciplinary IBD Center, we observed that those aged 55 and older at the time of IPAA were more likely to develop CADP compared with their younger counterparts when age was analyzed continuously as well as categorically. These findings were significant after adjusting for multiple potential confounders, including disease duration at the time of IPAA and a validated comorbidity index.

Given the overall trends in the aging IBD population and a recent meta-analysis suggesting that older-onset UC patients underwent surgery at a significantly higher rate compared with younger-onset UC patients,²¹ our finding of increased odds of CADP in older individuals who experience pouchitis symptoms may be informative to surgeons when counseling patients about both short- and long-term complications associated with the procedure. A majority of patients will experience at least one

episode of acute pouchitis after IPAA; however, it is the 19% of individuals who develop chronic pouchitis who are left with significant morbidity and burden due to cost of treatment as well as decreased quality of life.^{3,4,12,33}

Although the etiology of pouchitis is not well understood, dysbiosis is felt to contribute as most individuals with pouchitis experience a favorable response to antibiotics.³ Additionally, nonrelaxing pelvic floor dysfunction and altered post-surgical anatomy can result in fecal stasis which may promote a pro-inflammatory environment.^{14,34} As motility disturbance is more common with aging,³⁵ our results suggesting increased risk of CADP among older patients with an IPAA is not surprising. Given the retrospective nature of our database, we were not able to evaluate for motility outcomes or evidence of non-relaxing pelvic floor dysfunction among this population of patients with pouch-related disorders. Additionally, we were

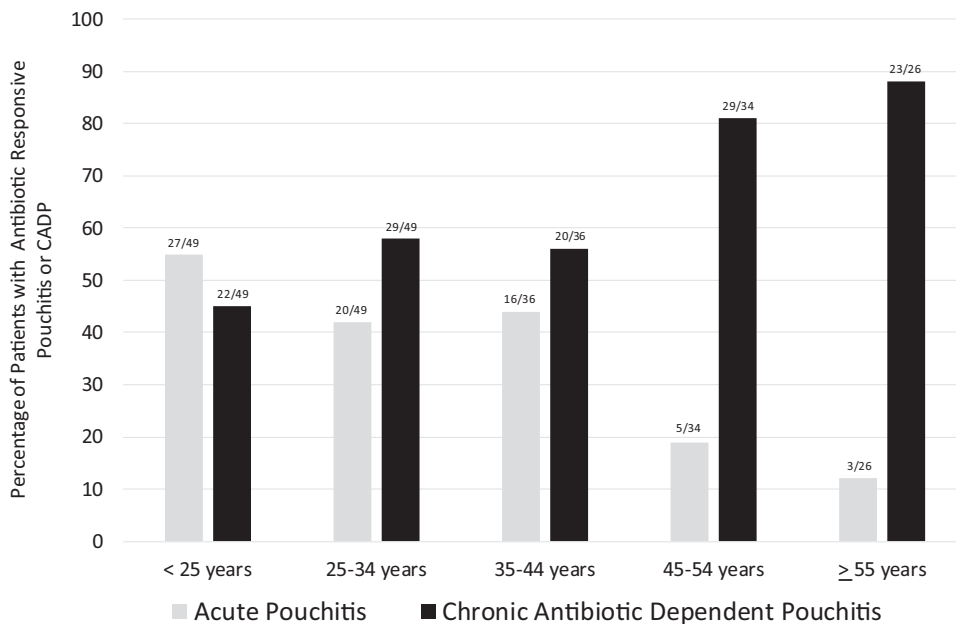


FIGURE 2. A comparison of age at time of proctocolectomy with ileal pouch-anal anastomosis among patients who developed chronic antibiotic dependent pouchitis and patients with antibiotic responsive pouchitis. Chi-square for trend, $P < 0.001$. Pairwise comparisons: >55 years vs $45-54$ years, $P = 1.000$; >55 years vs $35-44$ years, $P = 0.006$; >55 years vs $25-34$ years, $P = 0.009$; >55 years vs <25 years, $P < 0.001$.

TABLE 2. Predictors of Development of Chronic Antibiotic Dependent Pouchitis Among Patients Treated in a Multidisciplinary Inflammatory Bowel Diseases Center, Unadjusted and Adjusted Analyses

| | Unadjusted Analysis OR and 95% CI | Adjusted Analysis ^a OR and 95% CI | <i>P</i> ^b |
|--|-----------------------------------|--|-----------------------|
| Age ≥ 55 at time of IPAA surgery | 5.21 (1.51–18.1) | 4.35 (1.01–18.7) | 0.048 |
| Male sex | 1.62 (0.90–2.93) | 1.65 (0.89–3.05) | 0.114 |
| Disease duration at time of IPAA | | | |
| ≤ 2 years | Reference | Reference | |
| 3–7 years | 2.04 (0.93–4.47) | 1.92 (0.86–4.28) | 0.311 |
| ≥ 8 years | 2.11 (1.05–4.23) | 1.79 (0.87–3.70) | 0.418 |
| Charlson comorbidity score at time of IPAA | | | |
| 0 | Reference | Reference | |
| 1 | 2.01 (0.87–4.64) | 1.61 (0.67–3.86) | 0.332 |
| 2 or more | 2.27 (0.91–5.70) | 1.02 (0.33–3.19) | 0.705 |

IPAA, ileal pouch-anal anastomosis.

^aAll variables included in multivariable analysis are listed above.

^b*P* value for adjusted analysis is presented.

unable to assess the specific diagnostic workup for functional or mechanical pouch complications before or after a diagnosis of CADP was established.

Review of prior literature shows inconsistent results with regards to age as a risk factor for the development of pouchitis. Presumably, a majority of the reported cases of pouchitis are acute in nature but this is not detailed in these studies. Additionally, it is difficult to ascertain the age at which each individual underwent IPAA creation and the relationship to the development of pouchitis. A recent meta-analysis showed

a trend toward increased rates of pouchitis in younger individuals although this finding was not significant.³² The prospective analysis by Chapman et al³¹ examined postoperative complications, functional outcomes, and quality of life metrics among individuals who underwent IPAA through annual questionnaires to determine if age at the time of IPAA affected surgical outcomes. They observed that patients who underwent IPAA between the age of 46 and 55 years demonstrated significantly higher rates of pouchitis compared with individuals who were 45 years or younger when they underwent surgery.³¹ Although

these findings were not seen in those more than 55 years, the older population contained only 65 total patients, with fewer patients analyzed due to the dropout rate in response to questionnaires.

Compared with our cohort which contained only individuals with acute pouchitis or CADP, these prior studies looked at entire populations of patients who underwent IPAA with relatively low numbers of individuals with pouchitis and could have been underpowered for age comparisons. Understanding any increased risk for development of complications including CADP among older patients is particularly important when considering the effects that pouchitis can have on an individual's quality of life. Patients with pouchitis symptoms have demonstrated clinically significant decreases in patient-reported outcomes, such as pain, depression, and fatigue.⁴ The impact that older age at the time of IPAA may have on functional outcome and quality of life^{7,36} may warrant further discussion in preoperative counseling, although given the current evidence, it is not clear if a permanent ileostomy would offer a significantly improved quality of life compared with IPAA among older individuals.^{7,37}

A recent study by McKenna et al evaluated whether age at time of IPAA impacted short- and long-term complications as well as pouch function. Their cohort contained 911 patients who underwent IPAA with only 178 (20%) of individuals more than 50 years old at the time of pouch creation.¹¹ They collected long-term quality of life and functional data from an annual survey that was sent to patients and included patient reported episodes of pouchitis. Although the authors report no difference in pouchitis between the groups, their results are limited by poor survey response rates, particularly in the older age group. In contrast, our cohort included only individuals with pouch-related disorders so may have been a more appropriate patient study population to determine risk factors for chronic pouchitis given small numbers in prior studies. Additionally, we feel that our ability to adjust for the disease duration before colectomy was critical in assessing the impact of age at the time of IPAA on the development of CADP.

Strengths of our study include the large sample size of patients with acute and chronic pouchitis allowing for a more extensive evaluation of the relationship between age at the time of IPAA, other potentially relevant clinical factors, and CADP. Additionally, the significant number of patients over the age of 55 allowed for the comparisons by age in continuous and categorical analyses, the assessment of impact of comorbidities, and for the exploration of any cohort effects. We do acknowledge several limitations. Given the retrospective design, we were unable to assess change in the pouchitis disease activity index endoscopic subscore due to the nonuniform time of follow-up pouchoscopy after initial exam. However, prior studies have shown that visible inflammation within the pouch does not correlate with symptoms.³⁸ Our study utilized a database of patients with pouch-related disorders. While the prevalence of

pouch-related disorders in this group is higher than that of the larger population of patients with an IPAA, given that we are evaluating pouchitis-related outcomes, any perceived bias would be suspected to be nondifferential when comparing younger and older ages at the time of IPAA. Prior studies have identified primary sclerosing cholangitis (PSC) as a potential underlying driver of pouchitis and/or inflammation after IPAA.³⁹⁻⁴¹ We did not evaluate for a diagnosis of PSC at the time of colectomy or development of pouchitis, and thus we were unable to adequately evaluate the influence that a concomitant diagnosis of PSC might have in univariate or multivariable analyses.

In conclusion, patients that were 55 years or older at time of IPAA demonstrated increased odds of developing CADP, among patients with at least one episode of pouchitis. Although older age should not represent a barrier to IPAA, patients should be counseled on potential short- and long-term complications after IPAA including the risk to develop CADP, as chronic pouchitis is associated with significant morbidity and burden to patients with IPAA.

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