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Incidence, prevalence, and risk factors for pouchitis

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A B S T R A C T

Pouchitis is a complication of restorative proctocolectomy and ileal pouch-anal anastomosis surgery in patients who undergo the procedure for the treatment of inflammatory bowel disease or familial adenomatous polyposis. Patients can present with increased stool frequency, urgency, fecal seepage, and abdominal cramps. The reported cumulative frequency rates of pouchitis 10 years after IPAA surgery range from 23% to 60% in IBD patients and 0% to 11% in FAP patients. Although the pathogenesis of pouchitis is unclear, several risk factors for pouchitis have been identified including extraintestinal manifestations of inflammatory bowel disease, autoimmune disorder(s), severity of disease, serologic markers (serum IgG4, autoantibodies to bacterial antigens, p-ANCA, and anti-CBir1 flagellin antibody), genetic markers (NOD2 mutation), smoking, and certain dietary factors. In this review, we will focus on the incidence, prevalence, and risk factors associated with pouchitis.

Background

A total proctocolectomy followed by an ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for two diseases—ulcerative colitis (UC) and familial adenomatous polyposis (FAP). Ulcerative colitis is one of the chronic inflammatory bowel diseases (IBD) and it is estimated that approximately 907,000 people in the United States have UC.[1] Despite advances in medical therapy, as many as 20–30% of UC patients will eventually require surgical resection owing to disease refractory to medical treatment, medication intolerance, dysplasia, or colorectal cancer.[2–4] Additionally, 10–20% of patients admitted to the hospital with acute severe colitis will fail medical therapy and undergo colectomy.[5]

Familial adenomatous polyposis (FAP) is an inherited autosomal dominant disorder[6] characterized by the formation of multiple (> 100) colorectal adenomatous polyps. The disease is because of a germline mutation in the adenomatous polyposis coli (APC) gene.[7–9] In the classic form, approximately 50% of these patients form adenomas by the age of 15 years, which increases to 95% by 35 years of age. The lifetime risk of colorectal cancer approaches 100% by the age of 40 years.[10,11] Therefore, a prophylactic colectomy is required early in life to reduce or eliminate the risk of colon cancer.[12]

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) remains the definitive surgical therapy for patients with UC and FAP.[13] There are different types of ileal pouches but, currently, the J-pouch is the most common type. S or W pouches may also be constructed but are used less commonly given the technical aspects of their surgical creation. IPAA for severe fulminant colitis or toxic megacolon is typically performed in three stages. The mortality rate from acute severe colitis (ASC) has decreased dramatically from 70% in the 1930s to 20–25% in the 1950s when the importance of timely urgent colectomy was recognized.[14,15] However, postoperative adverse sequelae may include pouchitis, decreased female fecundity, irritable pouch syndrome, cuffitis, anastomotic leak, or stenosis and fecal incontinence.[16] In terms of UC, this can sometimes be further complicated by missed or de novo Crohn's disease. In all, 5–10% of patients with a preoperative diagnosis of UC are subsequently diagnosed as having Crohn's disease (CD) after IPAA.[17]

Incidence and prevalence

Multiple studies have shown that the incidence and cumulative risk for the first attack of pouchitis is highest during the first year after surgery, after which the incidence and risk levels off.[18–24] The cumulative frequency rates of pouchitis 10 years after IPAA surgery are reported to range from 23% to 60%.[23,25,26] Table 1 gives a summary of studies on the incidence of pouchitis in patients with ulcerative colitis.

Ulcerative colitis

The incidence of pouchitis in patients who undergo IPAA surgery for UC is significantly higher than that of patients with

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Table 1
Incidence of pouchitis after IPAA in patients with UC.

Study	Year	*n*	Patients with at least one episode of pouchitis, %
Lohmuller et al.[21]	1990	745	31
Stahlberg et al.[19]	1996	149	44
Romanos et al.[27]	1997	175	24
Keränen et al.[28]	1997	291	22
Simchuk and Thirlby[26]	2000	101	60
Ferrante et al.[29]	2008	182	46

n, number of UC patients who underwent IPAA.

FAP. It is estimated that approximately 50% of patients who undergo IPAA surgery for UC are diagnosed with at least one episode of pouchitis.[30]

Familial adenomatous polyposis

Although patients with FAP undergo the exact same IPAA procedure, the incidence of development of pouchitis is significantly less.[21,31] The reported incidence of pouchitis in patients with FAP ranges from 0% to 11% due to variable diagnostic criteria.[21,32,33] This suggests that the underlying inflammatory pathogenesis in UC may play a significant role in the development of pouchitis.[11]

Risk factors associated with pouchitis

Multiple mechanisms have been proposed as the pathogenic mechanisms of pouchitis as discussed in detail in *Chapter 2: Etiology and Pathogenesis of Pouchitis*. Identifying the risk factors associated with pouchitis may help to gain insight into the pathogenesis of this disease. Furthermore, the identification of these factors may identify those patients with more aggressive or medically refractory disease. These patients may require long-term maintenance therapy. Table 2 gives a summary of risk factors associated with the development of pouchitis.

Inflammatory bowel disease–associated risk factors

Extraintestinal manifestations

Inflammatory bowel disease is a systemic disease as it is commonly associated with extraintestinal manifestations and other autoimmune disorders. Extraintestinal manifestations (EIMs) are seen in 25–40% of IBD patients.[38] These include arthritis (axial and peripheral), aphthous stomatitis, iritis/uveitis, erythema nodosum, pyoderma gangrenosum, and primary sclerosing cholangitis (PSC). Multiple studies have confirmed a positive association between the presence of EIM and the development of pouchitis.[19,21,35,36,39] In particular, PSC, arthritis, and backwash ileitis[21,40,41] are all associated with the development of pouchitis.[19,21,35,36,42–44] Lohmuller and colleagues examined the association between EIMs of IBD and pouchitis in 734 patients who underwent IPAA between January 1981 and December 1988. Patients with preoperative and postoperative EIMs had a significantly higher rate of pouchitis than patients without EIMs (39% preoperative EIMs vs 26% with no EIMs, $P < 0.001$; 53% postoperative EIMs vs 25% with no EIMs, $P < 0.001$).[21,36,42,43,45] The increased risk of developing pouchitis in patients with extracolonic manifestations has been confirmed by additional studies with an OR of 2.4–3.5.[19,35,36,42–45] In a study of 1097 UC patients, in which 54 had concurrent PSC, the cumulative risk of pouchitis after IPAA in patients with both UC and PSC was significantly higher at 1, 2, 5, and 10 years compared with patients with UC alone (22%, 43%, 61%, and 79% vs 16%, 23%, 36%, and 46%, respectively).[23]

Autoimmune disorder(s)

Autoimmune disorders (ADs) have been shown to be more common in patients with IBD, when compared to patients without IBD, suggesting that they may share common etiologic factors.[46–48] The Cleveland Clinic carried out a large study to determine whether the clustering of immune-mediated diseases are associated with chronic antibiotic-refractory pouchitis (CARP). A study of 622 patients with underlying IBD enrolled at the Pouchitis Clinic at the Cleveland Clinic demonstrated that at least one concomitant autoimmune disorder at the time of pouch surgery has been associated with a twofold increase in the risk for developing CARP [OR = 2.29 (95% CI: 1.52–3.46)].[34] The ADs of interest were chosen due to the thought that their strong association with autoimmune pathogenic mechanisms: asthma, psoriasis, type 1 diabetes, rheumatoid arthritis, autoimmune thyroid diseases, psoriasis, systemic lupus erythematosus, autoimmune hemolytic anemia, vitiligo, celiac disease, pernicious anemia, idiopathic thrombocytopenic purpura, and multiple sclerosis.

Extent of disease

Some studies have identified pancolitis and extensive disease as significant risk factors for pouchitis.[35,49–51] In one study from Israel of 201 UC patients followed up in their pouch clinic, the results of a univariate analysis revealed that longer follow-up ($P = 0.01$), pancolitis ($P = 0.008$), and shorter disease duration ($P = 0.04$) were significant risk factors for chronic pouchitis.[49]

Serologic markers

Serologic factors associated with the development of pouchitis include high serum IgG4, autoantibodies to bacterial antigens as well as the host's self-tissue (p-ANCA and anti-CBir1 flagellin antibody),[34,49,52–55] and a positive serology for anti-neutrophil cytoplasmic antibody (ANCA).[56] In a systemic meta-analysis of six studies looking at the association of ANCA and chronic pouchitis, the odds of chronic pouchitis was 76% higher in ANCA-positive patients than those who were ANCA-negative (OR = 1.76; 95% CI: 1.19–2.61; $P < 0.01$).[56]

Genetic markers

The *NOD2* gene is primarily expressed in monocytes, and is associated with nuclear factor kappa B (NF-κB) activation.[57] *NOD2* has been identified as a susceptibility gene for the development of CD.[57,58] It is thought that the *NOD2* gene product may alter the recognition of the components of microbial pathogens and/or the over activation of NF-κB.[57] A North American multi-center trial of over 700 patients identified the *NOD2ins*C risk allele as an important single nucleotide polymorphism (SNP) in the *NOD2* gene. The *NOD2ins*C was a risk factor for chronic pouchitis and a CD-like phenotype (OR of 3.2 and 4.3, respectively).[37,59] Furthermore, a study done by Sehgal and colleagues demonstrated that patients with severe pouchitis, defined as >4 episodes per year for two consecutive years, or the need for continuous antibiotics, had the highest incidence of *NOD2* mutations (67%) compared with asymptomatic IPAA patients (5.4%, $P < 0.001$). This finding suggests that this group may have a compromised host defense mechanism to enteric bacteria.[59] An immunogenetics study has also been done on interleukin 1 receptor antagonist gene allele 2 (IL-1 receptor antagonist), which demonstrated that patients with pouchitis had a higher allele two carriage rate compared with those without pouchitis (72% vs 45%) although the study group was small.[60]