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The pathogenesis of primary pouchitis following ileal pouch-anal anastomosis: a review of current hypotheses

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ABSTRACT

Primary pouchitis is a common complication of ileal pouch-anal anastomosis following proctocolectomy in patients treated for ulcerative colitis (UC), but is unusual for those treated for familial adenomatous polyposis (FAP). While a number of theories as to the pathogenesis of this inflammatory condition have been proposed, no single one has been wholly satisfactory. Much research has been devoted to investigating a link between the pathogenic factors involved in UC, but not FAP, and those underlying pouchitis. The contribution of sulfate-producing bacteria has also been explored. The role of other intraluminal factors, such as short chain fatty acids and unconjugated bile salts, has also been investigated. A unifying theory of a multi-step process might explain the pathogenesis of pouchitis, but further research is required to proof causation. It is likely that pouchitis develops as a result of a combination of genetic, immunological, microbial and metabolic factors. Future insight into the causes of pouchitis may eventually allow for the development of more effective treatments.

Keywords: Pouchitis; Ileo-Pouch Anal Anastomosis; Pathogenesis

1. INTRODUCTION

Prior to the development of the ileal pouch-anal anastomosis technique (IPAA) patients requiring proctocolectomy were mandated to have an end-ileostomy. IPAA restore the continuity of the lower GI tract by creating a pouch of ileal loops directly anastomosed to the anal canal, and preserving the anal sphincter function. Restorative proctocolectomy followed by IPAA is currently the treatment of choice in the surgical management of refractory ulcerative colitis (UC) and familial adenomatous polyposis (FAP) [1,2]. Epidemiological studies show that at least 10% of patients with UC will undergo proctocolectomy during the course of their illness [3]. IPAA has been found to have a positive impact on global quality of life score as it provides symptomatic relief while preserving fecal continence [4,5]. However, the procedure is associated with significant short and long-term morbidity, including immediate post-operative comations, pouch failure, small bowel obstruction, sexual dysfunction, irritable pouch syndrome and pouchitis [2].

Of these, pouchitis is the most common long-term complication, occurring at a rate of 48% at 10 years and 70% at 20 years in patients with UC [6]. For patients who have had one episode of pouchitis, there is a 64% risk of recurrence [2]. In FAP, pouchitis is uncommon and approximated 5% in those treated with restorative proctocolectomy with pouch [7]. Overall similar rates of adverse post-operative outcomes have been reported in patients treated for UC and those treated for FAP [8]. There is however a marked difference in the risk of fistulisation and pouchitis [8]. Pouchitis is significantly more common in patients treated for UC than FAP, and this observation has formed the basis for a number of hypotheses of pathogenesis.

Pouchitis is an inflammatory condition of the ileal reservoir that is formed during IPAA [9]. It occurs as a single acute episode in a third of cases but most have recurrent acute episodes or a chronic course of disease [10]. Acutely, it can be distressing with symptoms of increased stool frequency, urgency, nocturnal incontinence and abdomino-pelvic pain, often accompanied by fever, weight-loss and bloody stools [5]. In chronic cases, pouchitis may be associated with reduced quality of life and the need for further surgery [9]. Currently, there are no consensus guidelines for diagnosis and in most cases a combination of clinical signs and symptoms and pouch

endoscopy are utilised. For research purposes, a number of detailed, standardised diagnostic tools have been developed which incorporate clinical, endoscopic and histological criteria. The most commonly used version is the Pouchitis Disease Activity Index (see **Table 1**) [11]. The complexity of these scores highlights the multifaceted nature of pouchitis.

Secondary pouchitis is diagnosed in 20% - 30% of patients presenting with pouchitis [12]. In these cases a specific causative factor is identified, for example *Candida* infection, *Clostridium difficile* infection, radiotherapy, chemotherapy, CMV infection or collagen deposition. The remainder of patients present with primary (idiopathic) pouchitis. To date, the pathogenesis of primary pouchitis has not been fully elucidated, but a number of theories have been proposed. The aim of this paper is to review the evidence for and against each of these theories.

The management of pouchitis includes confirmation and exclusion of other inflammatory conditions including Crohn's disease recurrence and secondary pouchitis. Both metronidazole and ciprofloxacin are effective in treating acute pouchitis [13,14] and continuous maintenance antibiotic therapy may be required for chronic pouchitis. Rifaximin, an oral broad-spectrum non-absorbed antibiotic was found be useful in an open-labelled maintenance study in the maintenance of remission [15]. For patients with chronic pouchitis in remission, the probiotic VSL#3 consisting of strains of lactobacilli, bifidobacteria and *Streptococcus salivarius subsp. thermophilus* significantly reduced recurrences of pouchitis from 100% in the placebo group to 15% [16]. Topical treatments using enemas may be effective. Resistant cases may respond to immunosuppressive therapies and infliximab has been used effectively in difficult-to-treat cases [17]. Finally, surgical reconstruction and excision may be required.

2. POUCHITIS AS A RECURRENCE OF ULCERATIVE COLITIS

Following an IPAA, the section of ileum used to fashion the fecal reservoir (pouch) takes on many of the histological features of colonic epithelium, probably as a result of prolonged fecal exposure [18]. These changes may render the pouch susceptible to conditions that primarily affect the colon. Thus, it has been suggested that pouchitis is a recurrence of UC.

There is significant overlap between UC and pouchitis at the clinical, endoscopic, histological and molecular levels, suggesting a common mechanism of pathogenesis. The characteristic endoscopic findings in pouchitis are oedema, granularity, friability, loss of vascular pattern, mucous exudates and superficial ulceration (see **Table 1**) [11]. Clearly, there are commonalities between these findings and the hallmarks of UC. At the molecular level, Amasheh *et al.* [19] have demonstrated changes in the expression of claudin-1 and claudin-2 in tissue taken from

Table 1. The pouchitis disease activity index. [10] Score range 0 - 18; ≥7 indicates pouchitis.

Criteria			Score
Clinical			
	Stool frequency	Usual postoperative frequency	0
		1 - 2 stools/day more than postoperative norm	1
		3 or more stools/day more than postoperative norm	2
	Fecal urgency/abdominal cramps	None	0
		Occasional	1
		Usual	2
	Rectal bleeding	None or rare	0
		Present daily	1
	Fever (temperature > 37.8˚C)	Absent	0
		Present	1
Endoscopic	inflammation	Oedema	1
		Granularity	1
		Friability	1
		Loss of vascular pattern	1
		Mucous exudates	1
		Ulceration	1
Acute histological inflammation	Polymorphonuclear leukocyte infiltration	None	0
		Mild	1
		Moderate and crypt abscess	2
		Severe and crypt abscess	3
	Ulceration per low field (mean)	None	0
		<25%	1
		25% - 50%	2
		>50%	3

patients suffering acute pouchitis. These proteins are components of epithelial tight junctions and altered expression of these proteins increases epithelial permeability via the paracellular route. Similar changes have been demonstrated in UC [20].

While pouchitis is prevalent in patients with a history of UC, it is very infrequently seen in those with a history of FAP. A large meta-analysis of studies comparing post-IPAA outcomes in UC and FAP patients found significantly higher rates of pouchitis in the UC population (OR 6.44; 95% CI: 3.21 - 12.93) [8]. These results certainly support the theory that the pathological mechanisms underlying UC, but not FAP, may be responsible for the development of pouchitis. That pouchitis is more common in patients with a history of pancolitis than those with left-sided colitis also lends weight to this theory [21]. **Table 2** lists some of the differences between UC and FAP in the risk of developing pouchitis.

Immunological features of pouchitis often mimic UC. CD19 + Ki-67 + cells and CD138 + Ki-67 + cells are increased in UC and represent immature plasma cells with increased proliferative activities. Similar cell phenotypes are found in pouchitis mucosa suggesting UC-derived abnormalities in the pathogenesis of pouchitis [22]. Pouchitis also correlated with decreased defensin expression in UC in addition to high expression of cytokines as opposed to FAP pouches that had increased expression of hBD-1 beta-defensin and low cytokine levels [23]. Toll-like receptors (TLR) are members of the pattern recognition family important involved in innate immunity. TLR-4 is specifically activated by lipopolysaccharide, an endotoxin produced by gram-negative bacteria. TLR-4 expression was found to be increased in pouches of UC patients in comparison with FAP patients, even in the absence of clinical or histological inflammation. This may result in increased intracellular pathway activity following activation by bacterial products in UC patients. [24] The observation that extraintestinal manifestations of UC often occur in parallel with pouchitis provides further support to a theory of common immunological pathogenesis. Lohmuller *et al*. [25] found that in a population of 734 patients who had undergone IPAA for UC, 53% of those with postoperative extraintestinal manifestations developed pouchitis compared to 25% of those without extraintestinal manifestations ($P < 0.001$). Seven patients with preoperative extraintestinal manifestations that resolved after IPAA had concomitant recurrence of the extraintestinal manifestations and acute pouchitis.

The most compelling refutation of this theory lies in the role of antibiotics in the treatment of pouchitis. Short courses of metronidazole and ciprofloxacin have traditionally been used in the treatment of acute cases [26]. It has been shown that treatment of pouchitis with metronidazole results in resolution of the characteristic histological changes of the condition [18]. UC is not routinely responsive to antibiotic therapy. While there is compelling evidence for a common pathogenesis between pouchitis and UC, the theory does not fully account for this discrepancy. Additionally, mucosal cytokine alterations found in pouchitis may simply reflect inflammatory activity independent to those underlying CD or UC. That is, cytokine changes are the result of inflammation rather than causative [27].

3. THE ROLE OF BACTERIA IN THE PATHOGENESIS OF POUCHITIS

Pouchitis appears to correlate with the presence of pouch dysbiosis. The efficacy of antibiotics in the treatment of acute pouchitis strongly suggests that

Table 2. Pouchitis risk and association with restorative procto-colectomy for ulcerative colitis (UC) versus familial adenomatous polyposis (FAP).

	Pouchitis association with UC as opposed to FAP
Epidemiology	• more common with UC
Clinical	• UC extraintestinal manifestations may occur in parallel with pouchitis
Endoscopic	• macroscopic and microscopic features of pouchitis are in common with inflammatory bowel diseases
Bacteria	• pouch dysbiosis and loss of microbial biodiversity in culture and molecular identification similar to UC • increased hydrogen sulfide-producing and sulfate-reducing organisms
Immune	• serological markers (pANCA) similar to UC • increased immature plasma cells with increased proliferative activities similar to UC
Molecular	• cytokine and defensin changes may reflect underlying UC pathogenesis • increased toll-like receptor 4 expression in UC pouches • altered tight junction proteins
Mucosal	• increased sulphomucin in UC pouches

pANCA = Perinuclear anti-neutrophil cytoplasmic antibody.

bacteria play a role in the pathogenesis of the condition. Loss of biodiversity occurs in pouches of UC patients but not in pouches following FAP. UC pouches in contrast to FAP pouches, there was increase in *Proteobacteria* ($P = 0.019$), decrease in *Bacteroidetes* ($P = 0.001$) and *Faecalibacterium prausnitzii* ($P = 0.029$). Furthermore, bacterial diversity was significantly greater in UC non-pouchitis compared with UC pouchitis ($P = 0.009$). [28] Mucosal *Clostridiaceae spp* colony forming units were significantly increased in patients with recurrent or chronic pouchitis compared to those with no- or single-episode pouchitis (OR:14. 95% CI: 0.887 - 224.021; $P = 0.045$) [29]. VSL#3, a probiotic, is effective in preventing relapse of chronic pouchitis and may prevent episodes of acute pouchitis [26]. Specific causative bacteria or differential bacterial count were not identified in the faeces of patients with or without pouchitis in another study [30]. However, negative findings may reflect older techniques in defining the microbiome. Patients with pouchitis have been found to have a greater anaerobe to aerobe ratio than those without [30,31]. Thus, it may be qualitative rather than quantitative differences in microflora that lead to the development of pouchitis. More recently, a role for sulfate-reducing bacteria has been proposed [32,33]. These bacteria are native to the human colon and produce hydrogen sulfide as a by-product of metabolism. Hydrogen sulfide is believed to compete with normal colonic metabolic substrates, leading to disruption of colonocyte metabolism and injury to the intestinal mucosa [32]. The quantity of hydrogen sulfide gas produced by the pouch contents of patients with active pouchitis is significantly greater than that produced by patients with no history of pouchitis and those receiving antibiotic therapy. In patients with FAP, the quantity of hydrogen sulfide produced is significantly less than in any group of UC patients [32]. Duffy *et al*. [33] report that sulfate-reducing bacteria are found in the pouches of patients with UC, but not those with FAP. Thus, this theory accounts for a number of the observed features of pouchitis: the efficacy of antibiotics, the lack of a single identifiable causative organism and the differences in incidence between UC and FAP patients.

The chief argument against a bacterial theory of pathogenesis is that there is no correlation between the characteristic histological changes of pouchitis and fecal aerobic or anaerobic counts [18]. Future studies examining the relationship between hydrogen sulfide production and mucosal morphology will, no doubt, be valuable.

4. THE ROLE OF OTHER INTRALUMINAL FACTORS

Pouch mucosal mucin characteristics appear to differ between UC and FAP pouches. The expression of sulphomucin is increased in the mucous gel layer of UC compared with FAP pouches. Differential mucin expression favours colonization by different organisms and sulphomucin expression was associated with sulphate-reducing bacteria and increased chronic inflammation [34].

Short-chain fatty acids (SCFAs) are produced by anaerobic bacteria through the fermentation of dietary fibre. They are the principle source of energy for colonocytes and are important for mucosal homeostasis. Clausen *et al.* [35] found that concentrations of SCFAs in the faeces of patients with pouchitis are lower than in those without pouchitis, albeit in a small sample of patients. This finding has led to the hypothesis that reduced availability of SCFAs in the ileal pouch plays a role in the development of pouchitis. However, this is unlikely to be the primary mechanism responsible for pouchitis for a number of reasons. Sandborn *et al*. [30] quantified SCFA concentrations in the faeces of UC patients, both with and without pouchitis, and FAP patients, finding no significant differences between the groups. This finding calls into question the role of SCFAs in the pathogenesis of pouchitis. Furthermore, it highlights the fact that this theory cannot account for the observed differences in incidence of pouchitis between patients with UC and FAP. Glutamine and butyrate suppositories have been trialled as therapy for chronic pouchitis on the basis that increasing concentrations of SCFAs in the pouch may reduce epithelial permeability, leading to symptomatic improvement. The clinical response rate in small, uncontrolled studies has been very low [26], further undermining this hypothesis.

Unconjugated bile acids are released from primary bile salts by the actions of anaerobic bacteria. These unconjugated bile acids are toxic to lipid membranes. High levels of unconjugated bile acids have been found in the feces of patients with ileal pouches, as compared to those who have undergone conventional ileostomy [36]. It has been suggested that this increase may predispose to pouchitis but others have not confirmed these findings. As for SCFAs, the concentrations of unconjugated bile acids are no different in UC and FAP patients [30]. If bile acids were the primary pathogenic factor, a similar incidence of pouchitis would be expected in the two groups. Thus, it is unlikely that bile acids are a major pathogenic factor in the development of pouchitis.

5. MULTI-FACTORIAL, MULTI-STEP HYPOTHESIS

None of the theories discussed above can explain the development of pouchitis fully on its own merit. Cof-

fey *et al*. [37] have proposed that pouchitis is the results of a multi-step process rather than anyone single factor. Their unifying theory is based on the following steps: First colonic metaplasia develops in the ileal pouch, which is followed by the production of sulphomycin by the goblets cells. Sulphomycin then provides the basis for sulfate-reducing bacteria colonisation. Hydrogen sulfide production by sulfate-reducing bacteria may cause apoptosis and reactive crypt cell hyperplasia. Hydrogen sulphide will then also cause inflammation and associated symptoms [37].

While the multi-step theory unifies current isolated findings, it does not fully explain the pathogenesis. It remains unclear why greater rates of colonic metaplasia occur in UC compare to FAP patients. So far only an association between sulfate-reducing bacteria colonisation and colonic metaplasia has been found and any causality is speculative.

6. CONCLUSIONS

Understanding of the pathogenesis of primary pouchitis remains incomplete. While a number of theories have been proposed, no single one fully explains the histological findings and the efficacy of certain treatments. The evidence for a shared pathological basis between UC and pouchitis is compelling, but it cannot explain the therapeutic benefit of antibiotics. There is mounting evidence that sulfate-reducing bacteria play a major role in the condition, while it seems unlikely that SCFAs or bile acid concentrations are the chief pathological culprits. Certainly it seems plausible that all of these factors may contribute to the development of pouchitis, in the context of unknown immunological factors unique to patients with UC. The multi-step process theory proposed by Coffey *et al*. aims to unify the current findings. Future studies may elicit a unifying link between the single hypotheses and proof or disproof the proposed multi-step model. Regardless, further investigation into the pathogenesis of primary pouchitis is warranted in the search for more efficacious treatments and preventative strategies.

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