Mediators of Inflammation, 7, 175–181 (1998)

Pouchitis

W. R. Schouten

Department of Surgery, University Hospital Dijkzigt, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

Tel: (+31) 10 4633100
Fax: (+31) 10 4635307

POUCHITIS is a major long-term complication of the continent ileostomy as well as the ileoanal pouch anastomosis. When diagnosed on the basis of clinical, endoscopic and histologic features, this syndrome has been demonstrated almost exclusively in patients with ulcerative colitis. The clinical course, the endoscopic findings and the histologic abnormalities resemble those of ulcerative colitis. The association with extra-intestinal manifestations further supports the hypothesis that pouchitis represents ulcerative colitis in the small bowel. All ileal reservoirs show bacterial overgrowth, especially of anaerobes. As a response to this altered intraluminal environment chronic inflammation and incomplete colonic metaplasia occur. The efficiency of metronidazole does suggest that bacteriological factors play an important role in the pathogenesis of pouchitis.

Key words: ulcerative colitis, ileostomy, ileoanal anastomosis, pouchitis, metronidazole

Introduction

In the past, a permanent Brooke ileostomy was inevitable for patients requiring a proctocolectomy for either ulcerative colitis or familial adenomatous polyposis. During the past two decades, the continent ileostomy, devised by Kock, and the ileoanal anastomosis, introduced by Parks and Utsunomiya, have evolved into attractive alternatives. Both procedures have the advantage of removing all diseased mucosa while avoiding a conventional and incontinent ileostomy. The construction of an ileal reservoir, however, frequently results in mucosal alterations. Although most of these alterations remain subclinical, some patients will develop a clinical syndrome known as pouchitis. Although it has been suggested that faecal stasis with subsequent alterations in bacterial flora might be important in the pathogenesis of pouchitis, the exact role of intestinal microflora remains controversial. Therefore it might be worthwile to review the current concepts with regard to pathogenesis and aetiology of pouchitis and to analyse the different treatment modalities.

History

In the 1940s and early 1950s it became apparent that mucosal inflammation immediately proximal to the ileostomy was a not uncommon complication after colectomy for ulcerative colitis.[1] This prestomal ileitis resulted occasionally in perforation of the diseased small bowel as described by Crandon *et al.* in 1944.[2] Initially this complication was felt to be related to preoperative 'backwash' ileitis.[1–4] In 1956 Counsell reported successful treatment of prestomal ileitis by stomal dilatation and lavage with a catheter. Since then it became widely accepted that prestomal ileitis was secondary to chronic ileostomy obstruction.[5] In 1976 Kock reported mucosal inflammation in 14 out of 164 patients in whom a continent ileostomy was constructed. The inflammatory changes in the reservoir occurred soon after pouch construction or as late as several years and were associated with an increase in ileostomy output and a foul-smelling bloody effluent. Other symptoms such as nausea, vomiting and fever were also present. All patients had been successfully treated by catheter drainage and sulphasalazine.[6] Kock suggested that this mucosal inflammation was due to fecal stasis and overgrowth of anaerobic bacteria and advocated the term pouchitis to describe this nonspecific ileitis. This syndrome, which also occurs in pelvic reservoirs after ileoanal anastomosis, has been described variably as stagnant loop syndrome[7] or mucosal enteritis.[8,9]

Incidence

The reported incidence of pouchitis following restorative proctocolectomy varies considerably from 10% to 50% (Table 1). This discrepancy is to a great extent due to the variability in definition, the different numbers of patients investigated and the different length of follow-up. Furthermore, in most series

complete details of endoscopic and histologic features have been infrequently described. Similar figures have been documented in consecutive series of patients with a continent ileostomy. Hultén *et al.*[33] reported that the cumulative probability of developing a first attack of pouchitis over a 10-year period is about 35% of patients with a Kock-pouch. Life table analysis of data derived from a register of all patients who have undergone ileoanal anastomosis at the Mayo Clinic revealed a cumulative risk of pouchitis of 31% for patients with ulcerative colitis.[21] Although pouchitis occurs both early and late following reservoir construction, most patients develop their first episode within 2 years postoperatively.[22,28] Approximately half of the patients have only one single episode, whereas the others present two or more episodes.[22,24] Rauh *et al.*[24] reported a preponderance of indeterminate colitis in patients with recurrent episodes of pouchitis. Although pouchitis has been reported to occur before ileostomy closure, this complication is seen predominantly after ileostomy closure.[28] Another intriguing observation is that pouchitis appears confined to patients operated on for ulcerative colitis, whether the pouch is placed in the pelvis or constructed as a continent ileostomy.[34] However, in 1990 Kmiot *et al.*[35] reported a fully documented case of pouchitis in a patient following ileal reservoir construction for familial adenomatous polyposis. A similar case has been described in 1991 by Rauh *et al.*[24] Reviewing their patients operated on for familial adenomatous polyposis, Lohmuller *et al.*[21] found a cumulative risk of pouchitis of 6%. However, in this study pouchitis was defined as present if patients had abdominal cramping, watery diarrhoea, urgency, incontinence, malaise and fever, without endoscopic evaluation and histopathologic confirmation. Despite these and other anecdotal reports it is widely accepted that pouchitis is confined to patients operated on for ulcerative colitis.

Table 1. Incidence of pouchitis following restorative proctocolectomy

Author	Year	Pouchitis (%)
Fonkalsrud[10]	1984	44
Nicholls *et al.*[11]	1985	11
Schoetz *et al.*[12]	1986	7
Becker and Raymond[13]	1986	18
O'Connell *et al.*[14]	1986	30
Gustavsson *et al.*[15]	1987	15
Pemberton *et al.*[16]	1987	14
Fleshman *et al.*[17]	1988	16
Pescatori *et al.*[18]	1988	14
Everett[19]	1989	27
Oresland *et al.*[20]	1989	30
Lohmuller *et al.*[21]	1990	29
Wexner *et al.*[22]	1990	27
DiFebo *et al.*[23]	1990	13
Rauh *et al.*[24]	1991	14
Santavirta *et al.*[25]	1991	30
De Silva *et al.*[26]	1991	21
McMullen *et al.*[27]	1991	15
Fozard and Pemberton[28]	1992	31
Clausen *et al.*[29]	1992	18
Gemlo *et al.*[30]	1992	31
Luukkonen *et al.*[31]	1994	23
Ståhlberg *et al.*[32]	1996	51

Diagnostic Criteria

Pouchitis has been defined using various criteria. Some authors have favoured a diagnosis based on clinical symptoms, whereas others recommended the use of endoscopic or histologic features. Because different diagnostic criteria have been adopted, it is difficult to interpret the reported data related to pouchitis. Taking this into account, it is obvious that there is a need for a gold standard in diagnosis. Recently, it has been advocated that an unequivocal diagnosis should be based on a diagnostic triad, consisting of the following components: clinical symptoms, endoscopic features of acute inflammation and histological evidence of a prominent polymorphonuclear cell exudate.[34]

Clinical symptoms

Watery and sometimes bloody diarrhoea is the major clinical symptom of pouchitis. The increased frequency of stools may be associated with abdominal discomfort, urgency, incontinence and even dehydration. Some patients also have fever and malaise. It has become apparent that pouchitis has the ability to evoke arthritis, skin lesions and eye problems, resembling the extra-intestinal manifestations of inflammatory bowel disease. Lohmuller *et al.*[21] showed that patients with preoperative extra-intestinal manifestations had significant higher rates of pouchitis than did patients without these manifestations (39% vs. 26%). They also described patients in whom extra-intestinal manifestations only recurred when pouchitis occurred and abated when pouchitis was treated.[21] This relationship is one of the intriguing findings suggesting that pouchitis is likely associated with the underlying pathophysiologic mechanism involved in ulcerative colitis.

Endoscopic features

As soon as faecal material enters the pouch, its endoscopic aspect begins to change. The mucosa becomes slightly swollen and somewhat redder in appearance.[36] These mild inflammatory changes, however, seem to be present in only a few cases. DiFebo *et al.*[23] found normal mucosa in 33 out of 41 asymptomatic patients with a pelvic reservoir, whereas endoscopy revealed focal lesions including oedema, petechiae and single ulcers in eight patients without clinical symptoms of pouchitis. Endoscopic

criteria for pouchitis are well known indicators of an acute non-specific inflammation: granularity, oedema, erythema, friability, petechiae, hypersecretion and multiple superficial erosive defects. Although these changes may be focal, they frequently affect all the mucosa, extending sometimes into the afferent limb of the ileum above. In the majority of cases the endoscopic features of pouchitis mimic those of ulcerative colitis. In some patients, however, endoscopic aspects resembles pseudomembranous enteritis, whereas in other patients ulcers are observed similar to those seen in Crohn's disease.[23] The degree of macroscopic inflammation seems to be related to the frequency of defecation as well as to the histological grade of acute inflammation.[37]

Histologic criteria

Several studies have shown that ileal pouch mucosa undergoes morphological changes as soon as faecal material enters the pouch. In the majority of patients mucosal biopsy specimens reveal a chronic inflammatory infiltrate in the lamina propria, including lymphocytes, plasma cells, eosinophils and histiocytes. Such an infiltrate, associated with some degree of villous atrophy and crypt hyperplasia, was found in 87% of the reservoirs, studied by Shepherd *et al.*[38] Patients with ulcerative colitis did not show a significant difference in chronic inflammatory score compared with those operated on for familial adenomatous polyposis. The histopathological appearance of chronic inflammation combined with villous atrophy resembles that of inactive ulcerative colitis. It has been noted that in patients with a conventional ileostomy the normal villous architecture of the prestomal mucosa is preserved, despite the presence of chronic inflammatory changes.[39] This finding indicates that flattening of the villi and crypt hyperplasia is more likely to be induced after construction of an ileal reservoir than after the creation of a conventional ileostomy. It has been suggested that these morphological changes, which are irrespective of the original diagnosis, reflect an adaptive response to the new luminal environment. The change from villous structure of small bowel to a glandular morphology of colon is sometimes so pronounced that biopsy specimens are indistinguishable from normal colon on routine histologic examination. Initially this metaplasia has been defined by means of the histological changes, such as villous atrophy, crypt hyperplasia and increased numbers of Goblet cells and lysozyme containing Paneth's cells. Recent histochemical studies, however, have shown that in 50% of the cases colonic metaplasia is also characterized by a change from small intestinal sialomucin to colorectal sulphamucin.[38,40] Despite this metaplasia, pouch mucosa retains small bowel characteristics, supported by the finding of sucrase-isomaltase activity in pouch specimens.[40] Furthermore, it has been shown that no alteration occurs in endocrine cell population.[41] In pouchitis the mucosa shows a dense acute inflammatory cell infiltrate, consisting of polymorphic granulocytes, associated with crypt abscesses and ulcerations. Frequently the villous atrophy becomes more extensive and subtotal. The histological grade of acute inflammation is significantly related to the clinical symptoms.[37] The histologic findings in pouchitis are very similar to those seen in acute ulcerative colitis.

Pathogenesis

Bacterial overgrowth

Faecal stasis with bacterial overgrowth has been considered a major contributing factor in the pathogenesis of pouchitis. Ileal reservoirs are colonized with large numbers of bacteria that outnumber the flora of the normal terminal ileum.[14,25,39,42–45] In ileal reservoirs, without signs of pouchitis, the microflora closely resembles the flora of the large bowel. This is mainly due to the large numbers of anaerobes (especially Bacteroides and Bifidobacteria), resulting in a greater ratio of anaerobes to aerobes.[25,42–46] In only one study bacterial counts in ileal reservoirs were identical with normal stool values.[47] Other studies, however, revealed that the microflora holds an intermediate position between ileostomy effluent and normal faeces.[42,46,48] It has been suggested that incomplete emptying of the pouch, which is associated with stasis of ileal contents, would result in an increase in the number of anaerobic bacteria. Comparing S and W reservoirs Sagar *et al.*[49] found a reduced efficiency of evacuation in S reservoirs. The effluent of these reservoirs had a significantly greater number of Bacteroides. In another study, however, bacterial overgrowth with an increased number of anaerobes was found in all pouches, irrespective of the efficiency of evacuation.[14] In both studies no correlation was found between the efficiency of evacuation and the grade of mucosal inflammation. Similar findings have been reported by others.[39,50] Therefore, it seems likely that exposure to the faecal stream, rather than the amount of stasis, is the 'threshold' factor for the development of mucosal changes found in ileal reservoirs. The increased numbers of bacteria appear responsible for the increased crypt cell production rate and villous atrophy observed in the pouch mucosa soon after the construction of the reservoir.[43] Nasmyth *et al.*[45] found a significant correlation between the number of isolated Bacteroides and the grade of villous atrophy. The greater the number of Bacteroides the more severe was the villous atrophy. Conversely, the higher the concentration of feacal butyrate the less severe was the villous atrophy.[45] Both findings appear to be contradictory, because volatile fatty acids, such as

butyrate, are the product of anaerobic bacterial fermentation of intraluminal carbohydrate. However, very few species of Bacteroides produce butyrate and it might be speculated that *in vivo* butyrate suppresses the growth of Bacteroides. It is yet not clear whether the grade of chronic inflammation correlates with the number of bacteria isolated. In two studies the score for chronic inflammation was correlated to the number of anaerobes.[25,51] However, other investigators could not demonstrate such a consistent correlation between bacterial counts and chronic inflammation.[45,52] The prompt response in some patients with clinical pouchitis to metronidazole suggests the possibility that overgrowth of anaerobes may be important. However, there is a great deal of controversy concerning the correlation between anaerobes and pouchitis. Several studies failed to show a quantitative or qualitative difference between the microbial findings in patients with and without pouchitis.[14,39,44,53] A recent study, conducted at our own institution, also failed to show significant differences in the total numbers of bacteria when pouch effluent from controls and patients was compared. However, patients with pouchitis had a different composition of the flora. Several anaerobes, such as bifidobacteria and anaerobic lactobacilli, disappeared in favour of aerobes. This was reflected in the ratio anaerobes to aerobes: patients without pouchitis harboured more than hundred times more anaerobes than aerobes. Patients with pouchitis had only two times more anaerobes.[54] These observations have been confirmed by Onderdonk *et al.*[55] who cultered significantly more aerobes from tissue biopsy samples from patients with pouchitis than from control patients. Our study also revealed that the flora of patients with pouchitis is rather unstable. We cultured several species that were not found in controls, such as fungi, Bacillus species and Candida species. Furthermore, *Clostridium perfringens* was detected in nearly every pouchitis, sometimes in very high numbers.[54] A selective increase of *Clostridium perfringens* has also been documented by Brandi and coworkers.[56] The exact role of C perfringens in the pathogenesis of pouchitis is still unknown.

Mucosal ischaemia

It has been suggested that transient ischaemia and subsequent reperfusion may be an aetiological factor in the pathogenesis of pouchitis. It is well known that the vessels supplying the terminal ileum are often under tension when the ileoanal anastomosis is completed. Frequently, these vessels must be divided to provide adequate length for performing the anastomosis. Using fluorescein flowmetry and laser Doppler flowmetry it has been shown that mucosal bloodflow in pelvic reservoirs is significantly reduced compared with the mucosal bloodflow in conventional ileostomies.[57,58] Sakaguchi *et al.* have reported that in patients with pouchitis the mucosal bloodflow was less than in healthy reservoirs.[58] In ischaemic tissues, xanthine dehydrogenase is converted to xanthine oxidase. During reperfusion this enzyme catalyses a reaction resulting in the liberation of oxygen-derived free radicals, which can be prevented by the administration of allopurinol. To investigate the role of this xanthine oxydase inhibitor Levin *et al.* conducted a study in patients with pouchitis. They found a benefical effect of allopurinol in 50% of the patients, either with acute or chronic pouchitis.[53] The results of this preliminary study are consistent with a role for mucosal ischaemia in the aetiology of pouchitis.

Short-chain fatty acids

Short-chain fatty acids (SCFAs) are the product of anaerobic bacterial fermentation of dietary fibres. They are the preferred energy substrates for colonocytes and have a trophic effect on the large bowel mucosa. It has been suggested that these SCFAs are also an important energy source for the pouch epithelium, which can undergo colonic metaplasia. Moreover, it has been shown that SCFAs are able to suppress enteropathic bacteria that produce toxic metabolites, which in turn may cause mucosal inflammation.[59] In view of the increased numbers of anaerobes, increased production of SCFAs might be expected in ileal reservoirs. Nasmyth *et al.*[45] demonstrated that the concentration of SCFAs in the effluent from normal pouches exceeds that from ileostomies. However, no significant difference was found between the SCFA-concentration in faecal specimens from pouch patients and normal subjects. The only difference between the effluent from pouches and that from normal subjects was a higher concentration of acetate in the effluent from the pouches.[45] In contrast with this finding, Ambroze *et al.*[60] reported lower concentrations of SCFAs in pouch effluent compared with normal stool. In a preliminary report Wischmeyer *et al.*[61] described reduced concentrations of SCFAs in patients with pouchitis compared with patients without pouchitis. Recently, this finding was confirmed by others.[29] It seems likely that the lower concentrations of SCFAs are due to the reduced numbers of anaerobes. Whether the reduced concentrations of SCFAs are the result rather than the cause of pouchitis has not been determined. The effect of local application of SCFAs on pouchitis has been studied by DeSilva *et al.*[62] Two patients with severe pouchitis that was resistant to treatment with metronidazole, 5-amino salicylic acid and corticosteroids, received 60 ml of a SCFA solution twice daily. Treatment was discontinued when deterioration was seen in both patients after 14 and 28 days respectively. Based on these results it seems unlikely that low concentrations of

SCFAs are important in the pathogenesis of pouchitis.[62]

Bile acids

It has been suggested that the bacterial overgrowth in ileal reservoirs might result in an increased bacterial deconjugation of bile acids. It is well known that the bacteria in the terminal ileum are able to hydrolyse the conjugated bile acids and to dehydroxylate the bile acids to secondary bile acids. It has been shown that desoxycholic acid (a secondary bile acid) causes a progressive increase in water and salt permeability followed by cell death in the rat colon.[63] Could secondary and deconjugated bile acids cause pouchitis? In one study, comparing patients with and without pouchitis, the concentrations of both total conjugated bile acids and tauroconjugated bile acids were found to be lower in pouchitis patients, which suggests an increased bacterial deconjugation in pouchitis.[59] In another study it has been shown that ileal pouch dialysate is cytotoxic to intestinal epithelial cell lines. This effect was inhibited by cholestyramine, which suggests that a bile acid may be the cytotoxic factor.[64]

Recurrence of ulcerative colitis

One of the most intriguing aspects of pouchitis is the observation that this complication occurs almost exclusively in patients who undergo colectomy for ulcerative colitis. Based on this finding, it has been suggested that ulcerative colitis and pouchitis share the same aetiology. The observation that some patients with inflamed reservoirs experience extraintestinal manifestations resembling those occurring in ulcerative colitis supports this theory. Many studies have confirmed that the pouch mucosa undergoes morphological changes and acquires characteristics resembling those of colonic mucosa. This colonic metaplasia seems to be a nonspecific adaptive response to the new luminal environment that favours the development of an ulcerative colitis-like condition.[65] Exposure to the faecal stream is probably the initiating event that allows the onset of inflammatory changes.[66] It has been shown that colonic mucin glycoproteins are altered in patients with ulcerative colitis.[67] It could be possible that the aberrated glycoproteins are more susceptible for bacterial enzymatic degradation, making the mucus barrier less resistant to toxins. The findings that pouch mucin resembles colonic mucin is therefore an important one. In recent years increasing numbers of data further support the hypothesis that pouchitis represents recurrent ulcerative colitis. In a study aimed to characterize the mucosal cellular infiltrate in ileal reservoirs, de Silva *et al.*[68] found increased RDF9+ macrophage subpopulations in pouchitis. This finding suggests that the effector mechanisms triggering pouchitis are similar to those in ulcerative colitis. In another study the production of eicosanoids, arachidonic acid and interleukin-1β was found to be elevated in inflamed reservoirs, indicating that in pouchitis the same inflammatory mediators are involved as in ulcerative colitis.[69] An increased expression of cell adhesion molecules (E selection and intercellular adhesion molecule-1) has been demonstrated in pouchitis, similar to that reported in ulcerative colitis.[70] Like ulcerative colitis, pouchitis is associated with an increased production of platelet-activating factor, indicating that both disorders share the same aetiology.[66] Merrett *et al.* reported fewer episodes of pouchitis in smokers than in non-smokers.[71] Such a 'protective' influence has previously been described in smokers with ulcerative colitis. All these data suggest that ulcerative colitis can occur in the small intestine on the condition that the luminal environment acquires certain colonic characteristics. Bacterial overgrowth is probably the initiating event in this process of colonic metaplasia.

Treatment

Numerous anecdotal reports have shown that pouchitis is responsive to antibacterial therapy with metronidazole. According to Fozard and Pemberton the majority of patients respond rapidly to a short course of treatment.[28] In their series only 3% of the patients were refractory to this therapy or had severe side effects. O'Connell reported that all his patients with pouchitis obtained prompt relief of symptoms.[14] Comparing pouchitis with and without mucosal ulceration, Zuccaro *et al.*[72] observed a therapeutic effect of metronidazole in 20% and 78% respectively. This finding indicates that antibacterial treatment is probably less effective than previously reported. Based on the observation that some patients do not respond to metronidazole, it has been suggested that there are at least two forms of pouchitis: a bacteriological one that responds to metronidazole and one that requires other medication. The effectiveness of metronidazole can only be assessed in a controlled trial, which is also necessary for proper recommendations regarding dosage schedules and duration of treatment. The observation that clinical symptoms are often resolved with a short course of metronidazole supports a bacteriological basis of pouchitis. However, the actual mechanism of action of metronidazole is still uncertain. Levin *et al.* suggested that metronidazole affects pouchitis not by an antibacterial action, but rather by its capacity to remove oxygen radicals.[53] Other workers raised the possibility that metronidazole has a therapeutic effect because of its immunosuppressive activity.[73] This is of interest as metronidazole does not appear to have a role in the treatment

of ulcerative colitis.[74] It is obvious that the mechanism of action of metronidazole can only be elucidated in a study comparing pouch microflora before and after treatment with metronidazole, whether the therapy is successful or not. Recent studies suggest that pouchitis is a chronic relapsing complication with reported recurrence rates varying between 50% and 80%[21,23,31,75] It appears that an increasing number of patients will require intermittent or maintenance therapy. The question is whether metronidazole is suitable for that purpose or not, particularly in the light of the potential for peripheral neuropathy and other side effects. Patients who are refractory to treatment with metronidazole might obtain relief of symptoms after the administration of enemas containing salicylic acid derivates.[76] Even the use of steroids has been advocated in the treatment of persistent pouchitis. However, continuous administration of steroids with the intention of saving a sick pouch is questionable. Despite their suggested role in the pathogenesis of pouchitis, short-chain fatty acids appear to be of no value in the treatment of pouchitis.[62] Recently it has been shown that oxygen-derived as well as leukocyte-derived free radicals are involved in the pathogenesis of ulcerative colitis. Levin demonstrated that allopurinol, a scavenger directed against oxygen-derived free radicals, induced a remission in 50% of the patients.[53] The value of other scavengers, directed against leukocyte-derived free radicals, such as superoxide dismutase, is still unknown.

There is growing evidence that the pouch flora is very susceptible to influences from outside, such as dietary variation, stress and bacterial contamination. This instability may lead to microbial imbalance, which might be a major contributing factor in the pathogenesis of pouchitis.[54] Based on this assumption it might be worthwhile to bring about a stable pouch flora. This might be realized by oral ingestion of lactobacilli, which has been proved to be successful in the treatment of intestinal infections and antibiotic associated diarrhoea.[54]

Summary

It might be possible that bacterial enzymes, such as glycosidases, degrade the protecting mucus, which may become more permeable to toxic bacterial metabolites and host-derived proteolytic enzymes, affecting the integrity of the mucosa. As a result bacterial antigens may cross the mucosal barrier. This translocation of bacterial antigens probably triggers a cascade of inflammatory events. Only in patients with ulcerative colitis these inflammatory events finally result in clinical pouchitis. Ulcerative colitis is a condition with the potential of neoplastic change in the large intestine. If pouchitis represents recurrent ulcerative colitis, then the pouch epithelium might be prone to malignant transformation. Although the colonic metaplasia is not complete, the reservoir mucosa shows hyperproliferation both in patients with pouchitis and in those without this syndrome.[65] Recently Löfberg *et al.*[77] reported dysplasia and DNA aneuploidy in the pelvic pouch of a patient with ulcerative colitis. Stern *et al.*[78] described the development of a carcinoma in an ileal reservoir of a colitis patient. Based on these findings long-term endoscopic surveillance of the reservoir mucosa has been recommended.

References

1. Lyons AS, Garlock JH. The complications of ileostomy. *Surgery* 1954; **36**: 784.
2. Crandon JH, Kinney TD, Walker IJ. Perforation of the ileum following late ileostomy for ulcerative colitis. *N Engl J Med* 1944; **230**: 419.
3. Colcocx BP, Mathieson WL. Complications of surgical treatment of chronic ulcerative colitis. *Arch Surg* 1956; **72**: 322.
4. McCready FJ, Bargen JA, Dockerty MB, Waugh JM. Involvement of the ileum in chronic ulcerative colitis. *N Engl J Med* 1949; **204**: 119.
5. Counsell B. Lesions of the ileum associated with ulcerative colitis. *Br J Surg* 1956; **44**: 276.
6. Kock NG. Present status of the continent ileostomy: surgical revision of the malfunctioning ileostomy. *Dis Colon Rectum* 1976; **19**: 200–206.
7. Schjonsby H, Halvorsen JF, Hofstad T, Hovdenak N. Stagnant loop syndrome in patients with continent ileostomy (intra-abdominal ileal reservoir). *Gut* 1977; **18**: 795–799.
8. King SA. Enteritis and the continent ileostomy. *Conn Med* 1977; **41**: 477–479.
9. Bonello JC, Thow GB, Manson RR. Mucosal enteritis: a complication of the continent ileostomy. *Dis Colon Rectum* 1981; **24**: 37–41.
10. Fonkalsrud EW. Endorectal ileoanal anastomosis with iso peristaltic ileal reservoir after colectomy and mucosal protectomy. *Ann Surg* 1984; **119**: 576–579.
11. Nicholls PJ, Moskowitz RL, Shepherd NA. Restorative proctocolectomy with ileal reservoir. *Br J Surg* 1985; **72**: 576–579.
12. Schoetz DJ, Coller JA, Veidenheimer MC. Ileoanal reservoir for ulecrative colitis and familial polyposis coli. *Arch Surg* 1986; **121**: 404–409.
13. Becker JM, Raymond JL. Ileal pouch-anal anastomosis. A single surgeon's experience with 100 consecutive cases. *Ann Surg* 1986; **204**: 375–383.
14. O'Connell PR, Rankin DR, Weiland LH, Kelly KA. Enteric bacteriology, absorption, morphology and emptying after ileal pouch-anal anastomosis. *Br J Surg* 1986; **73**: 909–914.
15. Gustavsson S, Weiland L, Kelly KA. Relationship of backwash ileitis to ileal pouchitis after ileal pouch-anal anastomosis. *Dis Colon Rectum* 1987; **30**: 25–28.
16. Pemberton JH, Kelly KA, Beart RW. Ileal pouch-anal anastomosis for chronic ulcerative colitis: long-term results. *Ann Surg* 1987; **206**: 504–513.
17. Fleshman JW, Cohen Z, McLeod RS. The ileal reservoir and ileo-anal anastomosis procedure: factors affecting technical and functional outcome. *Dis Colon Rectum* 1988; **31**: 10–16.
18. Pescatori M, Mattana C, Castagneso M. Clinical and functional results after restorative proctocolectomy. *Br J Surg* 1988; **75**: 321–324.
19. Everett WG. Experience of restorative proctocolectomy with ileal reservoir. *Br J Surg* 1989; **76**: 77–81.
20. Oresland T, Fasth S, Nordgren S, Hulten L. The clinical and functional outcome after restorative proctocolectomy: a prospective study in 100 patients. *Int J Colorect Dis* 1989; **4**: 50–56.
21. Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup D, van Heerden J. Pouchitis and extra-intestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. *Ann Surg* 1990; **211**: 622–627.
22. Wexner SD, Wong WD, Rothenberger DA, Goldberg SM. The ileoanal reservoir. *Am J Surg* 1990; **159**: 178–8512.
23. DiFebo G, Miglioli M, Lauri A, *et al.* Endoscopic assessment of acute inflammation of the ileal reservoir after restorative ileo-anal anastomosis. *Gastrointest Endosc* 1990; **36**: 6–9.
24. Rauh SM, Schoetz DJ, Roberts PL, Murray JJ, Coller JA, Veidenheimer MC. Pouchitis: is it a wastebasket diagnosis? *Dis Colon Rectum* 1991; **34**: 685–689.
25. Santavirta J, Mattila J, Kokki M, Matikainen M. Mucosal morphology and faecal bacteriology after ileo-anal anastomosis. *Int J Colorect Dis* 1991; **6**: 38–41.
26. De Silva HJ, de Angelis CP, Soper N, *et al.* Clinical and functional outcome after restorative proctocolectomy. *Br J Surg* 1991; **78**: 1039–1044.

27. McMullen K, Hicks TC, Ray IE, Gathright JB, Timmeke AE. Complications associated with ileal pouch-anal anastomosis. *World J Surg* 1991; **15**: 763–767.
28. Fozard BJ, Pemberton JH. Results of pouch surgery after ileo-anal anastomosis: the implications of pouchitis. *World J Surg* 1992; **16**: 880–884.
29. Clausen MR, Tvede M, Mortensen PB. Short-chain fatty acids in pouch contents from patients with and without pouchitis after ileal pouch-anal anastomosis. *Gastroenterology* 1992; **103**: 1144–1153.
30. Gemlo BT, Wong WD, Rothenberger DA, Goldberg SM. Ileal pouch-anal anastomosis. Patterns of failure. *Arch Surg* 1992; **127**: 784–787.
31. Luukkonen P, Järvinen H, Tanskanen M, Kahri A. Pouchitis: recurrence of the inflammatory disease? *Gut* 1994; **35**: 243–246.
32. Ståhlberg D, Gullberg K, Liljeqvist L, Hellers G, Löfberg R. Pouchitis following pelvic pouch operation for ulcerative colitis. Incidence, cumulative risk and risk factors. *Dis Colon Rectum* 1996; **39**: 1012–1018.
33. Hultén L. Pouchitis: incidence and characteristics in the continent ileostomy. *Int J Colorect Dis* 1989; **4**: 208–210.
34. Madden MV, Farthing MJG, Nicholls RJ. Inflammation in ileal reservoirs: pouchitis. *Gut* 1990; **31**: 247–249.
35. Kmiot WA, Williams MR, Keighley MRB. Pouchitis following colectomy and ileal reservoir construction for familial adenomatous polyposis. *Br J Surg* 1990; **70**: 1283.
36. Tytgat GNJ. The role of endoscopy in pouch monitoring and pouchitis. *Int J Colorect Dis* 1989; **4**: 210–213.
37. Moskowitz RL, Shepherd NA, Nicholls RJ. An assessment of inflammation in the reservoir after restorative proctocolectomy with ileoanal ileal reservoir. *Int J Colorect Dis* 1986; **1**: 167–174.
38. Shepherd NA, Jass JR, Duval I, Moskowitz RL, Nicholls RJ, Morson BC. Restorative proctocolectomy with ileal reservoir. Pathological and histochemical study of mucosal biopsy specimens. *J Clin Pathol* 1987; **40**: 601–617.
39. Nasmyth DG, Johnston D, Godwin PG, Dixon MF, Smith A, Williams NS. Factors influencing bowel function after ileal pouch-anal anastomosis. *Br J Surg* 1986; **73**: 469–473.
40. DeSilva HJ, Millard PR, Kettlewell M, Mortensen NJ, Prince C, Jewell DP. Mucosal characteristics of pelvic ileal pouches. *Gut* 1991; **32**: 61–65.
41. Lerch MM, Braun J, Harder M, Hofstadler F, Schumpelick V, Matern S. Postoperative adaptation of the small intestine after total colectomy and J-pouch-anal anastomosis. *Dis Colon Rectum* 1989; **32**: 600–608.
42. Brandberg A, Kock NG, Philipson B. Bacterial flora in intra-abdominal ileostomy reservoir. *Gastroenterology* 1972; **63**: 413–416.
43. Philipson B, Brandberg A, Jagenburg R, Kock NG, Lager I, Ahren C. Mucosal morphology, bacteriology and absorption in intra-abdominal ileostomy reservoir. *Scand J Gastroenterol* 1975; **10**: 145–153.
44. Luukkonen P, Valtonen V, Sivonen A, Sipponen P, Järvinen H. Fecal bacteriology and reservoir ileitis in patients operated on for ulcerative colitis. *Dis Colon Rectum* 1988; **31**: 864–867.
45. Nasmyth DG, Godwin PGR, Dixon MF, Williams NS, Johnston D. Ileal ecology after pouch-anal anastomosis or ileostomy. A study of mucosal morphology, fecal bacteriology, fecal volatile fatty acids and their interrelationship. *Gastroenterology* 1989; **96**: 817–824.
46. Go PMNYH, Lens J, Bosman IT. Mucosal alterations in the reservoir of patients with Kock's continent ileostomy. *Scand J Gastroenterol* 1987; **22**: 1076–1080.
47. Loeschke K, Bolkert T, Keifhaber P. Bacterial overgrowth in ileal reservoirs: extended functional studies. *Hepatogastroenterology* 1980; **27**: 310–316.
48. Hill MJ, Fernandez F. Bacteriology II. Workshop on pouchitis. *Int J Colorect Dis* 1989; **4**: 217.
49. Sagar PM, Godwin PGR, Quirke P, Holdsworth PJ, Johnston D. Ileal ecology and design of the pelvic reservoir. *Gut* 1990; **31**: A1172.
50. DeSilva HJ, Millard PR, Soper N, Kettlewell M, Mortensen N, JewellL DP. Effects of the fecal stream and stasis on the ileal pouch mucosa. *Gut* 1991; **32**: 1166–1169.
51. Nicholls RJ, Belliveau P, Neill M, Wilks M, Tabaqchali S. Restorative proctocolectomy with ileal reservoir: a pathophysiological assessment. *Gut* 1981; **22**: 462–468.
52. Moskowitz RL. Pathophysiology. Symposium: restorative proctocolectomy with ileal reservoir. *Int J Colorect Dis* 1986; **1**: 16–17.
53. Levin KE, Pemberton JH, Phillips SM, Zimsmeister AR, Pezim ME. Role of oxygen free radicals in the etiology of pouchitis. *Dis Colon Rectum* 1992; **35**: 452–456.
54. Ruseler-van Embden JGH, Schouten WR, van Lieshout LMC. Pouchitis: result of microbial imbalance? *Gut* 1994; **35**: 658–664.
55. Onderdonk AB, Dvorak AM, Cisneros RL, *et al*. Microbiologic assessment of tissue biopsy samples from ileal pouch patients. *J Clin Microbiol* 1992; **30**: 312–317.
56. Brandi G, Chaussade S, Ladiré M, *et al*. Analysis of ileal bacterial flora in patients with ileal-anal anastomosis with and without pouchitis. *Gut* 1992; **33**: S41.
57. Perbeck L, Lindquist K, Liljequist L. The mucosal bloodflow in pelvic pouches in man: a methodologic study of fluorescein flowmetry. *Dis Colon Rectum* 1985; **28**: 931–936.
58. Sakaguchi M, Hosie K, Tudor R, Kmiot W, Keighley MRB. Mucosal bloodflow following restorative proctocolectomy: pouchitis is associated with mucosal ischemia. *Br J Surg* 1989; **76**: 1331.
59. Gorbach SL, Nahas L, Weinstein L. Studies on intestinal microflora IV. *Gastroenterology* 1967; **53**: 874–880.
60. Ambroze WL, Pemberton JH, Bell AM, Haddad AC, Phillips ST. Faecal short-chain fatty acids after ileal pouch-anal anastomosis. *Gastroenterology* 1989; **96**: A11.
61. Wischmeyer PEM, Tremaine WJ, Haddad AC, Ambroze WL, Pemberton JH, Phillips SF. Fecal short-chain fatty acids in patients with pouchitis after ileal pouch-anal anastomosis. *Gastroenterology* 1991; **100**: A848.
62. DeSilva HJ, Ireland DP, Kettlewell M, *et al*. Short-chain fatty acids in the treatment of pouchitis. *N Engl J Med* 1989; **321**: 1416–1417.
63. Breuer NF, Rampton DS, Tammar A, Murphy GM, Dowling RH. Effect of colonic perfusion with sulfated and non-sulfated bile acids on mucosal structure and function in the rat. *Gastroenterology* 1983; **84**: 969–977.
64. Merrett MN, Crotty BJ, Mortensen N, Jewell DP. Ileal pouch dialysate is cytotoxic to I–407 and HT-29 cells: bile may be the active factor. *Gut* 1991; **32**: A1205.
65. Shepherd NA, Healey CJ, Warren BF, Richman PI, Thomson WHF, Wilkinson SP. Distribution of mucosal morphology and an assessment of colonic phenotypic change in the pelvic ileal reservoir. *Gut* 1993; **34**: 101–105.
66. Chaussade S, Denizot Y, Valleur P, *et al*. Presence of PAF-acether in stool of patients with pouch ileoanal anastomosis and pouchitis. *Gastroenterology* 1991; **100**: 1509–1514.
67. Tysk C, Riedesel H, Lindberg E, Panzini B, Podolsky D, Järnerot G. Colonic glycoproteins in monozygote twins with inflammatory bowel disease. *Gastroenterology* 1991; **100**: 419–423.
68. DeSilva HJ, Jones M, Prince C, Kettlewell M, Mortensen NJ, Jewell DP. Lymphocyte and macrophage subpopulations in pelvic ileal reservoirs. *Gut* 1991; **32**: 1160–1165.
69. Belluzi A, Gionchetti P, Campieri M, *et al*. Eicosanoids, arachidonic acid and interleukin-1β in pouchitis. *Gut* 1992; **33**: S41.
70. Merrett MN, Bloom SL, Mortensen NJ, Jewell DP. Increased expression of cell adhesion molecules in pouchitis. *Gut* 1992; **33**: S47.
71. Merrett MN, Mortensen NJ, Kettlewell MGW, Jewell DP. Smoking and pouchitis. *Gut* 1991; **32**: A1254.
72. Zuccaro G, Fazio V, Church JM, Lavery IC, Ruderman WB, Farmer RG. Pouch ileitis. *Dig Dis Sci* 1989; **34**: 1505–1510.
73. Scott AD, Phillips RKS. Ileitis and pouchitis after colectomy for ulcerative colitis. *Br J Surg* 1989; **76**: 668–669.
74. Chapman RC, Selby WS, Jewell DP. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in severe ulcerative colitis. *Gut* 1986; **27**: 1210.
75. Setti-Carraro P, Wilkinson KH, Ritchie JK, Nicholls RJ. The longterm results of restorative proctocolectomy for ulcerative colitis: a historical series. *Gut* 1993; **34**: S63.
76. Miglioli M, Barbara L, DiFebo G, *et al*. Topical administration of 5-aminosalicylic acid: a therapeutic proposal for the treatment of pouchitis. *N Engl J Med* 1989; **320**: 257.
77. Löfberg R, Liljequist L, Lindquist K, Veress B, Reinholt FP, Tribukait B. Dysplasia and DNA aneuploidy in a pelvic pouch. *Dis Colon Rectum* 1991; **34**: 280–284.
78. Stern H, Wälfisch S, Mullen B, Meleod R, Cohen Z. Cancer in an ileoanal reservoir: a new late complication. *Gut* 1990; **31**: 473–475.

Received 16 March 1998; accepted 18 March 1998