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Review

Pouchitis: a tridimensional view

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Summary. The preferred surgical treatment of ulcerative colitis (UC) and familial adenomatous polyposis (FAP) is represented by proctocolectomy with ileal pouch-anal anastomosis (IPAA). However, patients with UC who have undergone IPAA are prone to develop several complications, which include surgery related/mechanical complications; inflammatory or infectious disorders; functional disorders; dysplasia or neoplasia; and systemic or metabolic disorders. Pouchitis, which is defined as the acute and/or chronic inflammation of the ileal reservoir, represents the most common long-term adverse sequela after IPAA. Gut microbiota play a pivotal role in the initiation and disease progression of pouchitis. Pouchitis can be classified according to the activity of the disease, the duration of the symptoms, the pattern of the disease or response to antibiotic therapy. Patients with IPAA for UC tend to experience a variety of symptoms, ranging from mild pelvic or perianal discomfort to a debilitating complex of symptoms that may eventually lead to pouch excision thereby necessitating the construction of a permanent ileostomy. To date, the etiology, the diagnosis and the medical management of pouchitis represent a clinical challenge. In fact pouchitis range from a disease with an acute antibiotic-responsive presentation to a chronic antibiotic-refractory form, with subsequent different disease mechanisms and clinical course. A tridimensional and multidisciplinar approach, including endoscopy, histology, and laboratory testing is widely helpful to identify the different phenotypes of the disease and to manage correctly its treatment.

Key words: pouchitis, ulcerative colitis, Intestinal Bowel Diseases, dysbiosis

Epidemiology

The preferred surgical treatment of ulcerative colitis (UC) and familial adenomatous polyposis (FAP) is represented by proctocolectomy with ileal pouch-anal anastomosis (IPAA), which could be considered a better alternative to proctocolectomy with permanent ileostomy, since it preserves intestinal continuity and sphincter function and removes the entire colorectal mucosa. The IPAA consists of total abdominal colec-

tomy, stripping of the rectal mucosa with preservation of the anal sphincter, and the construction of an ileal pouch that is anastomosed to the anus (1).

In the case of UC, up to 30% of affected patients will require surgical management of their disease because of medically intractable disease, fulminant course, dysplasia or cancer and even due to patient preference not to take medication on an indefinite timeline (1).

However, patients with UC who have undergone IPAA are prone to develop several complications, which include surgery related/mechanical complications; inflammatory or infectious disorders; functional disorders; dysplasia or neoplasia; and systemic or metabolic disorders (2).

Pouchitis, which is defined as the acute and/or chronic inflammation of the ileal reservoir, represents the most common long-term adverse sequela after IPAA (3).

According to some series approximately 50% of patients can be expected to experience at least one

episode of pouchitis. In a study of complications and long-term outcomes in 1310 patients who underwent IPAA for chronic UC, 559 patients had at least one episode of pouchitis (4). The cumulative risk of having at least one episode was 18% at 1 year after surgery and 48% at 10 years. Approximately 394 of the 559 patients who had at least one attack of pouchitis had a second episode. The cumulative probability of having a second episode after an initial attack within 2 years of IPAA was 64%.

Several studies show that most cases of pouchitis occur within the first few years after IPAA (5) while others, conversely, report that risk could continue to increase during further follow-up (6) Interestingly, pouchitis rarely occurs in patients who have IPAA for familial adenomatous polyposis (FAP) (7).

Several risk factors for pouchitis have been reported, although they have not been demonstrated consistently. Extensive or severe UC (8) backwash ileitis (9) extraintestinal manifestations of UC (10,11) precolectomy thrombocytosis (12,13) pANCA positivity (14,15) nonsmoking status, and nonsteroidal antiinflammatory drug (NSAID) use (16-18) have all been reported as risk factors for the development of pouchitis.

However, there is little agreement in the literature as to which factors definitely increase a patient's risk for pouchitis. This discrepancy could be due to duration and intensity of follow up after IPAA (19); diagnostic criteria of pouchitis used; stratification of pouchitis — acute *versus* chronic pouchitis or a combination of both (20); inclusion or exclusion of CD of the pouch (18) or cuffitis (21); and the number of patients studied (22).

Classification

Pouchitis can be classified according to the activity of the disease, the duration of the symptoms, the pattern of the disease or response to antibiotic therapy. With regard to disease activity, pouchitis can be classified as in remission or mildly, moderately, or severely active, based on symptoms. With regard to duration, pouchitis can be classified as acute (<4 weeks) or chronic (more than 4 weeks). On the other hand, disease pattern can be classified as infrequent (1–2 acute episodes), relapsing (more than 3 acute episodes) or continuous. Relapsing pouchitis is also considered a form of chronic pouchitis. Finally, with regard to response to standard antibiotic therapy, pouchitis can be classified as responsive, dependent or refractory (23).

Clinical features

Patients with IPAA for UC tend to experience a variety of symptoms, ranging from mild pelvic or perianal discomfort to a debilitating complex of symptoms that may eventually lead to pouch excision thereby necessitating the construction of a permanent ileostomy. Clinicians typically base their suspicion of pouchitis on a constellation of clinical symptoms such as: an increase in stool frequency, tenesmus, change in stool consistency, abdominal cramps and rectal bleeding. Treatment is often prescribed based on these clinical symptoms alone.

However, diagnosis of pouchitis based on symptoms alone has been shown to be non-specific due to the fact that symptoms can originate from a myriad of aetiologies, not necessarily inflammatory in nature.

Etiology

Gut microbiota play a pivotal role in the initiation and disease progression of pouchitis (2).

The contribution of gut microbiota to the pathogenesis of pouchitis is multifaceted: firstly, through the dysbiosis (24-27) and therefore, through the emergence of pathogenic bacteria, fungi, or viruses (28). The role of dysbiosis in the pathogenesis of pouchitis is not yet fully clear, as it is in the field of inflammatory bowel disease (29)

The construction of the ileal reservoir provoke an altered bowel anatomy that can lead to fecal stasis and colonic metaplasia in the pouch body from the original ileal mucosa, thus creating an environment favourable to the development of inflammation (30).

Pathogen-associated pouchitis can occur in a subset of patients. *C difficile* infection (CDI) is common in symptomatic patients with IPAA. Other pathogens have been reported to be associated with episodes of active pouchitis, including *C perfringens*, *Campylobacter* species, group D streptococci (*Enterococcus* species), haemolytic strains of *E coli*, and cytomegalovirus (CMV) infection (31-35). These pathogenic microbes detected in pouchitis patients with systemic symptoms may contribute to disease episodes or be responsible for a refractory course to conventional antibiotic therapy (2). Furthermore, such bacterial species may exert different impacts on innate and adaptive mucosal immune function.

Table 1 shows the mechanisms of involvement of innate and adaptive immunity in the pathogenesis of pouchitis.

Work-up

At the initial occurrence of symptoms that might suggest a pouchitis, infectious aetiologies should be firstly ruled out, through stool for culture, Clostridium difficile toxin assay and cytomegalovirus tissutal polymerase chain reaction.

Once infectious aetiologies and other possible contributors have been excluded, pouch endoscopy should be performed. With regard to the opportunity to administer a trial of antibiotics as being both therapeutic and diagnostic of 'pouchitis', this practice should be avoided, because patients with pouch symptoms may respond quite rapidly to the administration of antibiotics without having evidence of the endoscopic or histological inflammation that is required to make a diagnosis of pouchitis.

On endoscopy, it is important: (a) to examine the pouch, the pre-pouch ileum and the rectal cuff;(b) the bioptic sampling of the pre-pouchileum and the rectal cuff; (c) the evaluation of the endoscopic features of pouchitis, that may range from anywhere between minimal changes, including erythema, friability and mucus exudate to ulcers and bleeding.

Table 1. Involvement of innate immunity in the pathogenesis of pouchitis

Mechanisms through which innate immunity is involved in the pathogenesis of pouchitis	Mechanisms through which adaptive immunity is involved in the pathogenesis of pouchitis
Colonic metaplasia related-dysbiosis, with specific regard to production of sulfate-reducing bacteria	Increased proliferation of immature plasma cells
Alterations in mucin glycoproteins	Increased production of proinflammatory cytokines, such as TNF, and proinflammatory neuropeptides
Increased permeability of the gastrointestinal mucosa	Increased production of cell adhesion molecules
Aberrant expression of Toll-like receptors	Increased production of platelet-activating factor
Altered expression of Paneth-cell–specific human defensin-5	Increased production of lipoxygenase products of arachidonic acids
	Increased production of VEGF

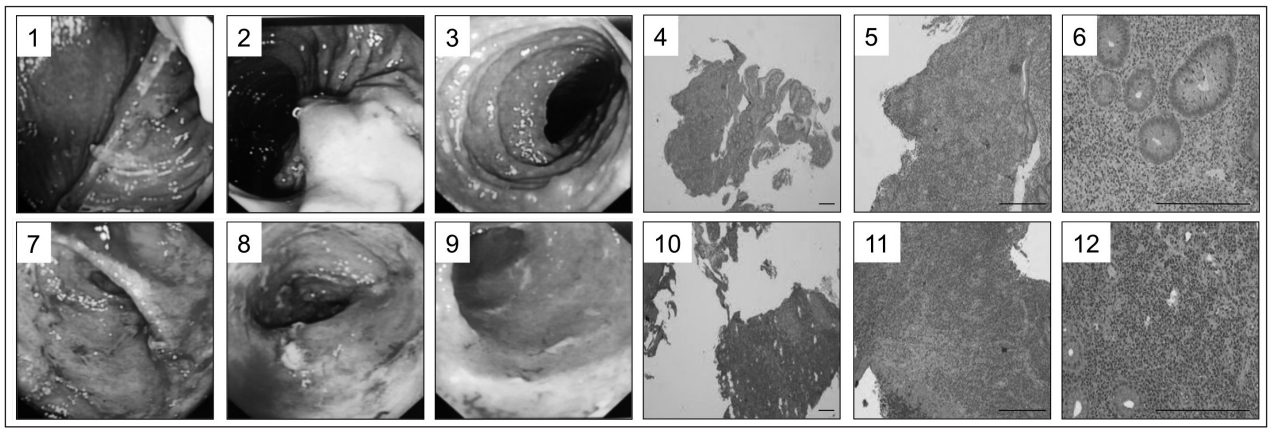

Figure 1. Endoscopic view of the pouch inlet in a patient with mild pouchitis.
Figure 2. Another endoscopic view of the pouch inlet in a patient with mild pouchitis.
Figure 3. Endoscopic view of an healthy pre-pouch ileal mucosa.
Figure 4. This edge of colonic mucosa shows the characteristics of an inflammatory infiltrate of mild intensity: reduction of the glandular amount of the epithelium, almost disappearance of the secreting activity and distortion of the residual glandular elements, due to the compressive effect of the inflammatory infiltrate. Bar: 200 micra.
Figure 5. A greater enlargement in which we find the same morphological characteristics previously described: reduction of the glandular elements and presence of a polymorphous inflammatory infiltrate, consisting of lymphocytes, plasma cells and granulocytes. Bar: 200 micra.
Figure 6. This further enlargement underlines the marked amount of granulocytes (settling element for the diagnosis of an inflammatory bowel disease), and shows also a certain degree of intraepithelial involvement from the inflammatory elements towards the glands. To notice some apoptotic nuclei at the base of the glandular elements. Bar: 200 micra.
Figure 7. Endoscopic view of the pouch inlet in a patient with severe pouchitis
Figure 8. Another endoscopic view of the pouch inlet in a patient with severe pouchitis
Figure 9. Endoscopic view of an inflamed pre-pouch ileal mucosa in a patient with severe pouchitis
Figure 10. In this second case, the intensity of the inflammatory infiltrate can be classified as severe. The inflammatory infiltrate, besides colonizing the proper foil giving all those morphological modifications described in Fig. 4, extends him to also involve the muscularis mucosae, transmurally. Bar: 200 micra.
Figure 11. In this greater enlargement it can be observed the total disappearance of the glandular amount of the epithelium, entirely replaced by the ulcerative inflammation. Bar: 200 micra.
Figure 12. Also in this figure, the eosinophylic component is preponderant. The polymorphous inflammatory infiltrate distorts and reduces in dimensions the small residual glands. Bar: 200 micra.

Two composite scores are used to the diagnostic and prognostic assessment of pouchitis. These are the pouchitis disease activity index (PDAI) (36) and the pouchitis activity score (PAS) (37)

In the first one, an overall score is calculated from three separate sixpoint scales including clinical symptoms, endoscopic findings and histological changes. Furthermore, the PDAI incorporates histological features of acute inflammation, and establishes a cut-off for differentiation between 'pouchitis' (≥7 points) and 'no pouchitis' (<7 points).

On the other hand, the PAS includes findings similar to those of the PDAI but also comprises the histological features of chronic inflammation, distinguishing three grades of pouch inflammation: mild adaptive, moderate pouchitis and severe pouchitis.

Recently, Elder and coworkers evaluated the endoscopic features associated with ileal pouch features (38). The authors concluded that distorted appearance of "beak" portion of owl's eyes along with Crohn's disease of the pouch or surgery-related complications, postoperative use of biologics, and persistent cuffitis were the risk factors associated with pouch failure, and that the assessment of endoscopic owl's eye structure may provide an additional clue to predict pouch outcome (38).

Histological assessment will focus on acute inflammatory infiltrates, however also dysplastic changes

should be ruled out in the rare case of progression to malignant transformation.
Abdominal and pelvic CT scan, pelvic MRI, perineal or transanal ultrasound, pouchography or examination under anaesthesia are requested in the case of signs of inflammation, fistulas, leaks or abscesses.

Medical management

Antibiotics showed widely their effectiveness in treating pouchitis (39). Oral metronidazole (at a dose of 1 to 2 g daily) (40,41) and oral ciprofloxacin (at a dose of 1 g daily) are an effective treatment for pouchitis (42,43). Treatment may be most effective with acute episodes, and was found to be less effective in patients with a chronic course of the disease.

Oral metronidazole, in a double-blind cross-over randomised trial, was associated with a significant reduction in stool frequency by three movements per day (versus an increase of one per day with placebo) even if absence of changes in the endoscopic or histologic grade of inflammation (39).

In another randomized trial consisting of 16 patients, assigned to either ciprofloxacin 1 g/day or metronidazole 20 mg/kg per day, a response to both drugs was showed, but a better improvement and fewer side effects (0 versus 33 percent) were found with ciprofloxacin (42)

For this reason, ciprofloxacin at 1 g daily is primarily used as the initial treatment for acute pouchitis, therefore reserving metronidazole for patients in which ciprofloxacin fails.

Rifaximin has also been used in pouchitis, even if it was not more effective than placebo in a small controlled trial (44). However, rifaximin maintenance therapy was effective in preventing relapse in 65 percent of patients with antibiotic-dependent pouchitis after induction of remission with a variety of antibiotics (45).

On the other hand, a combined approaches, including ciprofloxacin and rifaximin (46,47) metronidazole and ciprofloxacin (48) and ciprofloxacin and tinidazole (49)have also been found to be efficacious in the treatment of chronic refractory pouchitis (50).

Interestingly, in a study performed by McLaughlin and coworkers, fecal coliform sensitivity testing was showed to be helpful in clarifying the choice of effective antibiotics in patients with antibiotic-resistant pouchitis (51), allowing to achieve a clinical remission through an individualized therapy in 80 percent of patients.

In the case of antibiotic failure, budesonide may be a treatment option. Oral budesonide (9 mg/day for eight weeks) was effective in a series of patients with acute pouchitis refractory to antibiotics (52).

Budesonide suppositories for four weeks showed endoscopic improvement or remission at the end of the treatment in all patients with acute pouchitis (53), even if with a high degree of early recurrence. In another controlled trial, 26 patients were randomly assigned to budesonide enemas (2 mg per 100 mL at bedtime) plus placebo tablets or oral metronidazole (500 mg twice daily) plus placebo enemas (54). Both the treatment were associated with a clinical improvement but adverse effects were more common in patients receiving metronidazole.

With regards to probiotics, trials about the treatment of mild/moderate pouchitis are few, with small numbers of adult patients (55). To date, there is limited evidence for a role of probiotics as monotherapy for mild to moderate pouchitis at the present time, as showed by the trials performed by Kuisma, Laake and Gionchetti (56,57). On the other hand, two trials have studied whether there is an advantage to initiate probiotics immediately following ileal pouch-anal anastomosis to evaluate the eventual delay in onset of development of pouchitis (58,59).

Furthermore, small controlled trials have also suggested that at least one probiotic preparation (VSL#3™) may be effective in prevention of recurrent pouchitis after antibiotic induction of remission (60-63)

On the basis of the aforementioned data, clinical practice guidelines on management of pouchitis (64) suggested either VSL#3™ or chronic use of antibiotics for those patients with prompt recurrence of pouchitis following antibiotic usage or having multiple recurrences of pouchitis despite antibiotics, but does not suggest probiotics for acute treatment of pouchitis.

Glucocorticoid and/or mesalamine enemas followed by a short course of oral steroids if enemas cannot be retained can be used as a therapeutic trial (65)
Infliximab was effective long-term (20 months) in IPAA patients with refractory luminal inflammation and in three of seven patients with pouch fistulas (66).

However, risks and benefits need to be considered; and this treatment (such also the treatment with 6-mercaptopurine or azathioprine) is likely reserved for patients with the most severe symptoms.

Perspectives and conclusions

On the basis of the aforementioned data, we can deduce that microbiota play a pivotal role in the

pathogenesis of pouchitis. Conversely, the investigation of the role of gut microbiota in the etiopathogenesis of pouchitis has been difficult because most of gut bacteria are not culturable (67).

In fact molecular microbiology techniques for the qualitative and quantitative measurement of microbiota are expensive and labor-intensive, particularly for the identification of the individual responsible bacteria.. Therefore, the interpretation of the microbiota changes in cross-sectional studies comparing healthy and diseased pouches results challenging.

Due to the dysbiosis, despite intermittent or chronic antibiotic therapy or probiotic therapy, an abnormal mucosal immune response lead to chronic pouchitis or chronic antibiotic-refractory pouchits. Furthermore, patients with genetic susceptibility (such as those with a NOD2/CARD15 mutation) and/or systemic immune-mediated disorders (such as PSC, IgG4-associated systemic disorders) result mainly exposed to the development of chronic antibiotic-refractory pouchits. A molecular classification of pouchitis, with a combined assay of immunogenetic, serologic, and clinical markers, should be advisable (2).

As a consequence, patients with IPAA should be monitored closely. Pouchoscopy is the best way to monitor the anatomic status of the pouch, the degree of inflammation, and the structural abnormalities. For patients with the endoscopic finding of diffuse pouchitis and diffuse enteritis of the afferent limb, immune-mediated pouchitis/enteritis should be considered.

For patients with pouch inflammation that is distributed asymmetrically and has a clear demarcation of inflamed and noninflamed parts of the pouch body, ischemic pouchitis should be suspected.

When pouchoscopy shows abnormalities such as strictures, fistulas, and sinuses, CD of the pouch should be suspected, therefore abdominal and pelvic imaging or examination under anaesthesia are often requested.

In patients with typical symptoms (increased bowel frequency, watery stools, or urgency) antidiarrheal agents can be used first. If the symptoms do not improve in few days, the patient should be evaluated and in some cases treated empirically with antibiotics.

A prolonged course of dual antibiotic therapy may help induce remission in patients with chronic antibiotic-refractory pouchits. On the other hand, oral or topical mesalamine agents and a topically active corticosteroid agent (such as budesonide) are the preferred first-line drugs for immune-mediated pouchitis/ enteritis. Second-line therapies include immunosuppressants (such as 6-mercaptopurine/azathioprine, methotrexate, tacrolimus), or anti-TNF agents.

To date, the aetiology, the diagnosis and the medical management of pouchitis represent a clinical challenge. In fact pouchitis range from a disease with an acute antibiotic-responsive presentation to a chronic antibiotic-refractory form, with subsequent different disease mechanisms and clinical course. A tridimensional and multidisciplinar approach, including endoscopy, histology, and laboratory testing is widely helpful to identify the different phenotypes of the disease and to manage correctly its treatment.

References

1. Steinhart AH, Ben Bassat O. Pouchitis: a practical guide. Frontline Gastroenterol 2013;4:198-204
2. Shen B. Pouchitis: what every gastroenterologist needs to know. Clin Gastroenterol Hepatol. 2013 Dec;11(12):1538-49
3. Shen B. Diagnosis and Management of Postoperative Ileal Pouch Disorders. Clin Colon Rectal Surg. Dec 2010; 23(4): 259–268
4. Meagher AP, Farouk R, Dozois RR, et al. J ileal pouch–anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. Br J Surg 1998;85:800–803
5. Shepherd NA, Hulten L, Tytgat GN, et al. Workshop: Pouchitis. Int J Colorectal Dis 1989; 4: 205–29.
6. Simchuk EJ, Thirlby RC. Risk factors and true incidence of pouchitis in patients after ileal pouch-anal anastomoses. World J Surg 2000; 24: 851–6.
7. Sandborn WJ. Pouchitis: Definition, Risk Factors, Frequency, Natural History, Classification and Public Health Perspective. In: McLeod RS (ed) Trends in Inflammatory Bowel Disease

Therapy, 1996. Hingham, MA, USA: Kluwer Academic Publishers, 1997.
8. Fazio VW, Ziv Y, Church JM, et al. Ileal pouch-anal anastomoses complications and function in 1005 patients. Ann Surg. 1995;222: 120–127.
9. Schmidt CM, Lazenby AJ, Hendrickson RJ, et al. Preoperative terminal ileal and colonic resection histopathology predicts risk of pouchitis in patients after ileoanal pull-through procedure. Ann Surg. 1998; 227:654–662; discussion 63–65.
10. Lohmuller JL, Pemberton JH, Dozois RR, et al. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. Ann Surg. 1990;211:622–627; discussion 7–9.
11. Hata K, Watanabe T, Shinozaki M, et al. Patients with extraintestinal manifestations have a higher risk of developing pouchitis in ulcerative colitis: multivariate analysis. Scand J Gastroenterol. 2003;38: 1055–1058.
12. Okon A, Dubinsky M, Vasiliauskas EA, et al. Elevated platelet count before ileal pouch-anal anastomosis for ulcerative colitis is associated with the development of chronic pouchitis. Am Surg. 2005;71: 821–826.
13. Lian L, Fazio VW, Lavery IC, et al. Evaluation of association between precolectomy thrombocytosis and the occurrence of inflammatory pouch disorders. Dis Colon Rectum. 2009;52:1912–1918.
14. Fleshner PR, Vasiliauskas EA, Kam LY, et al. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. Gut. 2001;49:671–677.
15. Fleshner P, Ippoliti A, Dubinsky M, et al. Both preoperative perinuclear antineutrophil cytoplasmic antibody and anti-CBir1 expression in ulcerative colitis patients influence pouchitis development after ileal pouch-anal anastomosis. Clin Gastroenterol Hepatol. 2008;6:561–568.
16. Fleshner P, Ippoliti A, Dubinsky M, et al. A prospective multivariate analysis of clinical factors associated with pouchitis after ileal pouch-anal anastomosis. Clin Gastroenterol Hepatol. 2007;5: 952–958; quiz 887.
17. Achkar JP, Al-Haddad M, Lashner B, et al. Differentiating risk factors for acute and chronic pouchitis. Clin Gastroenterol Hepatol. 2005;3:60–66.
18. Shen B, Fazio VW, Remzi FH, et al. Comprehensive evaluation of inflammatory and noninflammatory sequelae of ileal pouch-anal anastomoses. Am J Gastroenterol. 2005;100:93–101.
19. Simchuk EJ, Thirlby RC. Risk factors and true incidence of pouchitis in patients after ileal pouch-anal anastomosis. World J Surg 2000;24:851–6.
20. Fazio VW, Tekkis PP, Remzi FH, et al. Quantification of risk for pouch failure after ileal pouch anal anastomosis surgery. Ann Surg 2003;238:605–17.
21. Lavery IC, Sirimarco MT, Ziv T, et al. Anal canal inflammation after ileal pouch-anal anastomosis. The need for treatment. Dis Colon Rectum 1995;38:803–6.
22. Shen B, Fazio WG, Remzi FH, Lashner BA, Clinical Approach to Diseases of Ileal Pouch-Anal Anastomosis. Am J Gastroenterol 2005;100:2796–2807
23. Pardi DS, Sandborn WJ. Systematic review: the management of pouchitis. Aliment Pharmacol Ther 23, 1087–1096
24. Duffy M, O'Mahony L, Coffey JC, et al. Sulfate-reducing bacteria colonize pouches formed for ulcerative colitis but not for familial adenomatous polyposis. Dis Colon Rectum 2002;45:384–388.
25. Nasmyth DG, Godwin PG, Dixon MF, et al. 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.
26. Komanduri S, Gillevet PM, Sikaroodi M, et al. Dysbiosis in pouchitis: evidence of unique microfloral patterns in pouch inflammation. Clin Gastroenterol Hepatol 2007;5:352–360.
27. Sokol H, Lay C, Seksik P, et al. Analysis of bacterial bowel communities of IBD patients: what has it revealed? Inflamm Bowel Dis 2008;14:858–867.
28. Shen BO, Jiang ZD, Fazio VW, et al. Clostridium difficile infection in patients with ileal pouch-anal anastomosis. Clin Gastroenterol Hepatol 2008;6:782–788.
29. Lim M, Sagar P, Finan P, et al. Dysbiosis and pouchitis. Br J Surg 2006;93:1325–1334.
30. Scarpa M, Grillo A, Faggian D, et al. Relationship between mucosa-associated microbiota and inflammatory parameters in the ileal pouch after restorative proctocolectomy for ulcerative colitis. Surgery 2011;150:56–67.
31. Shen B. Campylobacter infection in patients with ileal pouches. Am J Gastroenterol 2010;105:472–473.
32. Ingram S, McKinley JM, Vasey F, et al. Are inflammatory bowel disease (IBD) and pouchitis a reactive enteropathy to group D streptococci (enterococci)? Inflamm Bowel Dis 2009;15: 1609–1610.
33. Gosselink MP, Schouten WR, van Lieshout LM, et al. Eradication of pathogenic bacteria and restoration of normal pouch flora: comparison of metronidazole and ciprofloxacin in the treatment of pouchitis. Dis Colon Rectum 2004;47:1519–1525.
34. Muñoz-Juarez M, Pemberton JH, Sandborn WJ, et al. Misdiagnosis of specific cytomegalovirus infection of the ileoanal pouch as a refractory idiopathic chronic pouchitis: report of two cases. Dis Colon Rectum 1999;42:117–120.
35. Moonka D, Furth EE, MacDermott RP, et al. Pouchitis associated with primary cytomegalovirus infection. Am J Gastroenterol 1998;93:264–266.
36. Sandborn WJ, Tremaine WJ, Batts KP, et al. Pouchitis after ileal pouch–anal anastomosis: a pouchitis disease activity index. Mayo Clin Proc 1994;69:409–15.
37. Heuschen UA, Allemeyer EH, Hinz U, et al. Diagnosing pouchitis: comparative validation of two scoring systems in routine follow-up. Dis Colon Rectum 2002;45:776–88.
38. Elder K, Lopez R, Kiran RP, Remzi FH, Shen B. Endoscopic features associated with ileal pouch failure. Inflamm Bowel Dis. 2013 May;19(6):1202-9.
39. Navaneethan U, Shen B. Pros and cons of antibiotic therapy for pouchitis. Expert Rev Gastroenterol Hepatol 2009; 3:547
40. Sandborn WJ. Pouchitis following ileal pouch-anal anastomo-

sis: definition, pathogenesis, and treatment. Gastroenterology 1994; 107:1856.
41. Dozois RR, Goldberg SM, Rothenberger DA, et al. Restorative proctocolectomy with ileal reservoir. Int J Colorectal Dis 1986; 1:2.
42. Madden MV, McIntyre AS, Nicholls RJ. Double-blind crossover trial of metronidazole versus placebo in chronic unremitting pouchitis. Dig Dis Sci 1994; 39:1193.
43. Shen B, Achkar JP, Lashner BA, et al. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. Inflamm Bowel Dis 2001; 7:301.
44. Gosselink MP, Schouten WR, van Lieshout LM, et al. Eradication of pathogenic bacteria and restoration of normal pouch flora: comparison of metronidazole and ciprofloxacin in the treatment of pouchitis. Dis Colon Rectum 2004; 47:1519. Isaacs KL, Sandler RS, Abreu M, et al. Rifaximin for the treatment of active pouchitis: a randomized, doubleblind, placebo-controlled pilot study. Inflamm Bowel Dis 2007; 13:1250.
45. Shen B, Remzi FH, Lopez AR, Queener E. Rifaximin for maintenance therapy in antibiotic-dependent pouchitis. BMC Gastroenterol 2008; 8:26.
46. Gionchetti P, Rizzello F, Venturi A, et al. Antibiotic combination therapy in patients with chronic, treatmentresistant pouchitis. Aliment Pharmacol Ther 1999; 13:713.
47. Abdelrazeq AS, Kelly SM, Lund JN, Leveson SH. Rifaximin-ciprofloxacin combination therapy is effective in chronic active refractory pouchitis. Colorectal Dis 2005; 7:182.
48. Mimura T, Rizzello F, Helwig U, et al. Four-week open-label trial of metronidazole and ciprofloxacin for the treatment of recurrent or refractory pouchitis. Aliment Pharmacol Ther 2002; 16:909.
49. Tremaine WJ, Sandborn WJ, Wolff BG, et al. Bismuth carbomer foam enemas for active chronic pouchitis: a randomized, double-blind, placebo-controlled trial. Aliment Pharmacol Ther 1997; 11:1041.
50. Shen B, Fazio VW, Remzi FH, et al. Combined ciprofloxacin and tinidazole therapy in the treatment of chronic refractory pouchitis. Dis Colon Rectum 2007; 50:498.
51. McLaughlin SD, Clark SK, Shafi S, et al. Fecal coliform testing to identify effective antibiotic therapies for patients with antibiotic-resistant pouchitis. Clin Gastroenterol Hepatol 2009; 7:545.
52. Gionchetti P, Rizzello F, Poggioli G, et al. Oral budesonide in the treatment of chronic refractory pouchitis. Aliment Pharmacol Ther 2007; 25:1231.
53. Belluzzi A, Campieri M, Miglioli M, et al. Evaluation of flogistic pattern in "pouchitis" before and after the treatment with budesonide suppositories (abstract). Gastroenterology 1992; 102:A593.
54. Sambuelli A, Boerr L, Negreira S, et al. Budesonide enema in pouchitis--a double-blind, double-dummy, controlled trial. Aliment Pharmacol Ther 2002; 16:27.
55. Sinagra, E., Tomasello, G., Cappello, F., Leone, A., Cottone, M., Bellavia, M., et al. (2013). Probiotics, prebiotics and symbiotics in inflammatory bowel diseases: state-of-the-art and new insights. J Biol Regul Homeost Agents, 4(27(4)), 919-933.
56. Kuisma J, Mentula S, Jarvinen H, Kahri A, Saxelin M, Farkkila M. Effect of Lactobacillus rhamnosus GG on ileal pouch inflammation and microbial flora. Aliment Pharmacol Ther 2003;17:509515.
57. Laake KO, Bjorneklett A, Aamodt G, Aabakken L, Jacobsen M, Bakka A, Vatn MH. Outcome of four weeks' intervention with probiotics on symptoms and endoscopic appearance after surgical reconstruction with a J-configuration ileal-pouch-anal-anastomosis in ulcerative colitis. Scand. J. Gastroenterol. 2005; 40:43–51.
58. Pronio A, Montesani C, Butteroni C, Vecchione S, Mumolo G, Vestri A, Vitolo, D, Boirivant M. Probiotic administration in patients with ileal pouch-anal anastomosis for ulcerative colitis is associated with expansion of mucosal regulatory cells. Inflamm. Bowel. Dis. 2008;14: 662–68.
59. Gionchetti P, Rizzello F, Morselli C, Poggioli G, Tambasco R, Calabrese C, Brigidi P, Vitali B, Straforini,G, Campieri M. High-dose probiotics for the treatment of active pouchitis. Dis. Colon Rectum 2007, 50, 2075–2078.
60. Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. Gastroenterology 2003; 124: 12021209.
61. Mimura T, Rizzello F, Helwig U, Poggioli G, Schreiber S, Talbot IC, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. Gut 2004; 53: 108114.
62. Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. Gastroenterology 2003; 124: 12021209.
63. Shen B, Brzezinski A, Fazio VW, Remzi FH, Achkar JP, Bennett AE, Sherman K Lashner BA. Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: experience in clinical practice. Aliment. Pharmacol. Ther. 2005;22:721–28.
64. Pardi DS, D'Haens G, Shen B, Campbell S, Gionchetti P. Clinical guidelines for the management of pouchitis. Inflamm. Bowel. Dis. 2009;15:1424–1431.
65. Miglioli M, Barbara L, Di Febo G, et al. Topical administration of 5-aminosalicylic acid: a therapeutic proposal for the treatment of pouchitis. N Engl J Med 1989; 26:320.
66. Ferrante M, D'Haens G, Dewit O, et al. Efficacy of infliximab in refractory pouchitis and Crohn's disease related complications of the pouch: a Belgian case series. Inflamm Bowel Dis 2010; 16:243.
67. Zoetendal EG, Rajilic-Stojanovic M, De Vos WM. High-throughput diversity

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