

Diagnostic and management approach to pouchitis in inflammatory bowel disease

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Received: 16 September 2019

Accepted: 13 December 2019

ABSTRACT – In patients with ulcerative colitis refractory to medical therapy, total proctocolectomy and posterior ileal-anal pouch anastomosis is the standard surgical therapy. One of the possible complications is pouchitis. Depending on the duration of the symptoms, it can be classified as acute, recurrent, or chronic. The latter, according to the response to therapy, can be defined as antibiotic-dependent or refractory. The treatment of pouchitis is based on the use of antibiotics and probiotics. Thiopurine and biological therapy have been suggested in patients with refractory pouchitis. Special care should be taken in the endoscopic surveillance of these patients, especially if they present risk factors such as dysplasia or previous colorectal cancer, primary sclerosing cholangitis or ulcerative colitis for more than 10 years.

HEADINGS – Pouchitis, therapy. Restorative proctocolectomy. Ulcerative colitis.

INTRODUCTION

In patients with ulcerative colitis (UC) refractory to medical management, the surgical resolution with a total proctocolectomy and subsequent ileal-anal pouch anastomosis is the procedure of choice^(1,2). In general, there is a low rate of complications, even though surgical techniques are less invasive with laparoscopic procedures and robotic surgery⁽³⁻⁶⁾. Among the potential complications associated with this surgery, there are suture dehiscence, perianal abscesses, and one of the most frequent, pouchitis. One year after surgery, approximately 20% of patients develop pouchitis, which can reach an incidence close to 40% in the fifth year after surgery⁽²⁾.

In general, episodes of pouchitis are more associated with colectomy due to UC, than to neoplastic or familial polyposis syndromes. In these latter cases, the incidence of pouchitis ranges from 0% to 11%, which is lower than in colectomies secondary to UC, and could be explained by the immune-mediated etiology of UC⁽⁷⁻⁹⁾.

The objective of this review is to evaluate the best approach of pouchitis study and management, being necessary the study with pouchoscopy, for guiding the etiology and determining a more targeted treatment, discussing the different therapeutic alternatives, from the use of antibiotics, probiotics, even considering the use of immunomodulators, corticosteroids and biological therapies in case of refractory pouchitis, as well as the available surgical alternatives and their results⁽¹⁰⁾.

Anatomy and function of the pouch

For a better understanding of this condition, it is necessary to know the different anatomical configurations of the pouch. The most frequent is the J-pouch that uses two small bowel handles to generate the pouch; also, there is an S and a W configuration that use three and four handles respectively. The J-pouch has a smaller

volume compared to the other configurations (J=228 cc, S=320 cc, and W=440 cc) and it is made from only 30–40 cm of distal ileum, compared to the S-pouch and the W-pouch which require 50 cm each^(11,12). (FIGURE 1).

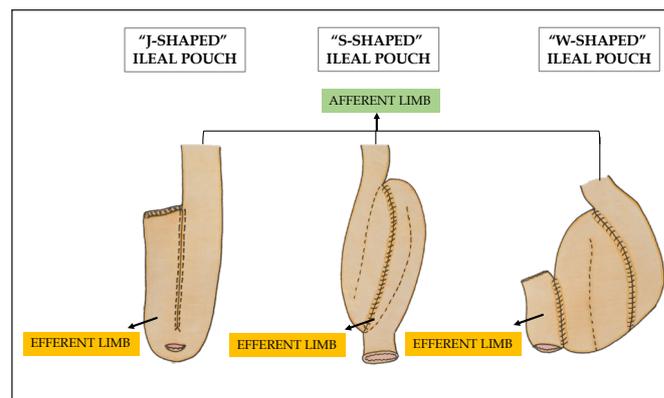


FIGURE 1. Pouch types.

One year after the J-pouch surgery, patients maintain 5–6 stools per day, with 1–2 stools at night; before this, the evacuation frequency may be higher until patients achieve adaptation to the pouch⁽¹³⁾.

Concepts and definitions in pouchitis

Acute pouchitis is characterized by local inflammation of the ileal pouch, which can persist up to four weeks. There is increasing number of bowel movements and lower consistency of the stools, sometimes being associated to mucus and blood. Rectal symptoms such as tenesmus, urgency and even incontinence, can also be seen. Occasionally, patients may also present with systemic manifestations as fever, weight loss and joint involvement⁽¹⁾.

Declared conflict of interest of all authors: none

Disclosure of funding: no funding received

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The symptoms of pouchitis are nonspecific, and their severity is not always directly related to the endoscopic/histological findings⁽¹⁴⁾. For this reason, the diagnosis must be accompanied by an endoscopic image and histological study⁽¹⁵⁾.

Pathogenesis

Although the pathogenesis of pouchitis is not yet clear, multiple factors have been involved in its development and evolution. After surgery intestinal mucosa changes, phenomenon known as colonic metaplasia. A significant reduction of the intestinal villi of the pouch area and an increase in the depth of the crypts occur, which correlates with a greater cellular proliferation associated with lymphoplasmacytic infiltrate in the lamina propria⁽¹⁶⁾.

Ischemic or mechanical post-surgical phenomena, immunological alterations, and dysbiotics processes have also been evidenced. The latter being observed in the context of good response to antibiotic and probiotic management^(8,17).

In the diagnostic evaluation, biopsies should be taken to rule out other pathologies that may present clinically similar to the ones previously described. Secondary causes and other differential diagnoses should be ruled out, such as cuffitis, which is the residual inflammation of the remaining rectum⁽¹⁸⁻²⁰⁾.

When pouchitis do not respond to antibiotic/probiotic therapy, and the condition persists for more than four weeks, it is called chronic pouchitis, which occurs in 10%–15% of all cases^(21,22). Chronic pouchitis can be classified into two entities: chronic antibiotic-dependent pouchitis, where pouchitis recurs at least three times a year after discontinuing antibiotic therapy, and chronic antibiotic-refractory pouchitis, when the condition does not respond to antibiotic therapy^(1,23,24).

DIAGNOSTIC APPROACHEMENT

To distinguish the different etiologies of pouchitis, it is essential to carry out complementary studies to the symptoms described by the patient.

Pouchoscopy

In clinical practice, pouchoscopy is one of the most useful and practical tools. During this procedure, it is essential to carefully evaluate the reference points of the pouch, including the afferent limb, the pouch, the junction or anastomosis, the efferent loop, and the rectal cuff, documenting each of them with images (FIGURE 2). It is important to describe the presence of edema, erythema, friabil-

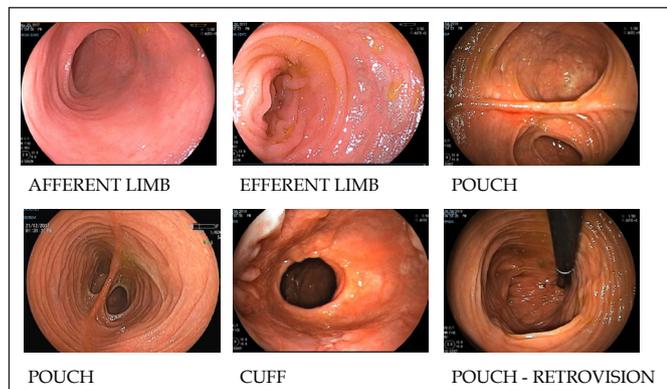


FIGURE 2. Endoscopic images of the pouch.

ity, spontaneous bleeding, erosions and ulcerations of the mucosa. Retrovision in the pouch is a safe technique⁽²⁵⁻²⁷⁾. According to the compromise of different areas of the pouch, etiological diagnosis of pouchitis can be oriented⁽²²⁾. (FIGURE 3).

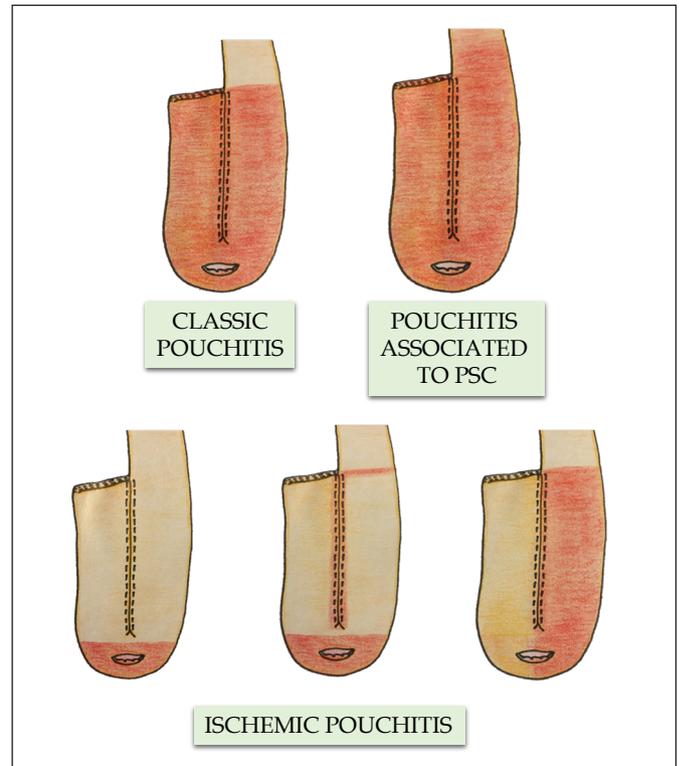


FIGURE 3. Pouchitis patterns.

There are two systems of objective evaluation of the index of inflammatory activity at the pouch level; PDAI (Pouch disease activity index) and PAS (pouchitis activity score). These indices combine clinical symptoms, endoscopic, and histological findings. However, they are not yet fully validated.

Histological study

As it was described, there is a phenomenon of usual colonic metaplasia accompanied by an infiltrate of inflammatory cells, and in pouchitis, some acute elements such as ulcerations or cryptic abscesses, appears⁽²⁸⁾. Histology allows differentiating of some secondary causes.

Imaging study

Computed tomography and magnetic resonance (MR) allow to evaluated the presence of abscesses, strictures, and inflammation of the pouch. MR has a higher sensitivity to detect compromise of the remaining rectum and rule out the presence of perianal disease⁽¹¹⁾. In a prospective study in patients with a pouch, a good correlation between the findings of the resonance and the endoscopic scores was found ($r=0.61$; $P=0.0005$), with a positive likelihood ratio (LR) of four and a negative LR of 0.18⁽²⁹⁾.

With these elements, we can differentiate whether it is a primary or secondary pouchitis. Primary or idiopathic pouchitis is characterized by the difficulty to investigate a triggering factor of the condition. It is believed that its origin lies in the presence of a mucosal

dysbiosis that would alter the immune response of the mucosa⁽³⁰⁾. Ruling out of secondary causes should support its diagnosis.

Secondary pouchitis may have several etiologies being the most frequent:

• Infectious pouchitis

They are mostly idiosyncratic, with a response rate to therapy close to 80%–85%. Classically it compromises the entire pouch. However, some agents must be discarded since they require specific treatment.

Of those refractory or recurrent, the most commonly described microorganism is *Clostridioides difficile* (*C. Diff*). The reported incidence is up to 10% in a North American study, which included symptomatic patients with pouches⁽³¹⁾. In this context, it is crucial to perform a microbiological study of fecal material, to be able to guide antibiotic therapy to the specific etiologic agent^(10,19,30). Recently published IDSA guidelines suggest to request PCR for *C. Diff*. alone or associated with toxin A and B and/or Glutamate dehydrogenase (GDH), in patients with high suspicion of *C. Diff*. infection⁽³²⁾. Most of the time, pouchoscopy can show slight alterations such as edema, loss of the submucosal vascular pattern, friability and less frequently, the classic pseudomembranes⁽³³⁾. In *C. Diff*. pouchitis that has not responded to standard therapy with vancomycin or fidaxomicin, the therapeutic alternative is the use of fecal microbiota transplantation. This technique has been used in cases of pouchitis with good results⁽³⁴⁾.

Another important agent to study is cytomegalovirus, which may have a clinical presentation similar to idiopathic pouchitis^(35,36). If suspected, pouch tissue samples should be studied with immunohistochemical staining or PCR. There is better performance with greater number of samples and when these are obtained from the base of ulcerative lesion^(37,38).

Other infectious agents such as *Candida sp.* have been reported in biopsies of patients with chronic pouchitis⁽³⁹⁾.

• Immunomediated pouchitis

This scenario is usually associated with a higher frequency of extraintestinal manifestations and autoimmune disorders, such as pouchitis associated with primary sclerosing cholangitis (PSC) and pouchitis associated with IgG4 disease. Both cases do not respond well to antibiotics and tend to be more severe and chronic. In the case of PSC, patients usually present altered function liver tests and biliary tract compromise in the magnetic resonance cholangiography.

A common finding in the pouchoscopy is the inflammation of the entire pouch and afferent loop^(40,41).

Frequent histologic findings in IgG4 associated pouchitis are the IgG4 plasma cells infiltration of the pouch's mucosa and marked cryptic apoptosis⁽³⁵⁾. Among the serologic tests, it is possible to find elevated serum IgG4 levels.

Given the increased risk of neoplasia of the pouch, these patients need to enter an endoscopic surveillance program which should be performed every one to two years⁽⁴²⁾. In both scenarios, immunosuppression is the therapy of choice.

Ischemic pouchitis

When the etiology suspected is ischemia, the usual finding is a characteristic inflammation pattern of the pouch, compromising only the efferent loop and respecting the afferent loop⁽⁴³⁾. These cases are usually related to post-surgical anatomical alterations, such as lack of irrigation of the distal ileum or, excessive tension

over the mesentery. The classic histological findings are hemosiderin deposits in the endothelium, as a marker of the increased oxidative stress at this level, which perpetuates the inflammation of the mucosa with the underlying inflammatory bowel disease⁽⁴³⁻⁴⁵⁾.

• Crohn's disease of the pouch

It can be evidenced immediately after surgery, where histological findings are compatible with Crohn's disease, or it can appear years after surgery, being considered a "de novo" disease. Its clinical presentation can be with any of the phenotypes of classic Crohn's disease, and its management must be aggressive and well-directed to avoid complications⁽⁴⁶⁾. Pouch's compromise is usually segmentary, stenosis or fistulas may appear at the ileoanal anastomosis or at the proximal end of the pouch, as well as in the afferent limb^(47,48). Histology does not always show the classic non-casing granuloma^(37,49-52).

• Neoplasia

The risk of malignancies in patients with a pouch is 0.9% at five years and 5.1% at 25 years. The history of dysplasia or colorectal cancer before the pouch are independent risk factors for pouch's neoplasia, with a relative risk of 3.76 for previous dysplasia and 24.69 for previous neoplasia⁽⁵³⁾. Patients with a pouch must have a screening endoscopy every one to three years⁽⁵⁴⁾. In patients with risk factors, such history of UC for more than 10 years, cuffitis, family history of colorectal cancer or PSC, should have endoscopic surveillance with biopsy every one or two years. Patients with previous neoplasia, surveillance should have annual surveillance with particular emphasis on the cuff and the anastomosis area^(40,42).

• Irritable pouchitis

In this scenario, symptoms are similar to acute pouchitis; however, no lesions are found in the pouch. It is a manifestation of irritable bowel syndrome; which treatment is based on tricyclic and antispasmodic antidepressants⁽⁵⁵⁾.

TREATMENT

Despite the progress of available therapies, there is still a lack of evidence to establish prevention and treatment of pouchitis.

Acute pouchitis

First-line therapy is based on antibiotics, such as ciprofloxacin and metronidazole, for 14 days^(56,57). However, these recommendations are based on low-quality evidenced studies with a small number of patients⁽⁵⁸⁾. One study administered ciprofloxacin 1000 mg/day to seven patients, and metronidazole 20 mg/kg/day to nine patients, observing that in the first group 100% achieved clinical remission vs 33% (3/9 patients) in the second group. Regarding adverse events, they were only observed in the metronidazole group (nausea, vomiting, dysgeusia and transient peripheral neuropathy) in three of the nine patients^(59,60).

A study that compared rifaximin vs placebo showed that only 25% (2/8) of patients receiving rifaximin achieved endoscopic remission at week four of treatment, vs 0% (0/10) of those receiving placebo. Adverse events were documented in six of eight patients in the first group vs five of 10 patients in the placebo group including diarrhea, flatulence, nausea, proctalgia, vomiting, thirst, candida infection, upper respiratory tract infection, increased liver enzymes, and cluster headache⁽⁵⁸⁾.

When there is intolerance to antibiotics, the use of budesonide enemas (2 mg/100 mL) for six weeks has been considered. The response to enemas and metronidazole was evaluated in a double-blind study. When comparing both strategies, there were no differences in the endoscopic and histological response⁽⁶¹⁾.

It is known that the use of NSAIDs in inflammatory bowel disease should be avoided due to the risk of reactivation of the disease. In a study that included 17 patients with recurrent pouchitis, it was demonstrated that the suspension of these drugs allowed a significant reduction in the PDAI index, and an increase in the quality of life index ($P < 0.02$ and < 0.05 respectively)⁽⁶²⁾.

Chronic pouchitis

The treatment of chronic pouchitis is, above all, empirical since quality studies are lacking. Around 5%–15% of patients can progress to chronicity. The first therapeutic approach is the use of antibiotics for periods longer than four weeks. Rifaximin, is the antibiotic of choice as maintenance therapy given its safety profile compared to other antibiotics⁽⁶³⁾. Some studies have proposed to study the pouch's microbiota and thus identifying the best antibiotic agent to be used in each patient as a personalized treatment strategy⁽⁶⁴⁻⁶⁶⁾. Alternative treatments suggest the use of ciprofloxacin followed by rifaximin, metronidazole, or tinidazole, for a variable period⁽⁶⁵⁻⁶⁷⁾.

Through a meta-analysis, it was possible to evaluate the different probiotics used in patients with pouchitis; showing that there is little evidence available regarding dosing and the ideal treatment length, concluding that there is a need of long-term studies to assess the real impact of probiotics in pouchitis⁽⁶⁸⁾.

The probiotic VSL # 3 has the highest number of studies, proving to be effective over placebo, but with a low level of evidence. Eighty-five percent (34/40) of patients who received VLS # 3 (2 sachets/day = 600 billion bacteria) maintained remission for 9 to 12 months compared to 3% (1/36) of patients who received placebo (RR 20.24; 95% CI 4.28 to 95.81)⁽⁶⁸⁾. Two percent (1/40) of participants who received VSL # 3 had an adverse event (abdominal pain, vomiting, and diarrhea), compared with 0% (0/36) of the participants who received placebo^(56,68-70).

Other studies with probiotics, such as *Lactobacillus rhamnosus* supplementation for three months, achieved changes in the bacterial flora of the pouch, however, there was no significant change in clinical or endoscopic response⁽⁷¹⁾.

Chronic antibiotic refractory pouchitis has challenging management, and there are no randomized studies that provide a better quality of evidence about treatment. Steroid therapy with budesonide 9 mg/day has been used for eight weeks, showing that four out of five patients achieved clinical and endoscopic improvement, without reporting adverse effects. In an Italian group of 20 patients, 75% achieved clinical remission and improvement in their quality of life with $P < 0.001$ ^(72,73).

Biological therapy has been used as a rescue treatment in those patients who have not responded to antibiotic therapy⁽⁷⁴⁾. In a retrospective Belgian study that included 28 patients with refractory pouchitis treated with infliximab 5 mg/kg every eight weeks, showed that 88% presented a clinical response at 10 weeks, which was maintained in 56% of patients at 20 weeks⁽⁷⁵⁾. A canadian

cohort of 42 patients, of whom 26 had refractory pouchitis and 16 Crohn's disease of the pouch, using infliximab 62.6% achieved partial clinical response and 29.6% a complete clinical response⁽⁷⁶⁾. For instance, infliximab in maintenance dose for at least one year, has shown to maintain clinical remission in 71.4% of patients, including the remission of extraintestinal manifestations⁽⁷⁷⁾.

Concerning adalimumab, there is a double-blind, multicenter study of patients with refractory pouchitis, who were randomized to adalimumab as induction therapy vs placebo. Of a total of 13 patients, only 9 of them managed to complete the 12 weeks of the study, so it was not possible to establish clinical or endoscopic differences in these two groups⁽⁷⁸⁾.

In a systematic review, which included 313 patients with inflammatory complications of the pouch (194 with infliximab and 119 with adalimumab) it was shown that when comparing Crohn's disease of the pouch vs refractory pouchitis, the effectiveness of the therapy was markedly superior for the first group 0.64 vs 0.1 with $P = 0.06$ ⁽⁷⁹⁾.

Experience with vedolizumab comes from a multicenter retrospective cohort study of five American academic centers with a total of 83 patients followed for 1.3 years on average (maximum 2.1 years). Clinical response was observed in 71.1% of cases, with remission achieved in only 19.3% of these. The endoscopic response rate was 54.1%, but with mucosal healing of only 17.6%. Thirty-six-point one percent suspended vedolizumab for clinical reasons, three patients for infusion reactions and another three for serious adverse events (C. Diff., norovirus and one patient with an abscess that required laparoscopic drainage)⁽⁸⁰⁾.

Regarding ustekinumab, there is a retrospective study of four American centers with a total of 56 patients (47 with Crohn's disease of the pouch and nine with chronic pouchitis). Of all patients, 73% had previously used an anti TNF or vedolizumab. In Crohn's group, 83% demonstrated clinical response after induction. An elevated BMI and being male were risk factors for inadequate response⁽⁸¹⁾. A second study included 42 patients with chronic antibiotic refractory pouchitis, 50% of whom had previously used biological therapy or immunomodulators. Twelve of the 24 (50%) patients achieved a post-induction clinical response with ustekinumab. Pouchoscopy was performed in 13 patients, in whom there was a decrease in PDAI from 5 to 4 points with $P = 0.016$ ⁽⁸²⁾.

When immune-mediated pouchitis, or Crohn's pouchitis, is investigated, the treatment of choice is immunosuppressive therapy, either with corticosteroids, immunomodulators, or in some cases, biological therapy with a good response as described in the treatment of refractory pouchitis^(83,84).

CONCLUSION

In patients with UC refractory to medical therapy, total proctocolectomy and subsequent ileal-anal pouch anastomosis remains the therapy of choice. Pouchitis is the most frequent complication in this group of patients, and the initial management is with antibiotics. However, a percentage of these patients may present with chronic or refractory pouchitis, and it is necessary to rule out secondary causes and define the best therapeutic strategy. Management algorithm attached in FIGURE 4.

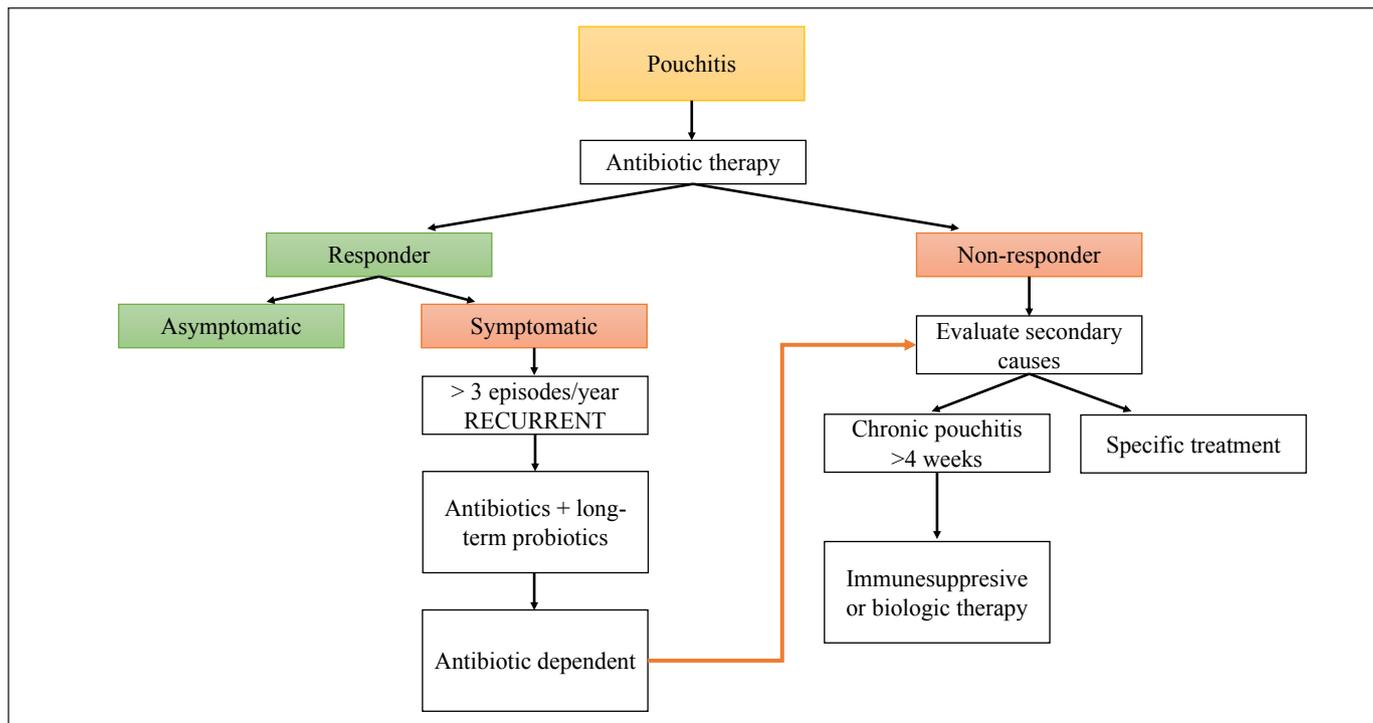


FIGURE 4. Management algorithm.

Authors' contribution

Sedano R, Nuñez P: review of literature and writing the text and final text approval. Quera R: writing the text, improvement of the final version and final text approval.

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Sedano R, Nuñez P, Quera R. Abordagem diagnóstica e de manuseio da pouchite em doença inflamatória intestinal. *Arq Gastroenterol.* 2020;57(1):100-6.

RESUMO – Em pacientes com colite ulcerativa refratária à terapia médica, a proctocolectomia total e anastomose de bolsa ileal-anal posterior é a terapia cirúrgica padrão. Uma das possíveis complicações é a pouchite. Dependendo da duração dos sintomas, pode ser classificada como aguda, recorrente ou crônica. Esta última, de acordo com a resposta à terapia, pode ser definida como dependente de antibióticos ou refratária a eles. O tratamento da pouchite baseia-se no uso de antibióticos e probióticos. A thiopurina e a terapia biológica têm sido sugeridas em pacientes com pouchite refratária. Um cuidado especial deve ser tomado na vigilância endoscópica desses pacientes, especialmente se apresentarem fatores de risco, como displasia ou câncer colorretal anterior, colangite esclerosante primária ou colite ulcerativa por mais de 10 anos.

DESCRIPTORES – Pouchite, terapia. Proctocolectomia restauradora. Colite ulcerativa.

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