Clinical and Experimental Gastroenterology

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REVIEW

Chronic Antibiotic-Refractory Pouchitis: Management Challenges

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Background: Pouchitis is the most common long-term complication in patients with ulcerative colitis who underwent restorative proctocolectomy with ileal pouch-anal anastomosis. The incidence of acute pouchitis is 20% after 1 year and up to 40% after 5 years. Chronic antibiotic-refractory pouchitis develops in approximately 10% of patients.

Aim: To present a narrative review of published literature regarding the management of chronic antibiotic-refractory pouchitis.

Methods: Current relevant literature was summarized and critically evaluated.

Results: Clear definitions should be used to classify pouchitis into acute versus chronic, and responsive versus dependent versus refractory to antibiotics. Before treatment is started for chronic antibiotic-refractory pouchitis, secondary causes should be ruled out. There is a need for validated scoring systems to measure the severity of the disease. Because chronic antibiotic-refractory pouchitis is a rare condition, only small studies with often a poor study design have been performed. Treatments with antibiotics, aminosalicylates, steroids, immunomodulators and biologics have shown to be effective and safe for chronic antibiotic-refractory pouchitis. Also, treatments with AST-120, hyperbaric oxygen therapy, tacrolimus enemas, and granulocyte and monocyte apheresis suggested some efficacy.

Conclusion: The available data are weak but suggest that therapeutic options for chronic antibiotic-refractory pouchitis are similar to the treatment strategies for inflammatory bowel diseases. However, randomized controlled trials are warranted to further identify the best treatment options in this patient population.

Keywords: chronic antibiotic-refractory pouchitis, inflammatory bowel disease, biologics

Introduction

Pouchitis is the most common long-term complication in patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP) who underwent restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA). Symptoms may include increased stool frequency and fluidity, rectal bleeding, fecal urgency, incontinence, abdominal cramps, fever and extra-intestinal manifestations.[1] Routine laboratory tests may be normal, or they may reveal anemia, an elevated C-reactive protein, electrolyte abnormalities, iron deficiency and vitamin D deficiency.[2,3] Fecal calprotectin and lactoferrin appear to be significant predictors of pouchitis.[4] A diagnosis of pouchitis can only be made after confirmation on endoscopy and eventual histological examination.

The incidence of acute pouchitis is estimated to be around 20% after 1 year and up to 40% after 5 years. Chronic antibiotic-refractory pouchitis develops in approximately 10% of patients.[5] Besides differences in length and type of follow-up, an

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Received: 1 February 2021
Accepted: 6 May 2021
Published: 14 June 2021

important reason for variation in incidence is the lack of universally accepted diagnostic criteria for pouchitis.[1]

Pouchitis can develop, based on the number of episodes and response to antibiotics, from acute antibiotic-responsive (one to three episodes a year) to chronic antibiotic-dependent (four or more antibiotic-responsive episodes a year or need for ongoing antibiotic use). In some patients, the symptoms persist despite a course of more than four weeks of antibiotic therapy (chronic antibiotic-refractory pouchitis or CARP).

In cases where chronic antibiotic-refractory pouchitis is suspected, it is important to rule out other diagnoses, such as a pouch outlet obstruction, strictures, pouch fistula, peripouch inflammation, cuffitis, prepouch ileitis, irritable pouch syndrome or secondary etiologies, such as infections (eg *Clostridium difficile* and cytomegalovirus), non-steroidal anti-inflammatory drug (NSAID) use, concomitant auto-immune disorders (eg coeliac disease) and pouch ischemia.[6] A relook at the colectomy specimen is warranted to rule out a missed diagnosis of Crohn's disease. Whether a pouch stricture, pouch fistula and prepouch ileitis are sufficient to diagnose Crohn's disease is still debated.

The etiology of pouchitis is considered to be multifactorial and suggests an abnormal immune response to an imbalanced gut microbiome[7] in genetically susceptible individuals[8] following triggering events.[9] Acute antibiotic-responsive pouchitis is predominately microbially mediated and chronic antibiotic-refractory pouchitis is predominately immune mediated. This may explain why chronic antibiotic-refractory pouchitis is more commonly seen in UC patients than FAP patients.[10]

Chronic antibiotic-refractory pouchitis is the most challenging form of pouchitis to treat. Because it is a rare condition, only small studies with often a poor study design are performed. Patients may end up therapy resistant and eventually need surgery with a permanent ileostomy.

Risk Factors

Assessing the presence of risk factors could eventually guide prophylaxis for pouchitis. These risk factors include the presence of primary sclerosing cholangitis (PSC)[11] and other extra-intestinal manifestations,[12] serological markers (IgG4, ANCA, ACCA and Omp),[13–15] extensive colitis,[16,17] backwash ileitis,[18,19] corticosteroid exposure before proctocolectomy,[20,21] periproctocolectomy thrombocytosis,[20] young age,[22–24] male sex,[24] construction of a J-pouch,[25] postoperative NSAID use[12] and non-smoking[20] (Table 1). Some genetic mutations (eg NOD2/CARD15 mutation[26]) are also associated with the development of pouchitis; however, testing is costly, not widely available and thus not routinely performed.

Prevention

The use of probiotics (VSL#3,[27,28] *Lactobacillus rhamnosus* GG[29] or *Clostridium butyricum* MIYAIRI[30]) is suggested for the prophylaxis of antibiotic-dependent pouchitis; however, evidence is not strong and conflicting. Sulfasalazine may be an alternative to more expensive probiotics for the long-term prevention of pouchitis development.[31] This should be combined with a diet balanced in fermentable fibers to establish a favorable microbiome. In a prospective cohort study including 172 patients with ileal pouches, lower fruit consumption was correlated with higher rates of pouchitis compared with higher fruit intake.[32]

Table 1 Risk Factors of Pouchitis

Primary Sclerosing Cholangitis	
Extra-intestinal manifestations	Arthritis, pyoderma gangrenosum, erythema nodosum, aphthous ulcers, uveitis, episcleritis
Serological markers	IgG4, ANCA, ACCA, Omp
Extensive colitis	
Backwash ileitis	
Corticosteroid exposure preproctocolectomy	
Thrombocytosis periproctocolectomy	
Young age	
Male sex	
J-pouch	
NSAID use postproctocolectomy	
Non-smoking	
Genetic mutations	NOD2/CARD15

Assessing Disease Activity of Pouchitis

When starting a treatment for pouchitis, we need to be able to measure the effect of the treatment in an objective way. That is why we need scoring systems that measure the severity of the disease and can be used for follow-up.

The most commonly used scoring systems are the pouch disease activity index (PDAI)[33] (Table 2), including clinical, endoscopic and histological features, and a more simplified modified PDAI (mPDAI),[34] not containing the histological criteria. Nevertheless, these scores are not validated and their routine use in clinical practice is rare. Also, these scoring systems do not take into account quality of life indicators that may be significant to the patient.

The Oresland score evaluates the functional outcome of the pouch. It includes 11 parameters, evaluating the 24-h stool frequency, nighttime defecation, the urgency of defecation, dyschezia, soiling and the use of pads, perianal skin irritation, dietary restrictions, regular medication for diarrhea and social handicap.[35] The value obtained in the Oresland score allows us to classify the pouch its functional outcome into three groups: good (0–4), moderate (5–7) and poor (8–15) (Table 3). Another score was presented by Brandsborg et al evaluating the function of the pouch and subsequently the quality of life of the patient.[36] The score takes into account the feeling of incomplete emptying, number of bowel movements, uncontrolled loss of stools, use of anti-diarrheal medication, urgency and the ability to defer the urge to defecate (Table 4). Despite its importance, these scores do not seem to be routinely used in clinical practice yet.

Treatment of Acute Pouchitis

Patients with acute pouchitis typically respond to antibiotic therapy. Ciprofloxacin is considered the first-line therapy for acute pouchitis. In a randomized clinical trial by Shen et al, the effectiveness and side effects of ciprofloxacin and metronidazole for treating acute pouchitis were compared.[37] Both antibiotics were effective with a significant reduction in PDAI; however, ciprofloxacin produced a greater reduction in the PDAI and a greater improvement in symptom and endoscopy subscores, and was better tolerated than metronidazole. Rifaximin might also be useful in treating acute pouchitis. A randomized placebo-controlled pilot trial showed that clinical remission occurred more frequently in patients treated with rifaximin, however, the difference was not significant.[38]

Table 2 The Pouch Disease Activity Index (PDAI)

Criteria		Score	Subtotal
Clinical	**Stool frequency**		
	Usual postoperative stool frequency	0	
	1–2 stools/day > postoperative usual	1	
	3 or more stools/day > postoperative usual	2	
	Rectal bleeding		
	None or rare	0	
	Present daily	1	
	Fecal urgency or abdominal cramps		
	None or rare	0	
	Occasional	1	
	Usual	2	
	Fever (temperature >37.8°C)		
	Absent	0	
	Present	1	
Endoscopic inflammation	Edema	1	
	Granularity	1	
	Friability	1	
	Loss of vascular pattern	1	
	Mucus exudates	1	
	Ulceration	1	
Acute histologic inflammation	**Polymorphic nuclear leukocyte infiltration**		
	Mild	1	
	Moderate + crypt abscess	2	
	Severe + crypt abscess	3	
	Ulceration per low power field (mean)		
	<25%	1	
	25–50%	2	
	>50%	3	
Total PDAI			

Table 3 The Oresland Score

	Score (0–15)		
	0	1	2
Bowel movements/24-h	<5	5	>5
Bowel movements/night	No	>1/week	≥2/night
Urgency	No	Yes	
Dyschezia	No	Yes	
Soiling daytime	No	≥1/week	
Soiling nighttime	No	≥1/night	
Protecting pads daytime	No	≥1/week	
Protecting pads nighttime	No	≥1/night	
Perianal skin irritation	No	Sometimes	Always
Diet alteration	No	Yes	
Use of antidiarrheals	No	Yes	
Social handicap	No	Yes	

Table 4 Score Evaluating the Function of the Pouch and Quality of Life Suggested by Brandsborg et al

Criteria	Score
How many times per 24 h in the last 2 weeks have you had a feeling of incomplete emptying?	
Never or < 1 per 24 h	0
1–4 per 24 h	1
More than 4 times per 24 h	2
Number of bowel movements per 24 h in the last 2 weeks	
Less than 10 per 24 h	0
10 or more per 24 h	1
How many times have you had uncontrolled loss of stools in the last 2 weeks?	
Never	0
Once or more	0
Have you used anti-diarrheal medication for pouch problems in the last 2 weeks?	
No	0
Yes	0,5
Did you have a sudden and severe urge to defecate in the last 2 weeks?	
No	0
If yes, how long can you defer the urge to defecate?	
More than 30 min	0
More than 5–30 min	1
5 min or less	3

Points	Pouch dysfunction	Definition
0	None	No symptoms
>0 - <2.5	Minor	Mild symptoms which does not interfere with QoL
≥2.5	Some/major	Moderate/severe symptoms which interfere with QoL

Treatment of Chronic Antibiotic-Refractory Pouchitis

Due to the lack of randomized controlled trials, the treatment of chronic antibiotic-refractory pouchitis is largely empirical. Over the years, immunomodulators, biologics and small molecules have been introduced, similar to the treatment strategies for inflammatory bowel diseases, considering chronic antibiotic-refractory pouchitis is predominantly immune mediated.

Antibiotics

Oral vancomycin has been successfully used to induce and maintain remission in PSC-associated chronic antibiotic-refractory pouchitis at the Cleveland Clinic.[39,40] Furthermore, it may also improve liver function tests.[41–43] There are no published data on the long-term efficacy or safety yet.

Several studies investigated the use of a combination therapy with ciprofloxacin and rifaximin[44,45] or tinidazole[46] and showed its effectiveness in treating patients with chronic antibiotic-refractory pouchitis (Table 5).

A study by McLaughin et al used fecal coliform sensitivity testing for targeted antibiotic treatment that appears highly effective in treating patients with antibiotic-resistant pouchitis. They recommend that all pouchitis patients who fail standard antibiotic treatment or develop resistance while on long-term antibiotic treatment undergo fecal coliform sensitivity testing to guide antibiotic therapy.[47] However, this is still not routinely used in clinical practice.

Aminosalicylates

While aminosalicylates form the basis for the treatment of ulcerative colitis and cuffitis, their efficacy in chronic antibiotic-refractory pouchitis is far from established. Topical and oral mesalazines have been tried in a small cohort of ten patients with chronic antibiotic-refractory pouchitis, demonstrating remission rates of 50%[46] (Table 5).

Table 5 Studies Investigating Antibiotics and Aminosalicylates for Chronic Antibiotic-Refractory Pouchitis

Study	Number of Patients	Treatment(s)	Response (Definition)	Remission (Definition)
Thind et al[40] 2018	1	Vancomycin 125mg 4x/d	1/1 (NA)	1/1 (no active disease in pouch body and rectal cuff on endoscopy at 1 year)
Gionchetti et al[44] 1999	18	Rifaximin 1g BID + Ciprofloxacin 500mg BID	16/18 (drop in PDAI ≥ 3 points at 15 days)	6/18 (PDAI = 0 at 15 days)
Abdelrazeq et al[45] 2005	8	Rifaximin 1g BID + Ciprofloxacin 500mg BID	7/8 (drop in PDAI ≥ 3 points at 2 weeks)	5/8 (PDAI = 0 at 2 weeks)
Shen et al[46] 2007	16	Ciprofloxacin 1g/d + Tinidazole 15mg/kg/d	14/16 (drop in PDAI ≥ 3 points at 4 weeks)	14/16 (PDAI < 7 at 4 weeks)
	10	Oral (4 g/d), enema (8 g/d) or suppository (1 g/d) mesalamine	5/10 (drop in PDAI ≥ 3 points at 4 weeks)	5/10 (PDAI < 7 at 4 weeks)

Abbreviations: NA, not available; PDAI, pouch disease activity index.

Steroids

Oral and rectal budesonide[48–50] and beclomethasone dipropionate[51] have been used successfully in inducing remission in chronic antibiotic-refractory pouchitis (Table 6). Nonetheless, prolonged use of steroids is discouraged to prevent serious side effects.

Immunomodulators

Historically, immunomodulators including azathioprine, mercaptopurine and methotrexate have been used as subsequent therapy for chronic antibiotic-refractory pouchitis. There are, however, little data on the use of immunomodulators for this indication.[52,53] The current position of immunomodulators in the treatment algorithm mainly depends on the availability and early access to biologics.

Biologics

Anti-TNF

In 2018, a systematic review with meta-analysis evaluated the efficacy of anti-tumor necrosis factor (TNF) therapy in patients with chronic antibiotic-refractory pouchitis. The rate of short-term clinical remission, evaluated at 8 weeks of induction therapy, was low (10%). However, the rate of long-term clinical remission at 12 months was 37%.[54–75]

Table 6 Studies Investigating Corticosteroids for Chronic Antibiotic-Refractory Pouchitis

Study	Number of Patients	Treatment(s)	Response (Definition)	Remission (Definition)
Gionchetti et al[48] 2007	20	Oral budesonide 9mg/d	NA	15/20 (clinical PDAI ≤ 2 and endoscopic PDAI ≤ 1 and total PDAI ≤ 4 at week 8)
Chopra et al[49] 2006	13	Oral budesonide	60% (Complete symptomatic remission or ability to completely wean off of prednisone with mild activity (1–3 stools/day) at week 8)	NA
Sambuelli et al[50] 2002	7	Budesonide enema 2mg/100mL	3/7 (drop in PDAI ≥ 3 points at week 6)	NA
Gionchetti et al[51] 2014	10	Oral beclomethasone diproprionate 10mg/d	10/10 (Improvement in pouch associated symptoms at week 8)	8/10 (clinical PDAI ≤ 2 and endoscopic PDAI ≤ 1 and total PDAI ≤ 4 at week 8)

Abbreviations: NA, not available; PDAI, pouch disease activity index.

A study from the Leuven group retrospectively assessed infliximab and adalimumab therapy in 23 and 13 chronic antibiotic-refractory pouchitis patients, respectively. At 14 weeks, clinically relevant remission was observed in 43.5% and 38.5% of patients in the infliximab and adalimumab group, respectively. At final follow-up, only 17.4% of patients in the infliximab group remained in clinically relevant remission. Anti-TNF therapy was discontinued in 40.7% of patients due to intolerance or drug reaction[76] (Table 7).

As the majority of UC patients who come to colectomy for refractory colitis nowadays have already been treated with anti-TNF therapy, the treatment of chronic antibiotic-refractory pouchitis with anti-TNF agents can always be hampered due to immunogenicity after a drug holiday. This may ultimately result in infusion reactions, primary non-response or loss of response. Therefore, biologics with another mode of action are probably indicated for the treatment of chronic antibiotic-refractory pouchitis in patients who previously failed both infliximab and adalimumab.

Vedolizumab

In the last few years, the efficacy and safety of vedolizumab has been reported more and more in case series and small observational studies for the treatment of chronic antibiotic-refractory pouchitis.[76–80]

A retrospective study from the USA included 19 chronic antibiotic-refractory pouchitis patients treated with vedolizumab and reported 32% clinical response after 3 months. Improvement of endoscopic and total mPDAI were seen in 74% of patients.[77] The retrospective study from Leuven also included 15 chronic antibiotic-refractory pouchitis patients treated with vedolizumab. Clinically relevant remission was observed in 60% of patients at week 14 and 53.3% of patients at the last follow-up[76] (Table 8).

We eagerly await the results of the EARNEST study (NCT02790138), a placebo-controlled study that evaluated the efficacy and safety of vedolizumab in the treatment of chronic pouchitis, to further decide if vedolizumab can be a beneficial treatment for this condition.

Ustekinumab

Only little is known about the role of ustekinumab in the treatment of chronic antibiotic-refractory pouchitis.

Weaver et al retrospectively described the largest pouchitis cohort of 56 patients treated with ustekinumab; however, only nine patients had chronic antibiotic-refractory pouchitis, while the remaining 47 patients had Crohn's disease-related complications of the pouch.[81] At 6 months, data were only available from six patients and five of them had a clinical response, but none were in clinical remission. Ollech et al performed a retrospective study including 24 patients with chronic antibiotic-refractory pouchitis who received ustekinumab treatment, leading to clinical improvement in 50% of patients, but none were in clinical remission[82] (Table 9).

A prospective Belgian multicenter open-label study (NCT04089345) is being performed to confirm these findings.

Small Molecules

There is only one case report published where a 20-year-old woman was treated with tofacitinib for chronic antibiotic-refractory pouchitis. She had already received treatments with anti-TNF therapy, systemic steroids and vedolizumab, but the response was unsatisfactory. Because the patient refused a permanent ileostomy, tofacitinib was started as a last resort. The therapy led to clinical and endoscopic improvement with a reduced mPDAI from 10 to 3.[83] Another case of chronic antibiotic-refractory pouchitis treated with tofacitinib has been reported in an observational study, however its details are unknown.[84]

A Phase 2 open-label prospective pilot study (NCT04580277) will start at Cedars-Sinai Medical Center to evaluate the effectiveness and safety of tofacitinib in subjects with chronic pouchitis.

Fecal Microbiota Transfer

Fecal Microbiota Transfer (FMT) may be an alternative approach to classical treatment of chronic antibiotic-refractory pouchitis given the role of bacteria in the pathogenesis.

Landy et al conducted a pilot study including eight patients with chronic antibiotic-refractory pouchitis who were treated with one single FMT via nasogastric administration.[85] After 4 weeks, two patients had a clinical response (decrease in PDAI with ≥ 3 points) but none achieved clinical remission (PDAI < 7). Stallmach et al conducted an observational study including five patients with chronic antibiotic-refractory pouchitis.[86] Administration of FMT was directly into the jejunum during esophagogastroduodenoscopy with an interval of 3–4 weeks. Within 4 weeks after the last FMT, all patients had clinical, endoscopic and histological responses. Selvig et al performed a pilot study including nineteen patients with chronic antibiotic-refractory pouchitis who were treated with a minimum of one FMT delivered via pouchoscopy.[87] After 4 weeks, total PDAI, endoscopic PDAI and histologic PDAI did not decrease

Table 7 Studies Investigating Anti-TNF Agents for Chronic Antibiotic-Refractory Pouchitis

Study	Number of Patients	Type of Anti-TNF	Short-Term Remission	Long-Term Remission	Definition of Remission
Kelly et al[55] 2016	42	Infliximab	48%	29.6%	mPDAI < 5
Robbins et al[56] 2015	25	Adalimumab	NA	72%	Absence of pouch failure
Iizuka et al[57] 2014	1	Infliximab	0%	100%	mPDAI < 5
Viazis et al[58] 2013	7	Infliximab	NA	85.7%	Cessation of diarrhea, urgency, incontinence, blood loss and abdominal pain and cessation of fistula drainage
Barreiro-de-Acosta et al[59] 2012	33	Infliximab	21.2%	27.3%	Cessation of diarrhea and urgency
Li et al[61] 2012	48	Adalimumab	50%	33.3%	mPDAI < 5
Barreiro-de-Acosta et al[60] 2012	8	Adalimumab	12.5%	25%	Cessation of diarrhea, urgency and blood loss
Haveran et al[62] 2011	13	Adalimumab	NA	53.8%	Complete closure of fistula; complete improvement of symptoms and confirmed on pouchoscopy
Yeates et al[63] 2010	1	Infliximab	0%	100%	Completely normal mucosa
Ferrante et al[64] 2010	28	Infliximab	35.7%	39.2%	Cessation of diarrhea, blood loss and abdominal pain; cessation of fistula drainage
Gionchetti et al[65] 2010	12	Infliximab	75%	NA	mPDAI < 5
Gionchetti et al[65] 2010	7	Adalimumab	71.4%	NA	mPDAI < 5
Akitake et al[66] 2009	1	Infliximab	0%	100%	Completely normal mucosa
Calabrese et al[67] 2008	10	Infliximab	90%	80%	mPDAI < 5
Shen et al[68] 2008	17	Adalimumab	41.2%	47.1%	Complete resolution of symptoms
Molnar et al[69] 2008	1	Infliximab	100%	100%	Complete regression of symptoms and endoscopic findings
Coburn et al[70] 2006	1	Adalimumab	NA	100%	Complete regression of symptoms
Kooros et al[71] 2004	4	Infliximab	50%	100%	Marked improvement clinically, endoscopically, and histologically

(*Continued*)

Table 7 (Continued).

Study	Number of Patients	Type of Anti-TNF	Short-Term Remission	Long-Term Remission	Definition of Remission
Viscido et al[72] 2003	7	Infliximab	71.4%	57.1%	Cessation of diarrhea, urgency, stool blood and abdominal pain
Colombel et al[73] 2003	26	Infliximab	61.5%	29.2%	Cessation of fistula drainage and total closure of all fistulas, or cessation of diarrhea, incontinence, and abdominal pain
Arnott et al[74] 2001	2	Infliximab	0%	0%	Cessation of diarrhea and urgency
Ricart et al[75] 1999	7	Infliximab	85.7%	71.4%	Cessation of fistula(s) drainage and total closure of all fistula(s), or cessation of diarrhea, incontinence, and abdominal pain
Verstockt et al[76] 2019	23	Infliximab	10/23	4/23	mPDAI < 5 and drop in mPDAI ≥ 2 points
Verstockt et al[76] 2019	13	Adalimumab	5/13	NA	mPDAI < 5 and drop in mPDAI ≥ 2 points

Abbreviations: NA, not available; mPDAI, modified pouch disease activity index; PDAI, pouch disease activity index.

Table 8 Studies Investigating Vedolizumab for Chronic Antibiotic-Refractory Pouchitis

Study	Number of Patients	Response (Definition)	Remission (Definition)
Verstockt et al[76] 2019	15	NA	9/15 (short-term = mPDAI < 5 and drop in mPDAI ≥ 2 points at 14 weeks)
			8/15 (long-term = mPDAI < 5 and drop in mPDAI ≥ 2 points at final follow-up)
Singh et al[77] 2019	19	6/19 (Clinical = drop in symptomatic mPDAI after 3 months)	NA
		14/19 (Endoscopic = drop in endoscopic mPDAI after 3 months)	
Philpott et al[78] 2017	4	4/4 (improved symptoms and endoscopy after 3 months)	NA
Bär et al[79] 2018	20	9/14 (drop in PDAI ≥ 3 points at week 14)	9/14 (PDAI < 7 at week 14)
Gregory et al[80] 2019	83	71.1% (Clinical = decrease in number of bowel movements, abdominal pain, or fistula drainage at any time point)	19.3% (Clinical = complete return to normal function at any time point)
		54.1% (Endoscopic = improvement in mucosal inflammation at any time point)	17.6% (Endoscopic = complete normal mucosa at any time point)

Abbreviations: NA, not available; mPDAI, modified pouch disease activity index; PDAI, pouch disease activity index.

significantly. However, there was a significant improvement in stool frequency and trend for improvement in abdominal pain. Finally, Herfarth et al performed a placebo-controlled trial of endoscopic and oral FMT in patients with chronic antibiotic-dependent pouchitis.[88] Patients were randomized to receive either active or placebo FMT via pouchoscopy followed by daily oral administration for 14 days. All six patients enrolled, failed to respond and needed antibiotic rescue therapy. In the open-label extension study, 1 out of 5 patients achieved antibiotic-free clinical remission (mPDAI < 4).

Although FMT is safe for chronic antibiotic-refractory pouchitis, the current data fail to prove efficacy. Because

Table 9 Studies Investigating Ustekinumab for Chronic Antibiotic-Refractory Pouchitis

Study	Number of Patients	Response (Definition)	Remission (Definition)
Weaver et al[81] 2018	9	5/6 (Clinical = decrease in the number of bowel movements or abdominal pain at 6 months)	0/6 (Clinical = complete return to normal function at 6 months)
Ollech et al[82] 2019	24	12/24 (Clinical = based on physician's clinic note after treatment)	NA
		In 13 patients, mean decrease from 5 to 4 (Endoscopic = drop in endoscopic PDAI after treatment)	0/13 (Endoscopic = endoscopic PDAI of 0 after treatment)

Abbreviations: NA, not available; PDAI, pouch disease activity index.

these data are limited by study heterogeneity, additional studies are required to guide the use of FMT in patients with chronic antibiotic-refractory pouchitis.

Miscellaneous

Several other treatment options were investigated for chronic antibiotic-refractory pouchitis; however, large randomized controlled trials are lacking to provide enough power to the data.

A study by Croagh et al explored the influence of a change in poorly absorbed short-chain carbohydrates (FODMAPs) in the diet, by virtue of their osmotic effect, on the frequency and quality of stool output from an ileal pouch.[89] Patients were asked to strictly follow a low FODMAP diet for 6 weeks. No response was seen in patients with pouchitis, but this diet might be efficacious in reducing stool frequency in patients who do not have active pouchitis or other inflammation associated with the pouch. A recently initiated study (NCT04640155) will further investigate whether a low FODMAP diet in patients with chronic antibiotic-refractory pouchitis might improve symptoms and pouch inflammation.

AST-120 is an agent that is comprised of highly adsorptive, porous carbon microspheres with the ability to adsorb small-molecular-weight toxins, inflammatory mediators and harmful bile acids. Shen et al conducted a trial to evaluate the efficacy and safety of AST-120 in patients with active pouchitis.[90] Twenty patients were included and received AST-120 2g three times a day for 4 weeks. Clinical response (reduction of PDAI with ≥ 3 points) was seen in 55% of patients and clinical remission (PDAI < 7) in 50% of patients. The agent was well tolerated.

Alicaforsen, an antisense enema to intercellular adhesion molecule-1, can improve the clinical symptoms, endoscopic mucosal appearance and histologic inflammation in patients with chronic antibiotic-refractory pouchitis. Miner et al carried out an open-label study including 12 patients with chronic pouchitis treated with one 240 mg Alicaforsen enema nightly for 6 weeks.[91] By week 6, seven of the 12 patients (58%) were in remission (PDAI < 7) with a mean decrease of six points in PDAI. A retrospective study by Greuter et al identified 13 patients treated with at least one dose of Alicaforsen for chronic antibiotic-refractory pouchitis.[92] At 2–3 months after therapy, clinical and endoscopic disease activity was significantly reduced. Finally, a randomized, placebo-controlled trial (NCT02525523) was performed including subjects with chronic antibiotic-refractory pouchitis, where patients were treated with the study drug (240 mg Alicaforsen or placebo enema) administered once nightly for 6 weeks. Results were disappointing with no significant reduction in relative stool frequency and no significant difference in endoscopic remission (absence of friability and ulceration).

Hyperbaric oxygen therapy (HBOT) for chronic antibiotic-refractory pouchitis was investigated in a retrospective case series of 28 patients treated with a median number of 30 HBOT sessions.[93] There was a significant reduction in the mean clinical mPDAI from 3.19 to 1.91 and mean endoscopic mPDAI from 2.34 to 1.29. Despite minor adverse events, HBOT was well tolerated. A prospective open-label pilot study (NCT03526796) is being performed in China to further investigate this modality.

In a prospective pilot study, ten patients with chronic antibiotic-refractory pouchitis were treated for eight weeks with a tacrolimus enema.[94] The mean PDAI decreased significantly from 15.9 to 7.8. Seven patients achieved complete remission of clinical symptoms, nine patients were clinical responders and three patients were in remission (PDAI < 7). No severe adverse events occurred. This small study suggested that the use of topical tacrolimus for the treatment of chronic antibiotic-refractory pouchitis is

safe and effective in the short term for clinical symptoms and may have early rescue efficacy.

Granulocyte and monocyte apheresis (GMA) has shown therapeutic efficacy in patients with active UC by modulating systemic and local inflammatory activities. Furthermore, several studies have reported that depleting granulocytes and monocytes by GMA leads to a diminished inflammatory profile in the intestinal mucosa, and remission of clinical symptoms in patients with active UC.[95–99] An open-label prospective study was done by Yamamoto et al to evaluate the efficacy of granulocyte and monocyte apheresis for chronic antibiotic-refractory pouchitis.[100] Thirteen patients were included and received 10 GMA sessions at 2 sessions/week over five consecutive weeks. Six patients responded to the treatment (reduction of PDAI with $\geq$ 3 points) but none achieved remission (PDAI < 4). GMA has a good safety profile, but its efficacy appears to be limited in the management of chronic antibiotic-refractory pouchitis. A large controlled study should be conducted to evaluate the efficacy of GMA therapy in patients with pouchitis at an earlier clinical stage, before the disease has become refractory to conventional medical therapy.

Surgery

Surgery may be a last resort for patients with chronic antibiotic-refractory pouchitis who are refractory to all medical treatments. An end ileostomy, with or without pouch excision, will be performed.

Conclusion

Pouchitis can be suspected based on clinical symptoms and laboratory findings, but should be confirmed with endoscopy and histology. Clear definitions should be used to classify pouchitis into acute versus chronic, and responsive versus dependent versus refractory to antibiotics. Before treatment is started for chronic antibiotic-refractory pouchitis, secondary causes should be ruled out. Also, scoring the disease, taking into account the quality of life of the patient, should guide you in choosing the best treatment option for your patient.

Managing patients with chronic antibiotic-refractory pouchitis remains a challenge for the treating gastroenterologist or abdominal surgeon. Because chronic antibiotic-refractory pouchitis is mainly immune mediated, therapeutic options are similar to the treatment strategies for inflammatory bowel diseases. Treatments with antibiotics, aminosalicylates, steroids, immunomodulators and biologics has been shown to be effective for chronic antibiotic-refractory pouchitis. However, randomized controlled trials are warranted to further identify the best treatment options in this patient population.

Abbreviations

CARP, chronic antibiotic-refractory pouchitis; FAP, familial adenomatous polyposis; FODMAP, Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols; GMA, granulocyte and monocyte apheresis; HBOT, hyperbaric oxygen therapy; FMT, Fecal Microbiota Transfer; IPAA, ileal pouch-anal anastomosis; mPDAI, modified pouch disease activity index; NSAID, non-steroidal anti-inflammatory drug; PDAI, pouch disease activity index; PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor; UC, ulcerative colitis.

Acknowledgments

Marc Ferrante is a Senior Clinical Investigator of the Research Foundation Flanders (FWO), Belgium.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval for the version to be published; and agreed to be accountable for all aspects of the work.

Disclosure

Marc Ferrante received financial support for research from AbbVie, Amgen, Biogen, Humira, Janssen, Pfizer, and Takeda; consultancy fees from AbbVie, Boehringer-Ingelheim, Celltrion, Janssen, Lilly, Medtronic, MSD, Pfizer, Sandoz, Takeda and Thermo Fisher; and speakers fees from AbbVie, Amgen, Biogen, Boehringer-Ingelheim, Falk, Ferring, Janssen, Lamepro, MSD, Mylan, Pfizer, Sandoz, Takeda and Truvion Healthcare. The authors report no other conflicts of interest in this work.

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