#MondayNightIBD: Management of Chronic #Pouchitis

Jean A. Donet, MD,[*] Florian Rieder, MD,[†] and Aline Charabaty, MD[‡]

We present a #MondayNightIBD case of chronic pouchitis and discuss key diagnostic and therapeutic challenges commonly encountered in clinical practice. We make reference not only to the limited published literature but also to the informed opinions of the #MondayNightIBD discussion participants, identifying gaps where management guidelines and research are needed. A #MondayNightIBD Algorithm for Pouchitis Management is proposed.

Lay Summary

Patients with inflammatory bowel disease may develop chronic inflammation of the pouch after intestinal restorative surgery. Our review of the scientific data and the @MondayNightIBD participants' opinions reveals consensus guidelines and research on diagnosis and treatment of this condition are needed.

Key Words: chronic pouchitis, diagnosis, management

CASE SCENARIO

Forty-three-year-old male patient with extensive ulcerative colitis, refractory to infliximab, underwent ileal pouch anal anastomosis (IPAA) 5 years ago. Three years after the surgery, he developed recurrent episodes of acute pouchitis, which progressed to antibiotic-dependent pouchitis on daily ciprofloxacin and metronidazole. Patient becomes symptomatic despite antibiotic therapy, pouchoscopy shows diffuse erythema and friability in the body of the pouch, with an otherwise normal endoscopic examination. Patient denies Non-steroidal anti-inflammatory drugs use. Stool testing is negative for *Clostridium difficile*. Pathology of pouch body biopsies is negative for cytomegalovirus infection. What is the next therapeutic step?

1. Anti-tumor necrosis factor (anti-TNF)
2. Vedolizumab or ustekinumab
3. Budesonide
4. Other

DISCUSSION

More than half of IPAA patients will develop pouch complications, including acute pouchitis, chronic pouchitis, Crohn disease-like phenotype of the pouch as well as functional or mechanical pouch disorders.[1] The diagnosis and therapeutic management of these disorders is challenging given the complexity of the disease, and the limited amount of data to guide best practices.

Diagnosis

#MondaynightIBD participants agreed on it can be very difficult to diagnose a specific type of pouch disorder with accuracy, despite the several different, but complementary tools available: history and physical examination, laboratory tests, pouchoscopy, imaging, and motility/functional studies.[2] A recommended key clinical hint was to elucidate the timing of onset of disease in relation to surgery, since symptoms that appear immediately or soon after surgery may suggest a surgical complication related to a vascular, mechanical or technical factor; whereas symptoms that start more than 6–12 months after surgery are most

Received for publications April 25, 2020; Editorial Decision May 26, 2020.

*Division of Gastroenterology, University of California San Francisco-Fresno, Fresno, California, USA; †Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic, Cleveland, Ohio, USA; ‡Division of Gastroenterology, Johns Hopkins School of Medicine, Sibley Memorial Hospital, Washington, District of Columbia, USA

Twitter: @jeandonet, @IBD_FloMD, @DCharabaty

Conflicts of Interest: Jean A. Donet: None. Florian Rieder: Grants from National Institute of Health, Crohn's and Colitis Foundation, Helmsley Charitable Trust, Pliant, BMS, Pfizer, AbbVie, UCB, Boehringer Ingelheim, and Rainin Foundation. Consulting or Advisory Board for Agomab, Allergan, AbbVie, Boehringer-Ingelheim, Celgene, Cowen, Genentech, Gilead, Gossamer, Helmsley, Index Pharma, Janssen, Koutif, Metacrine, Morphic, Pfizer, Pliant, Prometheus Biosciences, Receptos, RedX, Roche, Samsung, Takeda, Techlab, Thetis, and UCB. Aline Charabaty: Educational grant from Pfizer for @MondayNightIBD. Consulting and/or advisory board for Janssen, Abbvie, and Pfizer.

Data Availability: No data were created or analyzed.

Address correspondence to: Jean A. Donet, MD, Division of Gastroenterology, University of California San Francisco-Fresno, 2615 E Clinton Ave, Fresno, CA 93703 (jdonet@fresno.ucsf.edu).

doi: 10.1093/crocol/otaa071
Published online 24 August 2020

likely due to an inflammatory or functional pathology. At either time period, it is very important to test stool to rule out *C. difficile* infection.

Endoscopic examination

The key diagnostic tool for pouch disorders is a comprehensive pouchoscopy with proper identification of the anatomical landmarks of the pouch (Fig. 1). #MondaynightIBD participants of the conversation highlighted the lack of uniformity among gastroenterologists when describing and reporting the findings of the pouch endoscopic examination, which may lead to an inaccurate diagnosis. Educational videos on how to perform a high-quality pouchoscopy, developed by the Crohn's and Colitis Foundation Rising Educators, Academics, and Clinicians Helping IBD (REACH-IBD) group, are available at https://www.youtube.com/watch?v=NwwA56B3-ms. Diffuse inflammation of the pouch body without involvement of the afferent small bowel limb suggests "classic" pouchitis.[3] Ulcerations of the afferent small bowel limb beyond 10 cm from the pouch inlet, ulcers or strictures outside common locations for ischemic or mechanic injury (anastomosis, previous stoma site), late-onset perianal or vaginal fistula (more than 6–12 months after stoma closure), or finding or noncaseating granuloma on biopsies are more suggestive of Crohn disease-like phenotype of the pouch.[4]

During the #MondaynightIBD discussion, it was also pointed out that endoscopic scoring systems are under-utilized in clinical practice. The Pouchitis Disease Activity Index (PDAI) has been the most commonly scoring system used in research. Table 1 shows the elements of the PDAI.[5] The modified Pouchitis Disease Activity index (mPDAI) omits the histologic component of the PDAI, providing equivalent sensitivity and specificity. Pouchitis is defined as a total PDAI score ≥7 or a total mPDAI score ≥5.[6]

Pathology

Another agreed upon fact is that pathology is typically nonspecific, unless granulomas, viral inclusion bodies, or a positive IgG4 staining are found, which may point toward specific etiologies of the pouchitis.[7]

The #MondaynightIBD conversation revealed variability in regard to where the biopsies should be taken at the time of pouchoscopy. It was suggested biopsies should be segmental and include the rectal cuff, pouch body, and afferent limb.

Other testing

#MondaynightIBD participants typically reserve additional testing such as imaging (computed tomography enterography, magnetic resonance enterography, pelvic magnetic resonance imaging, and pouchogram) and functional testing (Magnetic Resonance or barium defecography, anorectal manometry) for patients with suspicion of a disorder different than "classic" pouchitis such as pelvic sepsis or pouch prolapse[2] or when there is not a clinical response to antibiotics.

Pouchitis

Pouchitis is the most common pouch disorder; nevertheless, participants called attention to the encountered variability when classifying pouchitis in clinical practice, due to the different criteria used in the published literature. Similarly, participants discussed that endoscopic features of pouchitis and Crohn-like disorder of the pouch often overlap, and both clinical entities are often included in published case studies

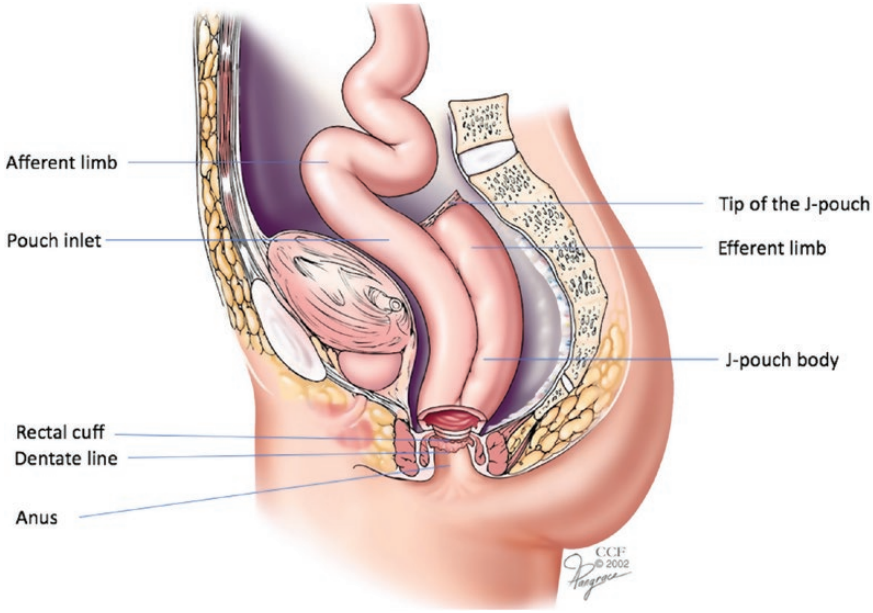

FIGURE 1. Anatomical landmarks of the J-pouch (image used by permission of Cleveland Clinic).

TABLE 1. Pouchitis Disease Activity Index*

Criteria	Score
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	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	
Polymorphonuclear 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

*Pouchitis is defined as a total PDAI score of greater or equal than 7.[5]

of treatment of chronic pouchitis. Table 2 delineates the most commonly used and accepted definitions.[1–3]

Treatment

Acute pouchitis

The first line of therapy for acute pouchitis is antibiotics. In line with the literature, ciprofloxacin and metronidazole are the most widely used antibiotics by the #MondaynightIBD discussion participants. In a nonblinded, randomized, clinical trial, ciprofloxacin (N = 7) was compared to metronidazole (N = 9) in 16 patients with acute pouchitis, defined as a PDAI score ≥7 and symptom duration ≤4 weeks; there was a significantly greater reduction in the ciprofloxacin group than in the metronidazole group in regard to the total PDAI score (6.9 vs 3.8; P = 0.002), symptoms score (2.4 vs 1.3; P = 0.03), and endoscopic score (3.6 vs 1.9; P = 0.03). None of the patients in the ciprofloxacin group experienced adverse effects, whereas 33% of the patients in the metronidazole group developed vomiting, dysgeusia, or transient peripheral neuropathy.[8] In a multicenter, randomized, double-blind, clinical trial, rifaximin (N = 8) was compared against placebo (N = 10) in 18 patients with active pouchitis, defined as PDAI score ≥7. Clinical remission (defined as PDAI score <7 points and a decrease in the baseline PDAI score of 3 points) occurred more frequently in the rifaximin group when compared to placebo (25% vs 0%; P = 0.20) but this difference was not statistically significant.[9]

TABLE 2. Commonly Used Definitions of Pouchitis

Pouchitis Type	Definition
Acute pouchitis	Duration of pouch-related symptoms of less or equal than 4 weeks
Chronic pouchitis	Duration of pouch-related symptoms of greater than 4 weeks
Antibiotic-responsive pouchitis	Symptomatic response to a 2-week course of single antibiotic therapy Less than or equal to 4 episodes per year
Antibiotic-dependent pouchitis	Requires continuous antibiotic therapy for maintenance of symptomatic remission. More than 4 episodes per year
Antibiotic-refractory pouchitis	No response to a 4-week course of antibiotics

Antibiotic-dependent pouchitis

There is limited controlled data for the therapy of patients with antibiotic-dependent pouchitis. #MondayNightIBD clinicians agreed on using the lowest effective antibiotic dose for patients who have to be maintained on antibiotics for symptoms control. This is particularly true for ciprofloxacin since it is better tolerated than metronidazole for chronic use.[8] An alternative recommended approach was to use rotating courses of different antibiotics, such as ciprofloxacin, metronidazole, and rifaximin, in order to decrease the risk of potential side effects and antibiotic resistance. Several #MondayNightIBD clinicians shared their positive experience using beta-lactams (such as aztreonam and ertapenem) that are poorly absorbed by the gastrointestinal tract; taking orally the IV solution of the antibiotic or using a compound pharmacy were cited as options.[10] Two randomized, placebo-controlled trials have shown that the so-called "DeSimone formulation," currently sold as Visbiome in the United States, may be effective for maintenance of remission in patients with recurrent or antibiotic-dependent pouchitis.[11,12] A Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis indicated low level of evidence supporting this outcome due to very sparse data.[13]

Combination antibiotic therapy is commonly used in patients with recurrent episodes of pouchitis and in patients who do not respond to a single antibiotic regimen. In a prospective study, a 4-week course of a combination of ciprofloxacin and metronidazole was given to 44 patients with antibiotic-refractory or recurrent pouchitis (defined in this study as history of pouchitis at least twice in the last 12 months or persistent pouchitis despite continuous intake of antibiotic, and a PDAI score ≥7 at the beginning of the study); 82% of the patients achieved remission (defined as a combination of a PDAI clinical score ≤2, endoscopic score ≤1, and total score ≤4); all treated patients demonstrated an overall reduction of 9 points in the median PDAI score and an improvement of 68.5 points in the median Inflammatory Bowel Disease Questionnaire (IBDQ) score after treatment with combination antibiotic therapy ($P < 0001$).[14] In another prospective study, a 4-week course of ciprofloxacin and tinidazole was given to 16 patients with chronic refractory pouchitis (defined as disease duration >4 weeks and failure to respond to >4 weeks of single antibiotic therapy); 87.5% of the patients achieved clinical remission (defined as PDAI score <7 after treatment); all treated patients demonstrated a reduction of 7 points in the median PDAI score ($P < 0.0001$) and improvement of 12.3 points in the median IBDQ score ($P > 0.0003$).[15] In a small case series, an 8-week course of oral ertapenem, following fecal coliform sensitivity testing, was given to 3 patients with antibiotic-refractory pouchitis (defined by the lack of response to a 2-week course of antibiotics); there was a reduction of 12 points in the median PDAI score after treatment.[10]

Antibiotic-refractory pouchitis and Crohn disease-like phenotype of the pouch

Immunosuppressants are typically reserved for patients with antibiotic-refractory pouchitis, antibiotic-dependent pouchitis with drug intolerance and Crohn disease-like phenotype of the pouch.

Steroids

In an open-label study, an 8-week course of oral budesonide was given to 20 patients with chronic antibiotic-refractory pouchitis who were not responding after 1 month of antibiotic treatment; 75% of the patients achieved remission (defined as a combination of PDAI clinical score ≤2, endoscopic score ≤1, and total PDAI score ≤4); budesonide treatment led to a reduction of 11 points in the median total PDAI score ($P < 0.001$) and improvement of 75 points in the median IBDQ score ($P < 0.001$).[16] #MondayNightIBD participants reaffirmed that budesonide, although effective for induction of remission, is not a long-term strategy due to its potential steroid side effects.

Anti-TNF

A systematic review with metanalysis of the efficacy of anti-TNF therapy, specifically infliximab (n = 194) and adalimumab (n = 119), for the treatment of antibiotic-refractory pouchitis and Crohn disease-like phenotype of the pouch showed that the rates of clinical remission at week 8 (short-term) and 12 months (long-term) after treatment were 50% [confidence interval (CI, 0.37–0.63); $I^2 = 0.57$] and 52% [CI (0.39–0.65); $I^2 = 0.59$], respectively.[17] Subsequently, in a small, multicenter, randomized, double-blind, controlled trial, a 12-week regimen of adalimumab (n = 6) was compared against placebo (n = 7) for the treatment of antibiotic-refractory pouchitis (defined as PDAI score ≥7 and continuous symptoms for >4 weeks despite antibiotic treatment); clinical improvement (defined as reduction in mPDAI ≥2 at any time within 12 weeks of treatment) was achieved by 50% of patients in the adalimumab group vs 43% in the placebo group (relative risk 2.92, CI 0.86–9.93), suggesting no clinical benefit of adalimumab. It has to be mentioned; however, that the study was small and of short duration; therefore, a potential benefit may have been missed.[18] In addition, the outcome measures used for pouchitis trials are not properly validated to date. In the case presented, about a quarter of poll participants chose an anti-TNF as the next step to treat this patient with a history of infliximab-refractory disease prior to colectomy. Participants agreed that reinducing with infliximab was a reasonable strategy particularly if there was no history of antidrug antibodies and if anti-infliximab antibodies were absent after the first reinduction infusion; otherwise, a biologic with a different mechanism of action or a different anti-TNF in combination with an immunomodulator may be preferred options. The strategy of re-using the same drugs to treat pouchitis when the patients had a prior primary or secondary nonresponse before colectomy needs further research.

Vedolizumab

Observational studies have shown vedolizumab is effective and safe in patients with antibiotic-dependent pouchitis, antibiotic-refractory pouchitis, and Crohn disease-like phenotype of the pouch. In a retrospective, US multicenter, cohort study, 83 vedolizumab-treated patients with Crohn disease-like phenotype of the pouch or chronic antibiotic-dependent or antibiotic-refractory pouchitis, were analyzed. Crohn disease-like phenotype of the pouch was defined as the presence of inflammation/stricture the of afferent limb/proximal small bowel, fistula involving the perianal region or small bowel, fistula greater than 6 months after surgery, or granulomas on biopsy. The median duration of follow-up while on vedolizumab was 1.3 years. 51.8% of the patients treated with vedolizumab achieved clinical response (defined as a decrease in the number of bowel movements, abdominal pain, or fistula drainage) at any time; 19.3% achieved clinical remission (defined as complete return to baseline post-IPAA bowel frequency with reported normal, nonbloody bowel movements without pain, urgency or increased nocturnal bowel movements, and the absence of fistula if this was previously present) at any time. Of the 74 patients with a follow-up pouchoscopy, 54.1% had endoscopic response [defined as any improvement in mucosal inflammation (ulcers

and erosions)] and 17.6% achieved mucosal healing (completely normal mucosa) at any time during follow-up.[19] In a retrospective study performed at the Cleveland Clinic, 19 vedolizumab-treated patients with chronic antibiotic-refractory pouchitis were assessed. Chronic antibiotic-refractory pouchitis was defined as pouchitis symptoms after receiving a 2-week course of ciprofloxacin, metronidazole, or rifaximin, with a total mPDAI ≥5, or if unavailable, a diagnosis of active pouchitis by the treating clinician. 53% of the included patients had prior exposure to anti-TNF after IPAA. Outcomes were assessed at 3 months after starting vedolizumab. 32% of patients had improvement in mPDAI symptoms subscore ($P = 0.031$), 74% had improvement in both the mPDAI endoscopic subscore ($P = 0.031$) and total modified PDAI score ($P = 0.031$).[20] In a different retrospective study from the Cleveland Clinic, 12 vedolizumab-treated patients with Crohn disease-like phenotype of the pouch were analyzed. Crohn disease-like phenotype of the pouch was defined by the treating clinician based on a combined assessment of endoscopic, histologic, and radiographic features. 66.7% of patients had prior exposure to anti-TNF. Outcomes were analyzed at 6 months after starting vedolizumab. 66.7% of patients demonstrated a reduction in mPDAI symptom subscore after treatment ($P = 0.015$); 83.3% of patients showed nonstatistically significant improvement of mPDAI endoscopy subscore in the afferent limb, pouch body, and cuff.[21]

A retrospective, European single-center study evaluated the efficacy and safety of infliximab, adalimumab, and vedolizumab for the treatment of chronic antibiotic-refractory pouchitis. A total of 23 patients received infliximab, 13 patients received adalimumab, and 15 patients were treated with vedolizumab. Clinical remission was defined as a mPDAI <5 and a reduction of mPDAI ≥2 points from baseline. 43.5% of the patients treated with infliximab, 38.5% of the patients treated with infliximab, and 60% of the patients treated with vedolizumab achieved clinical remission at week 14. More patients continued vedolizumab during follow-up up to 156 weeks compared to anti-TNF therapy ($P = 0.04$). Adverse events (mainly infusion reactions) were the cause of 40.7% of the patients discontinuing anti-TNF therapy, whereas discontinuation of vedolizumab was only related to lack of efficacy, highlighting its favorable safety profile.[22]

Ustekinumab

Ustekinumab has also been found to be effective for antibiotic-refractory pouchitis. In a single-center, retrospective cohort, 24 ustekinumab-treated patients with chronic antibiotic-refractory pouchitis were assessed. Chronic antibiotic-refractory pouchitis was defined as the presence of pouch inflammation on pouchoscopy and pouch symptoms

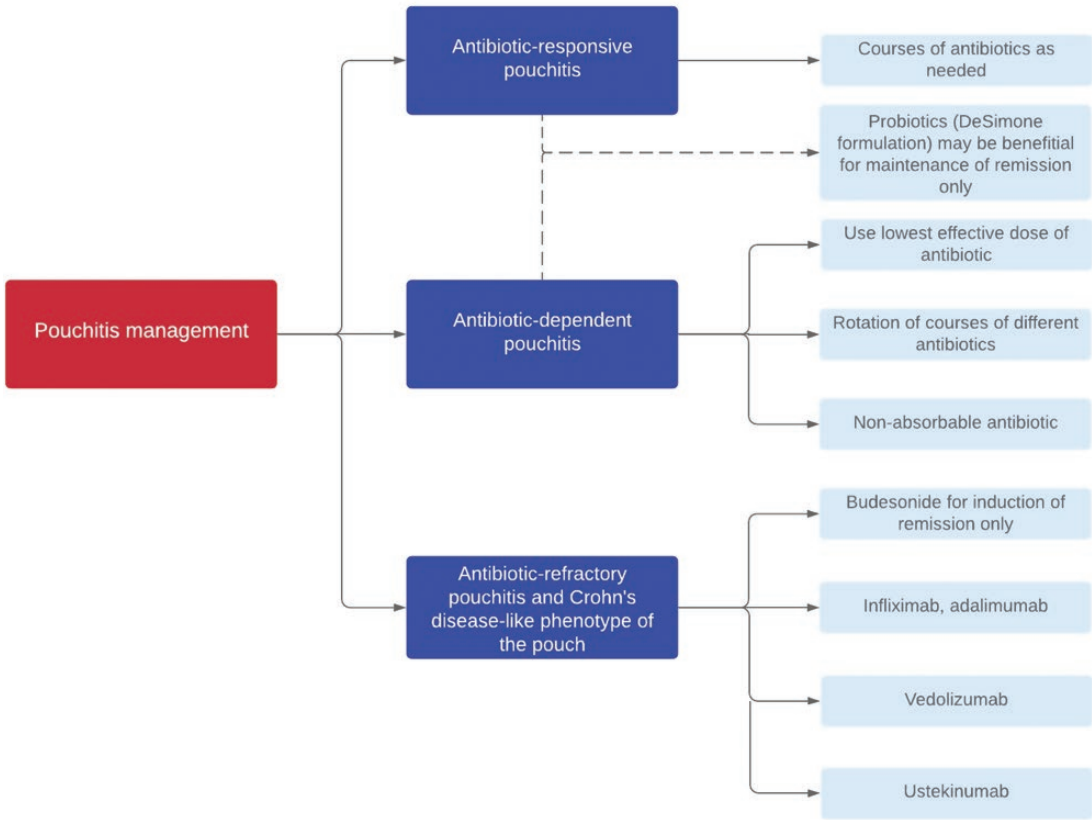

FIGURE 2. IBD Algorithm for Pouchitis Management.

despite >4 weeks of antibiotic treatment. 50% of the patients received prior biologic treatment for pouchitis. The median duration of follow-up was 12.9 months. 50% of the patients had a significant clinical response based on review of physician's clinic notes. All ustekinumab-treated patients who had a follow-up pouchoscopy available after treatment had a significant reduction in the PDAI endoscopic subscore ($P = 0.016$).[23] A different retrospective, multicenter, cohort study, assessed the efficacy of ustekinumab in 47 with Crohn disease-like phenotype of the pouch and 9 patients with chronic pouchitis (chronic antibiotic-dependent pouchitis or chronic antibiotic-refractory pouchitis) as defined by the treating clinician. 73% of the patients had prior exposure to anti-TNF agents, vedolizumab, or both, after IPAA. 83% of the ustekinumab-treated patients had a clinical response (defined as any improvement in symptoms) and 11% achieved clinical remission (defined as normal, nonbloody bowel movements, without pain, urgency or increased nocturnal bowel movements, and the absence of fistula if this was previously present) 6 months after starting treatment with ustekinumab.[24]

The majority of respondents would use vedolizumab or ustekinumab, for this patient with antibiotic-refractory pouchitis, and who was refractory to infliximab precolectomy. There is lack of published data regarding the efficacy and safety of tofacitinib and other emerging agents in pouch-related disorders, although tofacitinib has been used anecdotically with success.

Given the absence of head-to-head clinical trials that directly compare the efficacy of different biologics for the treatment of antibiotic-refractory pouchitis and Crohn disease-like phenotype of the pouch, the choice of biologic should take into account patient's characteristics, comorbidities, precolectomy treatment experience and reasons for treatment failure, as well as efficacy and safety features of the drug. In addition, data supporting specific treatment endpoints and a treat-to-target approach is lacking; until further research is done to increase our knowledge in these areas, #MondayNightIBD participants agreed, and it is also the authors' opinion, that treatment should aim for clinical remission and endoscopic improvement rather than mucosal healing.

Fecal microbiota transplant has been studied in a proof of concept, double-blind, placebo-controlled, clinical trial in patients with antibiotic-dependent pouchitis. The trial was stopped prematurely due to lack of response to combined endoscopic and oral fecal microbiota transplant and need for rescue antibiotic therapy. While the exact reason for the failure is unclear, poor donor microbiota engraftment was noted.[25]

Last but not least, it was highlighted during the discussion, the need to have complex antibiotic-refractory IPAA patients closely followed by a colorectal surgeon with expertise in pouch pathology as mechanical/technical complications related to the IPAA can mimic any of the other pouch disorders. Pouch repair, redo pouch, or pouch excision with end-ileostomy are therapeutic alternatives and should be performed at high-volume surgical centers.

RESULTS OF THE POLL (% OF ALL RESPONDENTS): TOTAL OF 365 VOTES

1. Anti-TNF: 26.3%
2. Vedolizumab or ustekinumab: 39.7%
3. Budesonide: 21%
4. Other: 12.9%

#MondayNightIBD #MedTwitter Teaching Points

- Based on available data, the 43-year-old male J-IPAA patient with antibiotic-refractory pouchitis could respond to any of the mentioned therapeutic options: anti-TNF, vedolizumab, ustekinumab, budesonide, or other, such as alternative antibiotics (Fig. 2).
- Choice of therapy should take into account precolectomy treatment experience, efficacy and safety of the drug in the context of the patient's characteristics and comorbidities.
- Randomized double-blind trials, head-to-head trials, treatment endpoints, and treat-to-target studies in this patient population are needed.
- Complex IPAA patients should be treated by an interdisciplinary team, ideally in expert centers.

REFERENCES

1. Shen B. Pouchitis: what every gastroenterologist needs to know. *Clin Gastroenterol Hepatol.* 2013;11:1538–1549. https://twitter.com/IBD_FloMD/status/1128055517295915009?s=20
2. Quinn KP, Lightner AL, Faubion WA, et al. A comprehensive approach to pouch disorders. *Inflamm Bowel Dis.* 2019;25:460–471.
3. Zezos P, Saibil F. Inflammatory pouch disease: the spectrum of pouchitis. *World J Gastroenterol.* 2015;21:8739–8752.
4. Wu H, Shen B. Crohn's disease of the pouch: diagnosis and management. *Expert Rev Gastroenterol Hepatol.* 2009;3:155–165.
5. Sandborn WJ, Tremaine WJ, Batts KP, et al. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. *Mayo Clin Proc.* 1994;69:409–415.
6. Shen B, Achkar JP, Connor JT, et al. Modified pouchitis disease activity index: a simplified approach to the diagnosis of pouchitis. *Dis Colon Rectum.* 2003;46:748–753.
7. Bilal M, Gulati A, Clarke K. Immunoglobulin G4 (IgG4)-associated pouchitis—part of IgG4 related disease? A case series and review of the literature. *Dig Liver Dis.* 2016;48:817–819.
8. Shen B, Achkar JP, Lashner BA, et al. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. *Inflamm Bowel Dis.* 2001;7:301–305.
9. Isaacs KL, Sandler RS, Abreu M, et al.; Crohn's and Colitis Foundation of America Clinical Alliance. Rifaximin for the treatment of active pouchitis: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis.* 2007;13:1250–1255.
10. Madirrala V, Rooney P, Heath RM, et al. Short article: Successful faecal coliform sensitivity-based oral ertapenem therapy for chronic antibiotic-refractory pouchitis: a case series. *Eur J Gastroenterol Hepatol.* 2016;28:277–280.
11. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology.* 2000;119:305–309.
12. Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut.* 2004;53:108–114.

13. Nguyen N, Zhang B, Holubar SD, et al. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Cochrane Database Syst Rev.* 2019;11:CD001176.
14. 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;16:909–917.
15. Shen B, Fazio VW, Remzi FH, et al. Combined ciprofloxacin and tinidazole therapy in the treatment of chronic refractory pouchitis. *Dis Colon Rectum.* 2007;50:498–508.
16. Gionchetti P, Rizzello F, Poggioli G, et al. Oral budesonide in the treatment of chronic refractory pouchitis. *Aliment Pharmacol Ther.* 2007;25:1231–1236.
17. Huguet M, Pereira B, Goutte M, et al. Systematic review with meta-analysis: anti-TNF therapy in refractory pouchitis and Crohn's disease-like complications of the pouch after ileal pouch-anal anastomosis following colectomy for ulcerative colitis. *Inflamm Bowel Dis.* 2018;24:261–268.
18. Kjaer MD, Qvist N, Nordgaard-Lassen I, et al. Adalimumab in the treatment of chronic pouchitis. A randomized double-blind, placebo-controlled trial. *Scand J Gastroenterol.* 2019;54:188–193.
19. Gregory M, Weaver KN, Hoversten P, et al. Efficacy of vedolizumab for refractory pouchitis of the ileo-anal pouch: results from a multicenter US cohort. *Inflamm Bowel Dis.* 2019;25:1569–1576.
20. Singh A, Khan F, Lopez R, et al. Vedolizumab for chronic antibiotic-refractory pouchitis. *Gastroenterol Rep (Oxf).* 2019;7:121–126.
21. Khan F, Gao XH, Singh A, et al. Vedolizumab in the treatment of Crohn's disease of the pouch. *Gastroenterol Rep (Oxf).* 2018;6:184–188.
22. Verstockt B, Claeys C, De Hertogh G, et al. Outcome of biological therapies in chronic antibiotic-refractory pouchitis: a retrospective single-centre experience. *United European Gastroenterol J.* 2019;7:1215–1225.
23. Ollech JE, Rubin DT, Glick L, et al. Ustekinumab is effective for the treatment of chronic antibiotic-refractory pouchitis. *Dig Dis Sci.* 2019;64:3596–3601.
24. Weaver KN, Gregory M, Syal G, et al. Ustekinumab is effective for the treatment of Crohn's disease of the pouch in a multicenter cohort. *Inflamm Bowel Dis.* 2019;25:767–774.
25. Herfarth H, Barnes EL, Long MD, et al. Combined endoscopic and oral fecal microbiota transplantation in patients with antibiotic-dependent pouchitis: low clinical efficacy due to low donor microbial engraftment. *Inflamm Intest Dis.* 2019;4:1–6.