

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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## Management of Chronic Antibiotic-Dependent and -Refractory Pouchitis



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### G&H How do you define chronic antibiotic-dependent and -refractory pouchitis?

**LR** It comes down to the patient's response to antibiotic treatment. Within chronic inflammatory pouch conditions, chronic antibiotic-dependent pouchitis refers to patients who experience recurrent episodes of pouchitis that responds to antibiotics but often relapses within days or weeks after the course of antibiotics is completed; thus, these patients have to resume their antibiotic treatment. Typically, these patients have completed at least 4 courses of antibiotics within a year for their chronic pouchitis. They feel better while taking antibiotics, a clear distinction to patients with chronic antibiotic-refractory pouchitis, who have symptoms despite taking antibiotics for at least 4 weeks. These patients do not notice any response to their course of antibiotics in terms of their symptoms. Clinicians often think something else is going on in these patients, such as an immune-mediated process or a complication that is mimicking pouchitis.

### G&H What diagnostic workup should be undertaken?

**LR** When dealing with chronic inflammatory conditions of the pouch, it is important to take a detailed history to understand the symptoms the patient is experiencing and consider the timing of those symptoms in relation to the surgery in which the pouch was created, along with other factors such as the function and emptying of the pouch. Once a thorough history is obtained, most of the time it can be helpful to perform a pouchoscopy. Ultimately, symptoms do not tend to correlate well with what is seen from an inflammation standpoint in the pouch, so a pouchoscopy is important. Depending on the

patient's symptoms, other diagnostic tests can also add helpful information. Magnetic resonance imaging of the pelvis can be helpful to look for structural problems of the pouch. Performing defecography studies to see how well the pouch empties with bowel movements can also be very informative. Clinicians should also not forget stool studies, whether to exclude infections or to obtain an indirect measure of inflammation such as with fecal calprotectin, which can be used longitudinally to monitor patients and their response to treatment.

### G&H Could you expand on how pouchoscopy findings and biomarkers can help confirm refractory disease?

**LR** Pouchoscopy in and of itself can provide a good deal of information about what is going on with the patient in terms of different patterns that can be seen endoscopically. It can help clinicians distinguish Crohn's disease of the pouch from chronic pouchitis. Features suggestive of Crohn's disease include a fistula or stricturing not associated with an anastomosis and inflammation extending more than 20 cm proximal to the pouch inlet. Additionally, the presence of deep serpiginous ulcers, even in the pouch, might make a clinician start thinking that the patient has Crohn's disease of the pouch. The clinician also can see different patterns of inflammation that may indicate pouch ischemia, such as segmental inflammation along an anastomosis or in the distal pouch. For example, a clinician may see a fairly clear demarcation of inflammation occurring in the distal pouch. In patients who are very tall or obese, there can be tension on the mesentery compromising blood flow to the distal pouch, resulting in ischemia. Additionally, when scoping a patient, the clinician can sometimes appreciate twisting of the pouch. In

these situations, the tip of the J-pouch may be situated in an orientation other than the patient's right side or there may be spiraling of the pouch inlet, which can lead to obstructive symptoms.

### **G&H** What is your algorithm for sequencing or combining antibiotics for pouchitis?

**LR** If a patient presents with symptoms suggestive of pouchitis, I often start with either ciprofloxacin or metronidazole as first-line treatment, typically for 2 weeks. If the patient starts to experience symptoms as they come off the antibiotics, I repeat that course. Sometimes, that is a good time to also introduce a second antibiotic, depending on how responsive the patient was to the first course of antibiotics. If I am adding a second antibiotic, I often add the ciprofloxacin or metronidazole that I did not use for the initial course. If a patient responds but has chronic antibiotic-dependent pouchitis and cannot seem to get off the antibiotics, I try to reduce to the lowest possible dose of the antibiotics they respond to, and ideally start to rotate their antibiotics. For example, I may prescribe 2 weeks of ciprofloxacin at a low dose (500 mg daily or even 250 mg daily), alternated with a low dose of metronidazole for several weeks, and then the patient continues to cycle back and forth. Clinicians can also try antibiotics beyond ciprofloxacin and metronidazole. If the patient is not getting a good response from ciprofloxacin or metronidazole, one of the antibiotics that has become beneficial in this patient population is oral vancomycin, particularly in patients with primary sclerosing cholangitis (PSC). The main point is that there is not a one-size-fits-all antibiotic. There may be a bit of trial and error to find the antibiotic(s) that the patient responds best to, and then I always try to keep the patient on the lowest dose possible and cycle those antibiotics.

### **G&H** Do you ever manage patients with long-term antibiotics?

**LR** Patients with chronic antibiotic-dependent pouchitis may need to be kept on long-term antibiotic therapy. As mentioned, I try to get those patients down to the lowest dose that will manage their symptoms. I slowly taper down the antibiotic, both by the dosage and how frequently it is taken. Once I find the sweet spot that manages their symptoms and is a lower dose, I continue it and use either fecal calprotectin or their symptoms as a guide on how the patient is responding to the antibiotics. In these patients with chronic antibiotic-dependent pouchitis, I perform a pouchoscopy typically once a year to screen for dysplasia and monitor the inflammatory burden in the pouch.

### **G&H** Could you discuss the use of vancomycin for pouchitis in patients who also have PSC?

**LR** This has been a great advancement in managing patients with chronic pouchitis. There have been some studies, most of which were fairly small, as well as anecdotal experience of oral vancomycin being used for pouchitis in patients with PSC. Several case series and case reports in PSC-associated pouchitis have shown a favorable response to oral vancomycin. There was even a small study demonstrating that oral vancomycin can help improve PSC. We know that patients with PSC are much more likely to develop chronic inflammation of their pouch. In fact, approximately 80% of PSC patients who have a pouch will develop chronic pouchitis. For a PSC patient who is getting a pouch, my current practice is typically to perform a scope fairly soon after the pouch is created and the patient resumes intestinal continuity (perhaps 3 to 6 months afterward) to see whether any inflammation is present in the pouch. If there is, I start oral vancomycin right away. In some cases, I even start oral vancomycin prophylactically as soon as the patient undergoes takedown of their diverting loop ileostomy and has their pouch in continuity to try to reduce the risk of chronic pouchitis. No study has looked at this approach, but I have had luck with it in my own practice. In my opinion, oral vancomycin is a great option for chronic pouchitis in patients with PSC.

### **G&H** What should be the next step after antibiotic failure?

**LR** I always go back to the patient's history to ensure I have a good understanding of what is driving their symptoms. I want to ensure there are no surgical complications such as an anastomotic leak that is mimicking a chronic inflammatory disorder of the pouch nor any mechanical complications associated with the pouch or functional complications such as pouch evacuation disorder clouding the clinical picture. Once I have ensured that I am comfortable with the diagnosis of chronic antibiotic-refractory pouchitis, I fairly quickly move to an advanced therapy to try to get the inflammation under control and reduce the patient's symptoms. I review the advanced therapies the patient was taking prior to colectomy and often try to find an advanced therapy they have not been exposed to that is appropriate, considering any comorbidities the patient may have. From there, I fairly quickly start the patient on an advanced therapy. If it is uncertain whether a patient truly has immune-mediated chronic antibiotic-refractory pouchitis, I may perform a trial of budesonide to see whether they respond. If they do, that gives me the confidence that moving forward with an advanced therapy makes sense.

### G&H Given the growing evidence for vedolizumab, ustekinumab, and anti-tumor necrosis factor agents in this setting, how can clinicians choose among them?

**LR** These are all great options, but it is ideal to identify an advanced therapy the patient has not already been exposed to prior to their colectomy. If the patient has been exposed to every class of drugs, at that point I would look to the drug they had the best response to prior to colectomy. That being said, the best data currently available involve vedolizumab (Entyvio, Takeda), which is the only advanced therapy that has undergone a large randomized controlled trial in chronic pouchitis or Crohn's disease of the pouch. Case series and smaller trials have looked at ustekinumab, interleukin-23 therapies, anti-tumor necrosis factor agents, and other advanced therapies, so I feel comfortable using any of them.

As for Janus kinase (JAK) inhibitors and other oral therapies, the delivery mechanisms may not allow for ideal absorption of these drugs when the patient does not have a colon. I have tried some of the JAK inhibitors in patients with pouches and have had variable success. The case series and reports of using JAK inhibitors are still quite small. This is an area clinicians can explore and try with their patients. I think the key is for the clinician to know that they can try to leverage any of the advanced therapies, if needed.

### G&H Is there a role for fecal microbiota transplantation in chronic antibiotic-refractory pouchitis?

**LR** A number of smaller studies have looked at fecal microbiota transplantation (FMT) in chronic antibiotic-refractory pouchitis, but no durable benefit has been seen. It appears that there is some difficulty with the engraftment of the healthy microbiome in the pouch. Work still needs to be done to understand how to leverage FMT in this patient population. There was an interesting proof-of-concept study in which the investigators used a donor with a healthy pouch to perform FMT into patients with unhealthy pouches. All 3 participants achieved clinical remission at 30 days, but the benefit was not sustained. Unfortunately, we are still not in a position to recommend FMT at this time for chronic antibiotic-refractory pouchitis.

### G&H When should surgery be considered?

**LR** In a patient with a surgical complication such as a

fairly significant leak at an anastomosis or twisting of the pouch, a colorectal surgeon should be involved. If a patient has chronic antibiotic-refractory pouchitis, is not responding to advanced therapies, and other potential causes of disease have been ruled out, there should be a discussion about how the patient's symptoms are impacting their quality of life and where they are emotionally with the idea of having a permanent ileostomy (whether a Brooke ileostomy or a Kock pouch). There are certain situations, particularly with some surgical or mechanical complications of the pouch, where revision of the pouch can be considered. However, a pouch redo procedure needs to be performed in the hands of a provider with experience in such surgery, which is complicated. This surgery is not appropriate for someone with an inflammatory condition of the pouch that has been refractory. It is most appropriate when dealing with a mechanical or surgical issue of the pouch.

### G&H What further research is needed?

**LR** I would love to see research continue to explore advanced therapies in both patients with chronic antibiotic-dependent pouchitis and patients with chronic antibiotic-refractory pouchitis to develop a better understanding of how to position such treatments in these patients. Hyperbaric oxygen therapy should also be studied in this area. Promising data have come out of hyperbaric oxygen therapy trials in acute severe ulcerative colitis, so I am hopeful that someday this approach can be explored in chronic pouch disorders as well.

### Disclosures

*Dr Raffals has no relevant conflicts of interest to disclose.*

### Suggested Reading

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