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AGA Clinical Practice Guideline on the Management of Pouchitis and Inflammatory Pouch Disorders

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Abstract

Background & Aims: Pouchitis is the most common complication after restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) for ulcerative colitis (UC). This American Gastroenterological Association (AGA) guideline is intended to support practitioners in the management of pouchitis and inflammatory pouch disorders.

Methods: A multi-disciplinary panel of content experts and guideline methodologists used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to prioritize clinical questions, identify patient-centered outcomes, conduct an evidence synthesis, and develop recommendations for the prevention and treatment of pouchitis, Crohn's-like disease of the pouch, and cuffitis.

Results: The AGA guideline panel made nine conditional recommendations. In patients with UC who have undergone IPAA and experience intermittent symptoms of pouchitis, the AGA suggests using antibiotics for the treatment of pouchitis. In patients who experience recurrent episodes of pouchitis that respond to antibiotics, the AGA suggests using probiotics for the prevention of recurrent pouchitis. In patients who experience recurrent pouchitis that responds to antibiotics but relapses shortly after stopping antibiotics (also known as chronic antibiotic-dependent pouchitis), the AGA suggests using chronic antibiotic therapy to prevent recurrent pouchitis; however, in patients who are intolerant to antibiotics or who are concerned about the risks of long-term antibiotic therapy, the AGA suggests using advanced immunosuppressive therapies (biologics and/or oral small molecule drugs) approved for treatment of IBD. In patients who experience recurrent pouchitis with inadequate response to antibiotics (also known as chronic antibiotic-refractory pouchitis), the AGA suggests using advanced immunosuppressive therapies; corticosteroids can also be considered in these patients. In patients who develop symptoms due to Crohn's-like disease of the pouch, the AGA suggests using corticosteroids and advanced immunosuppressive therapies. In patients who experience symptoms due to cuffitis, the AGA suggests using therapies that have been approved for the treatment of UC, starting with topical 5-aminosalicylates or topical corticosteroids. The panel also proposed key implementation

considerations for optimal management of pouchitis and Crohn's-like disease of the pouch and identified several knowledge gaps, and areas for future research.

Conclusions: This guideline provides a comprehensive, patient-centered approach to the management of patients with pouchitis and other inflammatory conditions of the pouch.

Keywords

Inflammatory bowel disease; pouchitis; ileal pouch-anal anastomosis; J-pouch; evidence synthesis

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) for patients with ulcerative colitis (UC) is associated with many short and long-term complications. Pouchitis is the most common complication after IPAA, affecting 48% of patients within the first 2 years after IPAA,[1] with up to 80% of patients developing pouchitis symptoms at some point after IPAA.[2, 3] Several new therapies have emerged for UC in recent years[4, 5] which have contributed to a decrease in the rate of colectomy over time,[6] with contemporary 5- and 10-years risk of colectomy being 7.0% and 9.6%, respectively. However, the overall incidence rates of pouchitis within the first 2 years after IPAA may have increased in the recent decades.[7] Pouchitis has significant impact on quality of life[3] of patients, and high cost burden.[8] In addition, approximately 17% patients may develop chronic symptoms of pouchitis, with relapsing-remitting course at varying intervals[9] and 10% patients may develop Crohn's-like disease of the pouch.[10]

Multiple strategies have been utilized in the treatment and prevention of pouchitis and inflammatory pouch conditions, including antibiotics, probiotics, corticosteroids and advanced immunosuppressive therapies including biologics and oral small molecule drugs. However, most of the evidence base is primarily derived from retrospective observational studies or comparisons of small cohorts. Data on patients' values and preferences for specific management decisions and treatment choices are also limited. This results in substantial practice variability. Despite this, important advances are being made in the field, for instance, the development of scoring systems to better characterize patient reported outcomes and endoscopic findings.[11–13] The recent randomized controlled trial (RCT) comparing vedolizumab to placebo in the treatment of patients with chronic refractory pouchitis (the EARNEST trial)[14] was a landmark study in the field providing guidance on trial design and outcomes for this disease.

Hence, the American Gastroenterological Association (AGA) prioritized the development of clinical guidelines informing the management of pouchitis and inflammatory pouch disorders in patients with UC who have undergone IPAA. This guideline will complement recent AGA Clinical Guidelines on the management of moderate to severe UC and moderate to severe Crohn's disease (CD).

OBJECTIVE

The objective of this guideline was to provide guidance in the management of pouchitis and other inflammatory disorders (such as Crohn's-like disease of the pouch and cuffitis) that can occur after colectomy with IPAA for UC. Aspects related to dysplasia surveillance in

the pouch, or issues unique to patients who undergo IPAA for established CD or for familial adenomatous polyposis will not be covered by this guideline.

TARGET AUDIENCE

The target audience for this guideline includes healthcare professionals (i.e., primary care, gastroenterology, and surgical professionals that care for patients after IPAA), patients and policy makers. This guideline is not intended to impose a standard of care, but rather provided the basis for rational, informed decisions for patients and healthcare professionals. Statements regarding the underlying values and preferences, as well as qualifying comments should not be omitted when quoting or translating recommendations from this guideline. Recommendations are intended to provide guidance for typical scenarios that arise among patients with pouchitis and other inflammatory conditions of the pouch; no recommendation can consider all unique circumstances that must be accounted for when making recommendations for individual patients. Shared-decision making with discussion of potential benefits and harms of therapy, particularly for conditional recommendations, and consideration for specific tradeoffs and patient preferences/values should be undertaken when making treatment decisions.

METHODS

Overview

This document represents official recommendations from the AGA. It was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for therapeutic strategies and adheres to best practices in guideline development, per the direction provided by the National Academy of Medicine.[15] The development of this document is fully supported by the AGA Institute.

Guideline Panel Composition and Conflicts of Interest

Members of the guideline and evidence synthesis panel were selected based on clinical and methodological expertise and experience, and after review of all conflicts of interest in a comprehensive vetting process. The multidisciplinary guideline panel included gastroenterologists with expertise in inflammatory bowel disease (IBD), guideline methodologists and general gastroenterologists. The *evidence synthesis team* consisted of six members, including three content experts (Edward Barnes, Gaurav Syal, and Laura Raffals) and three GRADE methodologists (senior methodologist and Co-Chair of the guideline: Siddharth Singh; junior methodologists: Elie Al Kazzi, John Haydek). The *guideline panel* consisted of five members including gastroenterologists and a colorectal surgeon focusing on the management of patients with IBD (Guideline Chair: Manasi Agrawal; guideline panel members: Ashwin Ananthakrishnan, Benjamin Cohen, Jana Hashash and Samuel Eisenstein). A patient representative was also involved in the development of guideline recommendations. Panel members disclosed all conflicts of interest, which were defined and categorized per AGA policies and the National Academy of Medicine and Guidelines International Network standards. No guideline panel member

was excused from participation in the process owing to disqualifying conflict. A full list of conflicts can be accessed at AGA's National Office in Bethesda, MD.

Formulation of Clinical Questions

The guideline panel and evidence synthesis teams developed clinically relevant and focused questions pertaining to prevention and treatment of inflammatory conditions of the pouch through an iterative process. Well-defined statements in the context of these focused questions, using the patients, intervention, comparator, and outcome (PICO) framework, were used to develop the literature search strategy, including inclusion and exclusion criteria. Broadly, the questions focused on the primary prevention of pouchitis after IPAA, treatment of pouchitis and prevention of recurrent and/or refractory pouchitis, treatment of Crohn's-like disease of the pouch, and treatment of cuffitis. The AGA Governing Board approved the final set of questions and statements in September 2022. The final focused questions and PICO questions are included in Table 1.

Outcomes of Interest

For PICOs focusing on the treatment of patients with symptoms of pouchitis, Crohn's-like disease of the pouch and cuffitis, the evidence synthesis team identified achieving significant clinical improvement, a patient-centered outcome, as the outcome of interest. This was prioritized over clinical remission since the latter was inconsistently defined and reported in observational studies. No standard definition of outcomes or disease activity index was uniformly used in included studies. The timeline for assessment of this outcome was preferentially within 8–14 weeks of intervention; alternative time points were used when the study did not report outcome within this time frame. For PICOs focusing on primary and secondary prevention of pouchitis, we focused on development of pouchitis symptoms as the outcome of interest. This outcome was preferentially examined 6–12 months after initiation of intervention. Endoscopic or histological outcomes were not prioritized as being critical for decision-making for these guidelines. Safety outcomes such as serious adverse events were considered important outcomes, and since data on these were inconsistently reported in included studies, we relied on prior systematic reviews on safety of different interventions in diverse diseases.

Search Strategy, Study Selection, Data Abstraction, and Statistical Analysis

Details of the approach to evidence synthesis are reported in the accompanying Evidence Synthesis document. Briefly, a comprehensive search of Ovid MEDLINE, Embase, and Wiley Cochrane Library, using a combination of controlled vocabulary terms and relevant keywords (Supplementary Table 1), from inception to October 20, 2022, was conducted by an experienced medical librarian, with input from the guideline methodologist. References of previous guidelines and consensus statements were reviewed to ensure that no relevant study was missed. Content experts provided insights into ongoing studies. All searches were limited to human subjects and the English language.

The inclusion and exclusion criteria were based on the formulated PICO questions. Both RCTs and observational studies reporting on the efficacy, effectiveness and adverse effects of therapies of interest (probiotics, antibiotics, corticosteroids, 5-aminosalicylates, and

advanced immunosuppressive therapies including biologics and small molecule drugs) for the prevention or treatment of the following inflammatory disorders of the pouch were included: pouchitis, Crohn's-like disease of the pouch, and cuffitis. Study selection was conducted in duplicate by a combination of a methodologist and content expert, and disagreements were resolved by consensus. From each study, pertinent data on patients, definition of disease entity, intervention (and comparator, for comparative studies or RCTs), outcome definition and timing of assessment was abstracted. For single-arm studies, we calculated pooled rates of achieving outcome with intervention; for comparative studies, pooled relative risk (RR) or odds ratios (OR) and 95% confidence intervals (CI), were calculated using the DerSimonian-Liard random-effects model. Statistical heterogeneity was assessed using the I^2 statistic. Small study effects were examined using funnel plot symmetry, though it is important to recognize that these tests are unreliable when the number of studies is <10 or there is considerable unexplained heterogeneity. All analyses were performed using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

In order to derive RR for evidence derived primarily from single-arm studies, we used hypothetical placebo rates (or spontaneous improvement rates) as comparator. This rate of spontaneous clinical improvement was estimated to be 40% (range, 30% to 50%), for patients experiencing infrequent episodes of pouchitis, and 30% (range, 20% to 40%) for patients experiencing chronic symptoms of pouchitis, pouchitis refractory to antibiotics or Crohn's-like disease of the pouch. These estimates are comparable to rates of clinical response observed in trials of patients with moderate to severe UC, moderate to severe luminal CD, and in the few trials of pouchitis that have been published.

Certainty of the Evidence

We use the GRADE approach to rate the certainty of evidence.[15] Briefly, using this approach, evidence from randomized clinical trials starts at high quality, and evidence from observational studies starts at low quality evidence. This evidence can be further rated down for risk of bias in the evidence, indirectness, inconsistency, imprecision and publication bias. In selected cases, particularly for observational studies, evidence may be rated up if a large treatment effect is observed, if there is a dose-response relationship or if all plausible confounding and bias would reduce a demonstrated effect or suggest a spurious effect if no effect was observed. Evidence profiles were developed for each intervention using the GRADEpro Guideline Development Tool (https://gradepro.org) (Supplementary Table 2).

Translating Evidence to Recommendations

The guideline panel and evidence synthesis panel met face-to-face on March 24, 2023, to discuss the evidence and to formulate recommendations. Based on the GRADE Evidence-to-Decision framework, we weighed the magnitude of and balance between the benefit and harms of interventions, patients' values and preferences, and the domains of feasibility, acceptability, and resource requirements and the impact on health equity. The panel reached a consensus for all guidelines. The certainty of evidence and the strength of recommendation are provided for each clinical question. Based on GRADE methodology, we label recommendations as "strong" or "conditional." The phrase "we recommend" indicates strong recommendations and the phrase "we suggest" indicates

conditional recommendations and provide the suggested interpretation of strong and weak recommendations for patients, clinicians, and health care policy makers (Table 2). In addition, the panel provided broad overarching, as well as recommendation-specific implementation considerations to provide context and facilitate real-world use and adoption of these recommendations, based on evidence and their clinical experience and practice.

Review Process

This guideline was submitted for public comment and external peer review and was approved by the AGA Governing Board.

DISCUSSION OF RECOMMENDATIONS

A summary of all the recommendations is provided in Table 3 and discussed below. Broad overarching considerations for implementing these recommendations in clinical practice are discussed below and in Table 4.

Key considerations for implementing these recommendations in clinical practice

1. **Normal bowel function after IPAA for UC, and typical symptoms of pouchitis:** After an initial period of postoperative adjustment, patients with IPAA can expect to average 4–8 bowel movements per day and 1–2 bowel movements per night.[2, 16] A variety of clinical symptoms have been described in patients with pouchitis, with typical symptoms being increased stool frequency, urgency, lower abdominal pain or cramping, and/or pelvic discomfort.[17, 18] Clinical symptoms of pouchitis do not necessarily correlate with findings on endoscopy or histology.[18]

2. **Pragmatic definitions of pouchitis** (Table 5): There is considerable heterogeneity in the clinical course of patients after IPAA for UC. To develop these recommendations, and facilitate their implementation, we propose pragmatic definitions of pouchitis and other inflammatory conditions of the pouch, to identify patients for whom specific recommendations would apply. (**A**) ***Intermittent pouchitis*** was defined as isolated and infrequent episodes of typical pouchitis symptoms that resolve with therapy (most commonly, antibiotics) or spontaneously, followed by extended periods of normal pouch function (typically months to years). Since antibiotics are the most commonly used therapy for symptoms of pouchitis, we anchored our functional definitions of pouchitis around response to antibiotic therapy. (**B**) ***Chronic antibiotic-dependent pouchitis*** was defined as recurrent episodes of pouchitis that responds to antibiotic therapy but relapses shortly after stopping antibiotics (typically within days to weeks), and often require recurrent or continuous antibiotic therapy or other advanced therapies to achieve symptom control. We did not define this entity based on a specific number of pouchitis episodes within a 12-month time period, since this is a continuum (some patients may require 3–4 courses of antibiotics per year, and others require almost continuous antibiotics) and patients' and providers' preferences for treatment approach varies depending on frequency of these episodes. (**C**) ***Chronic antibiotic-refractory pouchitis***

was defined as relapsing-remitting or continuous symptoms of pouchitis with inadequate response to typical antibiotic therapy (ongoing symptoms attributable to pouchitis), often needing escalation to other therapies. (**D**) ***Crohn's-like disease of the pouch*** was defined based on the most common and accepted diagnostic criteria for this condition, recognizing variability in prior literature. These diagnostic criteria include presence of a perianal or other fistula that developed at least 12 months after the final stage of IPAA surgery, stricture of the pouch body or pre-pouch ileum, and the presence of pre-pouch ileitis.[10] The panel recognized that pouchitis may often co-exist in patients with Crohn's-like disease of the pouch.

3. **Endoscopic evaluation in patients with pouch disorders**: The guideline panel felt that pouchoscopy should be performed in patients experiencing frequent recurrent episodes of pouchitis (suspected chronic antibiotic-dependent pouchitis), in patients with inadequate response to antibiotics before considering other therapies (suspected chronic antibiotic-refractory pouchitis), in patients experiencing atypical symptoms of pouchitis, and when the diagnosis of Crohn's-like disease of the pouch is being considered. The guideline panel felt routine pouchoscopy to confirm pouch inflammation in patients experiencing typical symptoms of pouchitis, prior to initiation of antibiotics, or in patients who experience infrequent episodes of pouchitis that respond to typical management, may not be required, although it may provide additional information on disease severity in this setting.

4. **Treatment goals and targets**: The guideline panel felt that the overall goal of treating patients with pouchitis is resolution of symptoms. There are emerging data suggesting that resolution of endoscopic and/or histologic inflammation may be associated with lower risk of future episodes of pouchitis, but endoscopic remission was not considered a critical outcome for decision-making. The guideline panel also did not make explicit recommendations around management of asymptomatic patients who have endoscopic and/or histologic evidence of inflammation in the pouch, due to paucity of evidence and high variability in patients' values and preferences for treatment.

5. **Use of calprotectin and other biomarkers:** The use of biomarkers has been evaluated for the management of UC and CD where recent AGA guidelines demonstrate the utility and practical implementation of biomarker testing in clinical practice.[19] Prior studies have demonstrated that fecal calprotectin is correlated with the pouchitis disease activity index (PDAI),[20] specifically endoscopic inflammation,[21] and that fecal calprotectin levels elevate prior to a clinical diagnosis of pouchitis.[22] Lactoferrin also appears to increase prior to a diagnosis of pouchitis and is correlated with endoscopic inflammation noted on pouchoscopy.[22] However, these guidelines did not systematically examine the utility of fecal calprotectin and other biomarkers in the management of inflammatory conditions of the pouch, and these are not routinely used in clinical practice.

6. **Alternative etiologies for patients with pouch disorders**: Although inflammatory conditions of the pouch reflect the most common complications after IPAA, other underlying disorders may also contribute to symptoms of pouch dysfunction after IPAA. Mechanisms that impair pouch emptying including stricture at the ileo-anal anastomosis, stricture at stoma takedown site and evacuation disorders such as non-relaxing pelvic floor dysfunction may contribute to atypical symptoms after IPAA, such as incomplete evacuation, straining, pelvic discomfort, etc.[23–25] Additionally, the evaluation of other potential inflammatory or infectious etiologies of pouch dysfunction must be considered. The benefit or role of routine *Clostridioides difficile* testing for each episode of pouchitis is not well defined despite the increased use of antibiotics among patients with pouchitis. However, in patients with pouchitis that is refractory to typical therapy, evaluating for *Clostridioides difficile* infection and other secondary or alternative etiologies of inflammation may be particularly beneficial.[16]

GUIDELINE RECOMMENDATIONS

PRIMARY PREVENTION OF POUCHITIS

Question 1. In patients who undergo ileal pouch-anal anastomosis for ulcerative colitis, what is the effectiveness of probiotics for the primary prevention of pouchitis?

Recommendation 1. In patients with ulcerative colitis who undergo IPAA, the AGA makes no recommendation in favor of, or against, the use of probiotics for primary prevention of pouchitis *(No recommendation, knowledge gap)*.

- **Comment:** There is a need for better evidence from clinical trials to inform the use of probiotics as a primary prevention strategy for pouchitis, especially given the potential cost and burden of long-term use with limited data on potential benefits.

Summary and Certainty of the Evidence—A primary prevention strategy for pouchitis is based on several factors. It is recognized that a significant proportion of patients will develop pouchitis within the first year[26] after IPAA. Intestinal bacteria are believed to play an important role in the pathogenesis of inflammatory bowel disease,[27] including pouchitis, and thus probiotics have been proposed as a potential mechanism for primary prevention of pouchitis. We identified four RCTs that utilized probiotics as a method of primary prevention of pouchitis,[26, 28–30] however, one RCT did not contribute any events in the intervention or comparator arm.[29] On meta-analysis, the RR for the development of pouchitis among patients receiving probiotics for the prevention of pouchitis when compared to placebo was 0.18 (95% CI 0.05 – 0.62) (eFigure 1). It is unclear whether multi-strain probiotics are more effective than single-strain probiotics and whether a specific probiotic strain is more effective than another. The overall body of evidence was rated as very low certainty, being rated down for risk of bias, very serious imprecision (due to very low event rate <35), and strong concern for publication bias. (Table 6A).

Benefits and Harms (Downsides)

No prevention with probiotics.: In current practice, a vast majority of patients undergoing IPAA for UC do not employ a primary preventive strategy. Most patients who develop pouchitis respond well (and rapidly) to an initial course of antibiotics and thus the potential downside of developing pouchitis if not employing a preventive strategy may be offset by the benefit of not taking a daily preventive therapy.

Prevention with probiotics.: Probiotics are not associated with substantial risk of serious adverse events and are generally well tolerated. The cost and burden of chronic preventive therapy with probiotics may be substantial, although a formal cost-effectiveness analysis has not been conducted.

Rationale—Overall, the benefit of probiotics for primary prevention of pouchitis was uncertain, and while there was no direct harm, there was concern for high burden, cost, and overall utility of chronic, primary prevention strategy for most individuals who have undergone IPAA. The vast majority of patients who develop pouchitis will respond well to the initial treatment with 2–4 week course of antibiotics. The duration of primary prophylaxis is also unclear and could potentially be lifelong, since it is unclear whether limited duration of probiotics early after IPAA fundamentally prevents any future development of pouchitis. Moreover, given limited insurance coverage, feasibility of widespread implementation is unclear, with substantial concern of exacerbating inequities. The efficacy of different probiotics may be different, and there was limited data informing the choice of one over another. Hence, overall, the panel recommended neither in favor of, nor against, the use probiotics for primary prevention of pouchitis. A subset of patients at high risk of pouchitis, and/or of chronic pouchitis, such as those to primary sclerosing cholangitis, may consider using probiotics for primary prevention though the effectiveness of this strategy has not specifically been studied in these high-risk populations. Future larger RCTs on primary prevention strategies, particularly in patients at high risk of recurrent pouchitis, are warranted.

Question 2. In patients who undergo ileal pouch-anal anastomosis for ulcerative colitis, what is the effectiveness of antibiotics for the primary prevention of pouchitis?

Recommendation 2. In patients with ulcerative colitis who undergo IPAA, the AGA suggests against using antibiotics for the primary prevention of pouchitis (*Conditional recommendation, very low certainty of evidence*).

- **Comment:** There is a need for better evidence from clinical trials to inform the use of antibiotics as a primary prevention strategy for pouchitis, especially given the potential side effects and burden of long-term use with limited data on potential benefits.

Summary and Certainty of the Evidence—We identified one RCT evaluating the effectiveness of tinidazole for primary prevention of pouchitis after proctocolectomy with IPAA for UC.[31] In this study, oral tinidazole (2/25; 8.0%) was more effective than placebo

(5/13; 38.5%) (RR 0.21; 95% CI 0.05–0.93) in preventing pouchitis. Interestingly, three patients developed pouchitis, 4–10 months after stopping tinidazole. The overall body of evidence was rated as very low certainty, due to risk of bias, and very serious imprecision due to very low event rate (Table 6B).

Benefits and Harms (Downsides)—The potential benefit of primary prophylaxis with antibiotics is prevention of initial episode of pouchitis after IPAA. However, there are several adverse effects associated with long-term use of antibiotics. These include drug intolerance, *Clostridioides difficile* infection, and promoting colonization of drug-resistant organisms. In addition, long-term effects on the microbiota of the pouch from chronic early antibiotic exposure is unknown to date.

Rationale—Although pouchitis is the most common complication after IPAA, the majority of patients will respond well to the initial treatment with antibiotics within 2–4 weeks of therapy. Indefinite therapy with antibiotics for primary prevention in an asymptomatic patient is associated with several potential adverse effects with risks higher than sporadic courses of antibiotics for treatment of pouchitis. The duration of chronic antibiotic therapy for primary prophylaxis is unclear, and in the clinical trial of tinidazole, some patients develop pouchitis within one year of stopping antibiotics. It is unclear which patients progress from sporadic episodes of pouchitis to chronic symptoms of pouchitis, or other inflammatory conditions of the pouch, and whether primary prophylaxis with chronic antibiotic therapy would modify that risk. Hence, the panel suggested against the use of antibiotics for primary prevention of pouchitis.

TREATMENT OF POUCHITIS

Question 3. In adult outpatients with pouchitis, what is the effectiveness of antibiotics for treatment of pouchitis?

Recommendation 3. In patients with ulcerative colitis who have undergone IPAA and experience infrequent episodes of pouchitis, the AGA suggests using antibiotics for treatment of pouchitis *(Conditional recommendation, very low quality of evidence)*.

Implementation Considerations

- Based on available evidence, ciprofloxacin and/or metronidazole are the preferred antibiotics for treatment of pouchitis.
- The typical duration of antibiotic therapy for the treatment of pouchitis is 2–4 weeks.
- An approach using a combination of antibiotics may be more effective in patients who do not respond to single antibiotic therapy.
- Alternative antibiotic regimens, such as oral vancomycin, may be considered in patients who do not respond to initial course of antibiotics, or have allergies or intolerance to ciprofloxacin and/or metronidazole.

Summary and Certainty of the Evidence—Antibiotics remain the primary initial treatment for pouchitis. We identified four small RCTs evaluating antibiotics for treatment of pouchitis, of which two were placebo-controlled. In these two trials, 11/19 antibiotic-treated vs. 3/21 placebo-treated patients had clinical improvement (RR, 3.45; 95% CI, 0.29–41.82). We subsequently focused on eight single-arm observational studies examining the effectiveness of different antibiotics for treatment of pouchitis (ciprofloxacin, metronidazole, rifaximin, vancomycin; either alone or in various combinations), and used data from four arms of RCTs of antibiotics to estimate pooled response rate. On pooled analysis, 160/239 patients (pooled response, 65%; 95% CI, 52–75) treated with antibiotics had marked improvement in symptoms (eFigure 2). Overall response rates were similar across different antibiotics, and use of single vs. combined antibiotics. With assumed spontaneous improvement rates (placebo response rates) of 40% (range, 30–50%) in patients experiencing infrequent episodes of pouchitis, antibiotics were associated with 67% higher risk of clinical response (RR, 1.67; 95% CI, 1.34–2.01). The overall body of evidence derived from these observational studies was rated down for risk of bias in included studies and inconsistency due to diverse patient population with varying levels of prior antibiotic-responsiveness, leading to overall very low certainty of evidence (Table 7).

Benefits and Harms (Downsides)—Antibiotics are the most common treatment for intermittent episodes of pouchitis. Short courses of antibiotics are safe; however it is recognized that antibiotic exposure may have effects on the underlying microbiome including patterns of genetic resistance that may play a role in the physiology of the pouch and may have long-term implications.[32] All antibiotics are associated with specific side effects. For example, ciprofloxacin has been associated with increased risk of tendonitis and tendon rupture. However, in the absence of effective alternative therapies for intermittent bouts of pouchitis, withholding antibiotics for pouchitis may significantly impact quality of life.[8]

Rationale—Most patients experience infrequent episodes of pouchitis which respond well to short courses of antibiotic therapy. Much of our understanding of the treatment of infrequent episodes of pouchitis has been experiential rather than based on large RCTs or comparative effectiveness studies. Multiple antibiotic therapies have been used for the treatment of pouchitis, however ciprofloxacin and metronidazole remain the most well studied and most commonly used antibiotics for intermittent pouchitis. In one cohort study, vancomycin 125 mg orally twice daily demonstrated effectiveness in this setting,[33] however most patients in this cohort had been treated with multiple other antibiotic therapies and thus it is not known if vancomycin would be more effective if used earlier in the treatment algorithm. Rifaximin has also been evaluated as a treatment for intermittent pouchitis in one pilot trial, where patients treated with rifaximin demonstrated a numerically greater (although not statistically significant) increase in clinical remission compared to placebo.[34]

Several other factors should be considered when choosing an antibiotic for the treatment of pouchitis. Medication allergies and prior tolerance of antibiotics may inform antibiotic selection. The standard recommended duration of ciprofloxacin and metronidazole has been 2-weeks.[35] Ciprofloxacin 500 mg orally twice daily and metronidazole 500 mg orally twice

or 3 times daily, for 2 weeks, is the standard practice of the guideline panel; ciprofloxacin may generally be better tolerated than metronidazole.[36] Although expert opinion indicates that some gastroenterologists may choose a 4-week course,[16] or a combination of antibiotics (such as ciprofloxacin and metronidazole) for an initial episode of pouchitis, both of these approaches have typically been reserved for patients with incomplete response to an initial treatment or recurrent episodes of pouchitis.[37]

Question 4. In adult outpatients with pouchitis, what is the effectiveness of probiotics for the treatment of pouchitis?

Recommendation 4. In patients with ulcerative colitis who have undergone IPAA and experience infrequent episodes of pouchitis, the AGA makes no recommendation in favor of, or against, the use of probiotics for the treatment of pouchitis *(No recommendation, knowledge gap)*.

Summary and Certainty of the Evidence—We identified three studies (one RCT, two cohort studies) evaluating the effectiveness of probiotics for the treatment of pouchitis.[38–40] All three cohorts utilized different probiotic formulations: one cohort used the De Simone formulation,[38] one cohort used a combination of *Lactobacillus* and *Bifidobacteriae*[41] and the RCT utilized *Lactobacillus rhamnosus GG*.[40] The defined outcome in these three studies was clinical remission or response along with a predefined decrease in the endoscopic subscore of the PDAI. The pooled rate of clinical response was 47/84 (52%, 95% CI 27–76) (eFigure 3A). Assuming a spontaneous improvement rate of 40% (range, 30–50%) in patients with infrequent episodes of pouchitis, probiotics would be associated with 40% higher likelihood of clinical response compared with no treatment (RR, 1.40; 95% CI, 1.12–1.86). In the single RCT evaluating the efficacy of probiotics for the treatment of pouchitis, 1/10 patients treated with *Lactobacillus rhamnosus GG* responded compared to 0/10 patients treated with placebo.[40] The overall body of evidence was rated down for risk of bias in included studies; inconsistency due to diverse interventions and outcomes, use of a hypothetical placebo/spontaneous improvement rate; imprecision due to very low event rate; and concern for publication bias (very limited evidence base, despite widespread use and availability) leading to overall very low certainty of evidence (Table 8A).

Benefits and Harms (Downsides)—Side effects are infrequent with probiotics and they are generally well tolerated. Probiotics can be expensive and may not be covered by insurance. The evidence demonstrating the potential benefits of probiotics in the treatment of pouchitis are limited to the 3 formulations and thus recommendations regarding other formulations cannot be made. Moreover, there is lack of regulatory requirements for over-the-counter probiotics since they are largely considered dietary supplements or medical foods, which can affect effectiveness in clinical practice. Use of probiotics in this situation may delay use of antibiotics, which have been consistently effective for treatment of pouchitis.

Rationale—The benefit of probiotics for treatment of infrequent episodes of pouchitis is uncertain, with limited, very-low-quality evidence. In the collective experience of the

panel, probiotics in real-world practice have not been very effective for the treatment of pouchitis. In comparison to antibiotics as a treatment for intermittent pouchitis, although the relative risk was similar in magnitude with probiotics, there is greater body of evidence and clinical experience with antibiotics. Additionally, this recommendation is also informed by the potential differences in the utility of different probiotic formulations, with limited studies demonstrating the effectiveness of specific formulations in this setting. Finally, given the demonstrated effectiveness of antibiotics in the treatment of pouchitis, there is potential that delaying therapy or using probiotics when they are not as effective as antibiotics may have significant impact on an individual patient's quality of life. Larger, high-quality RCTs of probiotics, preferably comparing them against antibiotics such as ciprofloxacin, are warranted to better understand the role of probiotics for treatment of pouchitis.

Question 5. In adult outpatients with pouchitis, what is the effectiveness of probiotics for the prevention of recurrent pouchitis?

Recommendation 5. In patients with ulcerative colitis who have undergone IPAA and experience recurrent episodes of pouchitis that respond to antibiotics, the AGA suggests using probiotics for preventing recurrent pouchitis (*Conditional recommendation, low certainty of evidence*).

Comment: Patients, particularly those with infrequent episodes of recurrent pouchitis or where the burden of long-term probiotic treatment is excessive, may reasonably choose avoiding any treatment to prevent recurrence of pouchitis.

Implementation consideration

- De Simone formulation of multi-strain probiotics was used in clinical trials of prevention of pouchitis.

Summary and Certainty of the Evidence—We identified three RCTs[29, 42, 43] evaluating the efficacy of the De Simone formulation to prevent the relapse of pouchitis in patients with antibiotic-responsive pouchitis. On meta-analysis, use of probiotics was associated with 87% lower risk of relapse over 12 months (6/45 vs. 36/41; RR, 0.17; 95% CI, 0.09–0.34) (eFigure 3B). The overall body of evidence was rated as low-quality, being rated down for imprecision due to low event rate and suspected publication bias (limited evidence base, despite widespread use and availability; clinical practice does not mirror the high efficacy observed in clinical trials) (Table 8B).

Benefits and Harms (Downsides)—Recurrent pouchitis significantly impacts patients' quality-of-life, and is associated with increased healthcare costs and utilization;[8]. By reducing the incidence of recurrent pouchitis, probiotics can favorably impact these outcomes. However, there is limited data on cost-effectiveness of long-term probiotic therapy. As noted previously, the cost of probiotics may be prohibitive for some patients. Individual patients' and providers' threshold for establishing how many episodes of pouchitis are too-frequent, may vary, and this would influence their acceptance of long-term probiotic therapy.

Rationale—The body of evidence favoring the use of probiotics for preventing recurrence of pouchitis is limited to the De Simone formulation, and to patients who are antibiotic-responsive. In these RCTs, patients were treated with an initial course of antibiotics and required to achieve remission prior to initiating probiotic therapy, providing a potential model for future implementation in clinical practice. In the study by Gionchetti et al., one month of ciprofloxacin 1 g daily and rifaximin 2 g daily was used to achieve clinical and endoscopic remission prior to randomization to receive De Simone formulation 6 g per day or placebo.[42] Similarly, in the study by Mimura and colleagues, patients with active recurrent or refractory pouchitis were treated with a combination of metronidazole 400 mg or 500 mg twice daily and ciprofloxacin 500 mg twice daily for 4 weeks. Those patients who achieved a combined clinical and endoscopic remission were randomized to receive De Simone formulation 6 g per day or placebo.[43] In contrast to these 2 studies, Pronio et al. conducted a randomized, open-label parallel-arm trial assessing the efficacy of the De Simone formulation among patients at different periods after surgery who were not taking any medications at study entry.[29]

The thresholds for defining frequency of recurrence in patients with recurrent pouchitis may vary. While those patients who experience multiple recurrent episodes of pouchitis annually (or experience continuous symptoms in the absence of therapy) are more likely to desire chronic preventive therapy with probiotics, the efficacy of probiotics in these situations is unclear. In the collective experience of the panel members, use of these probiotics has not been associated with a large reduction in risk of recurrent pouchitis as seen in RCTs.

Question 6. In adult outpatients with pouchitis who have adequate response to antibiotics, but relapse shortly after stopping antibiotics, what is the effectiveness of using chronic antibiotic therapy to treat recurrent pouchitis?

Recommendation 6. In patients with ulcerative colitis who have undergone IPAA, and experience recurrent pouchitis that responds to antibiotics but relapses shortly after stopping antibiotics (commonly referred to as *chronic antibiotic-dependent pouchitis*), the AGA suggests using chronic antibiotic therapy to treat recurrent pouchitis (*Conditional recommendation, very low certainty of evidence*).

Implementation consideration

- The panel suggests endoscopic evaluation of the pouch with confirmation of inflammation and ruling out alternative etiologies in patients with recurrent pouchitis.
- Lowest effective dose of antibiotics (for example, ciprofloxacin 500mg daily or 250mg twice daily) with intermittent gap periods (such as approximately one week/month), or use of cyclical antibiotics (such as rotating between ciprofloxacin, metronidazole, vancomycin, etc. every 1–2 weeks) may be considered to decrease risk of antimicrobial resistance.

Summary and Certainty of the Evidence—There is a paucity of studies evaluating the effectiveness of chronic antibiotic therapy in patients experiencing frequent episodes

of recurrent pouchitis, which relapses shortly after stopping antibiotics. As noted in PICO #3, antibiotics are very effective in treatment of infrequent episodes of pouchitis. In the collective experience of the panel, chronic antibiotic use in patients whose disease relapses shortly after stopping antibiotics is effective in preventing recurrent episodes. The overall body of evidence was rated as very-low certainty, given indirectness in applying findings from very low quality evidence supporting the use of antibiotics for treatment of infrequent episodes of pouchitis.

Benefits and Harms (Downsides)—Chronic antibiotic use has been associated with increased rates of antimicrobial resistance, colonization with drug-resistant organisms, disruption of normal gut flora and potentially increasing the risk of chronic diseases such as diabetes, cardiovascular diseases, and cancers, besides risks with individual antibiotics such as neuropathy with chronic metronidazole use and tendinopathy with chronic ciprofloxacin use. There are limited studies on the safety of chronic antibiotic use in patients with recurrent pouchitis. In a cohort of 205 patients, 167 (81.5%) used antibiotics at some point for pouchitis with long-term antibiotic use increasing from 18% at 5 years post-IPAA to 42% at 20 years post-IPAA.[44] In this analysis, there was no association between antibiotic use and the development of resistant infections, with overall adverse event rates for the most common antibiotics utilized being low (ciprofloxacin 1 per 10,000 use-days and metronidazole 6 per 10,000 use-days). Chronic antibiotic therapy may not significantly increase the risk of *Clostridiodes difficile* infection in patients with IPAA.[45]

Rationale—There is marked variability in frequency of recurrent pouchitis, with some patients experiencing infrequent pouchitis, others experiencing episodes every 2–4 months, and yet others experiencing near continuous symptoms of pouchitis. Patients' preference for treatment may vary depending on the frequency of these episodes, their impact on quality of life, as well as the effectiveness, safety and tolerability of the proposed treatment. Historically, chronic antibiotic-dependent pouchitis has defined as greater than 3 episodes of pouchitis per year. However, in the collective experience of the panel, and with input from the participating patient stakeholder, chronic antibiotic therapy may not be warranted or acceptable to patients who experience episodes of pouchitis every 2–4 months, where they may prefer intermittent antibiotic therapy for 6–12 weeks per year. Chronic antibiotic therapy may be more acceptable and applicable to patients who experience near constant symptoms of pouchitis, which relapse within days to weeks of stopping antibiotics. To minimize risk of antibiotic-resistant bacteria and side effects associated with long-term antibiotic use, the panel suggested that the lowest dose of antibiotics (such as ciprofloxacin 500 mg daily or 250 mg twice daily), or cyclical course of antibiotics (cycling from one antibiotic to another every 1–2 weeks), with intermittent periods off antibiotics (approximately 1 week per month) may be helpful to consider. The response to such an approach will likely be guided by both the patient's symptoms (i.e., how a patient feels when on a low-dose of antibiotics, different antibiotics on a cyclical course of antibiotics, and in the time period off antibiotics) as well as objective data that a gastroenterologist and the patient have established as a reliable method of disease monitoring. Although ciprofloxacin and metronidazole are established as the most common initial approaches to the treatment of acute or intermittent pouchitis, multiple antibiotic regimens can be used in the treatment

of chronic or recurrent pouchitis.[46] Communicating both the need for chronic antibiotics as well as the rationale for chronic antibiotics is paramount to ensuring patient compliance with a prescribed regimen as well as appropriate feedback if antibiotic therapy is not effective.

Question 7. In adult outpatients with pouchitis who have adequate response to antibiotics, but relapse shortly after stopping antibiotics, what is the effectiveness of using advanced immunosuppressive therapies to treat recurrent pouchitis?

Recommendation 7. In patients with ulcerative colitis who have undergone IPAA, and experience recurrent pouchitis which responds to antibiotics but relapses shortly after stopping antibiotics (commonly referred to as *chronic antibiotic-dependent pouchitis*), the AGA suggests using advanced immunosuppressive therapies to treat recurrent pouchitis (*Conditional recommendation, very low certainty of evidence*).

Implementation consideration

- The panel suggests endoscopic evaluation of the pouch with confirmation of inflammation and ruling out alternative etiologies in patients with recurrent pouchitis.
- Advanced immunosuppressive therapies approved for treatment of UC or CD may be used, including TNF-α antagonists (infliximab, adalimumab, golimumab, certolizumab pegol), vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib. Vedolizumab is the only advanced therapy to date that has received regulatory approval from the European Medical Agency for this indication.
- Advanced immunosuppressive therapies may be used in lieu of chronic, continuous antibiotic therapy, particularly in patients who are intolerant to antibiotics or where patients and/or providers are concerned about risks of long-term antibiotic therapy.
- Advanced immunosuppressive therapies that patients have used prior to colectomy may be reconsidered.

Summary and Certainty of the Evidence—In the EARNEST trial evaluating the efficacy of vedolizumab for the treatment of chronic pouchitis, patients were treated with concomitant oral ciprofloxacin 500 mg twice daily from randomization through week 4 of the study, and 53% of patients reported continuous use of antibiotics immediately before the baseline visit.[14] In this trial, 18/51 patients receiving vedolizumab achieved mPDAI-remission at week 14 compared to 5/51 patients receiving placebo; data was not specifically presented for a subset of patients with chronic antibiotic-dependent pouchitis, although ~21% patients continued to require at week 34 after initiation of vedolizumab. When this RCT was considered separately, evidence was rated as low certainty (rated down for very serious imprecision due to low event rate). Data on the effectiveness of advanced immunosuppressive therapies in patients with chronic antibiotic-dependent pouchitis and chronic antibiotic-refractory pouchitis was not presented separately. We opted to analyze data for all advanced therapies together as observational studies, and identified

31 cohort studies evaluating the effectiveness of advanced immunosuppressive therapies in patients with chronic pouchitis,[14, 47–72] including patients with chronic antibiotic-dependent pouchitis as well as chronic antibiotic-refractory pouchitis. On pooled analysis of 31 cohort studies, the overall response rate with advanced immunosuppressive therapies was 50% (95% CI, 43–57; 287/560 patients) (eFigure 4). Assuming a spontaneous improvement rate (or placebo response rate) of 30% (lower limit 20% and upper limit 40%) in patients with chronic antibiotic-dependent pouchitis, use of advanced therapies was 71% more effective than no intervention (95% CI 1.28–2.56). The overall body of evidence was rated as very low certainty, derived primarily from observational studies, at high risk of bias with use of non-standard outcome metrics, inconsistency due to diversity of patients evaluated, along with varying levels of disease severity and antibiotic-refractoriness, and use of a hypothetical spontaneous improvement rate (Table 9).

Benefits and Harms (Downsides)—Advanced immunosuppressive therapies are effective in treating chronic antibiotic-dependent pouchitis. These immunosuppressive therapies may also be effective in treating extra-intestinal manifestations that may be associated with chronic pouchitis in some patients. The safety profile of different types of immunosuppressive therapies has been well-established in patients with UC and CD. They may increase the risk of serious infections, some malignancies such as lymphoma, with risks varying with different therapies. Adverse events unique to the use of these advanced therapies in patients with recurrent pouchitis have not been identified. In the absence of effective therapy, patients with chronic antibiotic-dependent pouchitis would require chronic antibiotic therapy. We did not identify any evidence specifically comparing the effectiveness and safety of these therapies compared with chronic, continuous antibiotic therapy, in patients who experience near-continuous symptoms of pouchitis. The avoidance of long-term antibiotics may be particularly appealing to patients with a history of intolerance or allergic reactions to antibiotic therapy or those that are concerned about the long-term risks of antibiotic exposure. Although the risk of adverse events associated directly with chronic antibiotic use appears low, individual patients and providers may place greater value on these risks for antimicrobial resistance and changes in the microbiome and thus prefer earlier introduction of advanced immunosuppressive therapy. In the experience of the guideline panel, some patients who initiate immunosuppressive therapy are unable to completely discontinue antibiotics and may still require intermittent courses of antibiotics; in the EARNEST trial, approximately one in five patients with chronic pouchitis continued to require antibiotics at week 34.

Rationale—While there is considerable paucity of published evidence on the effectiveness and safety of chronic, long-term antibiotic therapy for patients with chronic antibiotic-dependent pouchitis, we identified several cohort studies as well as the recent EARNEST demonstrating high effectiveness of advanced immunosuppressive therapies in these patients. In addition to the available studies demonstrating the effectiveness of advanced therapies in the treatment of recurrent pouchitis, this recommendation is also informed by treatment experience with both UC and CD where the use of these therapies is well established. Large, comparative studies of advanced immunosuppressive therapies and chronic antibiotic use are warranted to better inform optimal treatment approach in patients

with chronic antibiotic-dependent pouchitis. In retrospective analyses, 29–39% of patients with acute pouchitis progress to chronic pouchitis in a median interval of 0.6–1.1 years after acute pouchitis diagnosis.[73, 74] Among patients who develop chronic pouchitis, 23% initiate biologic therapy within 10 days of diagnosis.[73] However, it is unclear what proportion of patients with chronic antibiotic-dependent pouchitis may evolve into chronic antibiotic-refractory pouchitis, Crohn's-like disease of the pouch and pouch failure, and whether early use of advanced immunosuppressive therapies may be able to decrease this risk. A small subset of patients with refractory pouchitis and pouch failure may require pouch excision.

Question 8. In adult outpatients with pouchitis who have inadequate response to antibiotics, what is the effectiveness of advanced immunosuppressive therapies?

Recommendation 8. In patients with ulcerative colitis who have undergone IPAA, and experience recurrent pouchitis with inadequate response to antibiotics (commonly referred to as *chronic antibiotic-refractory pouchitis*), the AGA suggests using advanced immunosuppressive therapies (*Conditional recommendation, low [vedolizumab] to very low certainty of evidence [other advanced immunosuppressive therapies]*).

Implementation considerations

- The panel suggests endoscopic evaluation of the pouch with confirmation of inflammation and ruling out alternative etiologies in patients with recurrent pouchitis.
- Immunosuppressive therapies approved for treatment of ulcerative colitis or Crohn's disease may be used, including TNF-α antagonists (infliximab, adalimumab, golimumab, certolizumab pegol), vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib. Vedolizumab is the only advanced therapy to date that has received regulatory approval from the European Medical Agency for this indication.
- Advanced therapies that patients have used prior to colectomy may be reconsidered.
- A subset of patients may continue to derive partial symptomatic benefit from antibiotics and may benefit from ongoing use of antibiotics besides advanced immunosuppressive therapies.

Summary and Certainty of the Evidence—We identified two RCTs conducted evaluating the efficacy of biologic therapies in the treatment of chronic pouchitis (vedolizumab[14] and adalimumab[75]). In the RCT of adalimumab, 3/6 patients with chronic pouchitis treated with adalimumab achieved response at 12 weeks compared to 3/7 patients receiving placebo.[75] In the EARNEST trial, 32/51 patients receiving vedolizumab achieved response at week 14 compared to 17/51 patients receiving placebo.[14] Combining the results of these 2 trials yields a RR of 1.78 (95% CI 1.18–2.68) for clinical response when compared to placebo. In addition, we identified 31 cohort studies or case series[14, 47–72] evaluating the effectiveness of advanced therapies in the treatment of recurrent pouchitis, with the majority of patients in these studies experiencing chronic antibiotic-refractory

pouchitis. The overall response rate was 50% (95% CI, 43–57; 287/560 patients) (eFigure 4). With a hypothetical spontaneous improvement rate of 30% (range, 20–40%) in patients with recurrent episodes of pouchitis with inadequate response to antibiotics, use of advanced therapies was associated with a 71% higher likelihood of clinical improvement compared with no therapy (RR, 1.71; 95% CI, 1.28–2.56), similar to observations in the two RCTs. This body of evidence is also supported by the established efficacy of advanced immunosuppressive therapies in patients with UC and CD. The overall body of evidence was rated as very low certainty, derived primarily from observational studies, at high risk of bias with use of non-standard outcome metrics, inconsistency due to diversity of patients evaluated, along with varying levels of disease severity and antibiotic-refractoriness, and use of a hypothetical spontaneous improvement rate (Table 9).

We also examined different classes of advanced therapies for individual pooled response rates. Among all TNFα antagonists (14 cohorts, n=245), the pooled rate of response was 54% (95% CI, 42–66). In nine cohorts treated with vedolizumab (n=194), the pooled rate of response was 52% (95% CI, 39–65). There were considerably small cohorts of patients treated with ustekinumab (2 cohort, n=31), with a pooled rate of response of 72% (95% CI, 4–99), and with tofacitinib (2 cohorts, n=13), with a pooled rate of response of 31% (95% CI, 2–92). No significant differences were identified in response rate with different advanced therapies (p=0.24).

Benefits and Harms (Downsides)—Continuous symptoms of pouchitis that are refractory to antibiotic therapy have significant impact on quality-of-life. In addition, chronic antibiotic-refractory pouchitis is one of the most common causes of pouch failure.[16] Hence, inadequate treatment of antibiotic-refractory pouchitis or delays in appropriate therapy may have significant downstream consequences for individual patients. There is considerable experience with advanced immunosuppressive therapies for UC and CD, confirming overall safety of these therapies, although they are associated with increase in risk of serious infections, and some malignancies such as lymphoma, with risk varying between different therapies. Adverse events unique to the use of these advanced therapies in patients with recurrent pouchitis have not been identified.

Rationale—In examining the effectiveness of advanced therapies in the treatment of recurrent pouchitis, it was important to not only define pouchitis that is not responsive to antibiotics but also to examine the underlying physiology in comparison to other pouch-related disorders. Although symptoms of intermittent pouchitis are believed to be mediated by changes in the microbiota,[16, 32, 76] chronic pouchitis may be mediated through immunological mechanisms.[77–79] In a recent evaluation, a computational algorithm using microRNA expression profiles in conjunction with clinical factors demonstrated high levels of accuracy in predicting patients who would develop chronic pouchitis.[77] A prior meta-analysis has also suggested an increased risk of chronic pouchitis among patients who were ANCA-positive,[78] however these studies did not further stratify chronic pouchitis based on antibiotic responsiveness. Genetic polymorphisms such as the NOD2insc variant have also been associated with an increased risk for chronic pouchitis.[79] Given the apparent effectiveness of biologic and other immunosuppressive therapies in the

treatment of chronic pouchitis that is not responsive to antibiotics, it would appear that the underlying immunologic mechanisms may be similar to those in UC and CD. An improved understanding of the risk factors for chronic pouchitis and the underlying pathophysiology may allow for earlier introduction of effective therapy in those at the highest risk of developing this phenotype.

Several advanced immunosuppressive therapies have been used for the treatment of antibiotic-refractory pouchitis. The efficacy of vedolizumab in patients with recurrent pouchitis was established in EARNEST, a RCT comparing 51 patients treated with vedolizumab to 51 treated with placebo.[14] To be eligible, patients were required to have at least 3 recurrent episodes of pouchitis in the 12 months prior to the screening visit which were treated with antibiotics or other prescription therapies, or treated with continuous antibiotics for at least 4 weeks immediately before the baseline endoscopy visit. All enrolled patients received concomitant oral ciprofloxacin 500 mg twice daily from randomization through week 4, with additional antibiotics permitted for pouchitis symptoms that occurred after week 14 of the study. The primary endpoint of EARNEST was modified pouchitis disease activity index[17] (mPDAI)-defined remission at week 14 (mPDAI score of ≤4 and a reduction from baseline of ≥2 points in the total mPDAI score). Of note, among 51 patients treated with vedolizumab, 57% reported continuous use of antibiotics immediately before baseline with 22.2% and 21.2% of patients continuing to use antibiotics at week 14 and week 34 assessments, respectively. While vedolizumab was the only therapy studied in a rigorous RCT, it was slow to recruit highlighting challenges in generating high quality evidence in this field. We relied on observational studies to inform the effectiveness of other advanced immunosuppressive therapies, which demonstrated similar response rates to those observed in the RCT. We opted not to infer on relative efficacy of one medication over others or recommend the use of one medication over others. Future prospective studies will be informative on the appropriate positioning and sequencing of these therapies in patients with refractory pouchitis.

Based on our review of available literature, it may be reasonable to reconsider advanced therapies that individual patients have utilized prior to undergoing colectomy for UC. Whether the recycling or reuse of these advanced therapies (or the same class of therapies) is associated with decreased effectiveness has not been definitively demonstrated to date. In early evaluations of the effectiveness of using TNFα antagonist therapy for the treatment of Crohn's-like disease of the pouch in patients who had received TNFα antagonist therapy prior to colectomy, 71% of patients responded to repeat use of this drug class after IPAA.[80] More recent evaluations have suggested the potential for decreased effectiveness of biologic therapies when recycling therapies or mechanisms.[48, 81] In one retrospective study, acute infusion reactions or delayed hypersensitivity reactions were common reasons for discontinuation of infliximab therapy among patients being treated for chronic antibiotic-refractory pouchitis with a history of infliximab therapy prior to colectomy.[60] In a separate evaluation of patients with chronic inflammatory conditions of the pouch receiving biologic therapy, patients who received TNFα antagonists prior to colectomy and after IPAA were less likely to achieve clinical remission compared to those patients who were TNFα antagonist-naïve or were treated with a different class of therapy post-IPAA (OR, 2.0; 95% CI, 0.06–0.61).[48]

Question 9. In adult outpatients with pouchitis who have inadequate response to antibiotics, what is the effectiveness of corticosteroids?

Recommendation 9. In patients with ulcerative colitis who have undergone IPAA, and experience recurrent pouchitis with inadequate response to antibiotics (commonly referred to as *chronic antibiotic-refractory pouchitis*), the AGA suggests using corticosteroids (Conditional recommendation, very low certainty of evidence)

Implementation considerations

- Controlled ileal-release budesonide is the preferred corticosteroid formulation.
- Corticosteroids should generally be used for a short duration (<8–12 weeks) with consideration of steroid-sparing therapies for long-term use.
- The panel suggests endoscopic evaluation of the pouch with confirmation of inflammation and ruling out alternative etiologies in patients with recurrent pouchitis.

Summary and Certainty of the Evidence—We identified two cases series,[82, 83] including a total of 30 patients with antibiotic-refractory pouchitis, who received oral beclomethasone (n=10) or oral budesonide therapy (n=20). Of these, 23 patients achieved clinical response, leading to a pooled response rate of 77% (95% CI, 58–88%). With a hypothetical spontaneous improvement rate of 30% (range, 20–40%) in patients with recurrent episodes of pouchitis with inadequate response to antibiotics, corticosteroids are associated with 2.3-fold higher likelihood of achieving clinical response (RR, 2.30; 95% CI, 1.91–3.83). The overall body of evidence was rated as very low certainty, derived primarily from observational studies, at high risk of bias with use of non-standard outcome metrics, clinical inconsistency due to diversity of patients evaluated, along with varying levels of disease severity and antibiotic-refractoriness, and use of a hypothetical spontaneous improvement rate, and imprecision, due to very low event rate (Table 10A).

Benefits and Harms (Downsides)—Improvement in symptoms of pouchitis symptoms is an important benefit of corticosteroids, for example, when using an interim therapy to bridge to more advanced immunosuppressive therapies. However, these benefits are to be weighed against potential harms associated with repeated and/or prolonged courses of corticosteroid therapy, especially when using systemic corticosteroids.

Rationale—There is paucity of evidence on the effectiveness of corticosteroids in patients with chronic antibiotic-refractory pouchitis, with only two reported case series with 30 patients. Considering the effectiveness of corticosteroid therapy in patients with UC and CD, it would be reasonable to consider for short-term symptomatic management. While we did not identify any specific studies on rectal corticosteroids, corticosteroid foam or enema formulations may also be effective. When initiating corticosteroids, careful discussion and planning for steroid-sparing therapy should be initiated. Use of, and responsiveness to, corticosteroids is not mandatory prior to switching to advanced immunosuppressive

therapies in patients with chronic antibiotic-refractory pouchitis and objective evidence of inflammation of the pouch. Given that budesonide, which undergoes first pass metabolism in the liver and is therefore better tolerated and safer than other systemic corticosteroids, has been studied in the context of pouchitis, and is released in the terminal ileum which is used to create the pouch, we suggest its use over other corticosteroids. The long-term use of budesonide in CD appears to be safe.[84]

Question 10. In adult outpatients with pouchitis who have inadequate response to antibiotics, what is the effectiveness of mesalamine?

Recommendation 10. In patients with ulcerative colitis who have undergone IPAA, and experience with recurrent pouchitis with inadequate response to antibiotics (commonly referred to as *chronic antibiotic-refractory pouchitis*), the AGA suggests against the use of mesalamine for treatment of pouchitis (*No recommendation, knowledge gap).*

Implementation considerations

- While sulfasalazine may be effective in patients with infrequent episodes of pouchitis, its effectiveness in patients with chronic antibiotic-refractory pouchitis is unknown.

Summary and Certainty of the Evidence—We did not identify any studies evaluating the effectiveness of mesalamine for the treatment of pouchitis. We identified one case series evaluating the use of sulfasalazine in the treatment of acute pouchitis, where acute pouchitis was defined as a PDAI > 7 lasting less than 4 weeks.[85] As such, the patients treated in this cohort did not necessarily have antibiotic-dependent or antibiotic-refractory pouchitis. In this pilot study of 11 patients, where patients received sulfasalazine 3g by mouth daily (1g three times per day), all 11 patients achieved clinical response at the 8-week outcome assessment. With a hypothetical spontaneous improvement rate of 40% (range, 30–50%) sulfasalazine may be associated with 2.5-fold higher likelihood of clinical improvement (RR, 2.50; 95% CI, 2.00–3.33). The overall certainty of evidence was rated as very low, rated down for risk of bias in a small case series, indirectness (effectiveness would likely be lower in patients with chronic antibiotic-refractory pouchitis, compared with patients included in this trial with acute pouchitis), and imprecision due to very low event rate (Table 10B).

Benefits and Harms (Downsides)—Mesalamine is a very safe medication; however, there is paucity of evidence attesting to its effectiveness in patients with pouchitis, particularly those with antibiotic-refractory pouchitis. The use of mesalamine for the treatment of recurrent or chronic pouchitis may potentially delay the initiation of potentially more effective therapies. The potential benefits of sulfasalazine demonstrated in this pilot study indicate that sulfasalazine may have a role in the treatment of acute pouchitis. Whether this extends to the treatment of antibiotic-refractory pouchitis is unknown. Additionally, there may be harms related to the use of sulfasalazine itself including known adverse effects such as headache, nausea, rash, fever, and reversible issues with male fertility, and need for frequent laboratory monitoring.[86]

Rationale—The effects of sulfasalazine in the treatment of pouchitis may be due to inherent properties of sulfasalazine, including the potential anti-microbial effect of the sulfa components of sulfasalazine. Thus, it is unknown whether these same benefits will extend to mesalamine, or to patients with antibiotic-refractory pouchitis.

TREATMENT OF CROHN'S-LIKE DISEASE OF THE POUCH

Question 11. In adult outpatients with Crohn's-like disease of the pouch, what is the effectiveness of corticosteroids?

Recommendation 11. In patients with ulcerative colitis who have undergone IPAA, and develop symptoms due to Crohn's-like disease of the pouch, the AGA suggests using corticosteroids (*Conditional recommendation, very low certainty of evidence*)

Implementation considerations

- Controlled ileal-release budesonide is the preferred corticosteroid formulation.
- Corticosteroids should generally be used for a short duration (<8 weeks) with consideration of steroid-sparing therapies for long-term use.
- The panel suggests endoscopic evaluation of the pouch to confirm Crohn's-like disease of the pouch.

Summary and Certainty of the Evidence—We did not identify any studies on the effectiveness or safety of corticosteroids for Crohn's-like disease of the pouch. Based on indirect data on the effectiveness of corticosteroids in patients with moderate to severe luminal CD, very low certainty evidence suggests it would be effective in patients with Crohn's-like disease of the pouch.[87]

Benefits and Harms (Downsides)—Improvement in symptoms due to Crohn's-like disease of the pouch is an important benefit of corticosteroids, for example, when using an interim therapy to bridge to more advanced therapies. However, these benefits are to be weighed against potential harms associated with repeated and/or prolonged courses of corticosteroid therapy, especially when using systemic corticosteroids.

Rationale—There is paucity of evidence on the effectiveness of corticosteroids in patients with Crohn's-like disease of the pouch. However, given extensive experience and evidence on the efficacy of systemic steroids as well as high first-pass metabolism corticosteroids such as controlled ileal release budesonide in patients with luminal CD, these medications are likely to be effective in the management of Crohn's-like disease of the pouch.

Question 12. In adult outpatients with Crohn's-like disease of the pouch, what is the effectiveness of advanced therapies (biologics and oral small molecule drugs)?

Recommendation 12. In patients with ulcerative colitis who have undergone IPAA and develop symptoms due to Crohn's-like disease of the pouch, the AGA suggests using

advanced immunosuppressive therapies (*Conditional recommendation, very low certainty of evidence*).

Implementation considerations

- Immunosuppressive therapies approved for treatment of UC or CD may be used, including TNFα antagonists (infliximab, adalimumab, golimumab, certolizumab pegol), vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib.
- Advanced therapies that patients have used prior to colectomy may be reconsidered.
- A subset of patients may continue to require chronic antibiotics for associated pouchitis and ongoing symptom management despite the use of advanced immunosuppressive therapies.
- The panel suggests endoscopic evaluation of the pouch to confirm Crohn's-like disease of the pouch.

Summary and Certainty of the Evidence—We identified 10 cohort studies or case series examining the use of advanced therapies in the treatment of Crohn's-like disease of the pouch.[53, 54, 88–95] Across these studies, the most common diagnostic criteria for Crohn's-like disease of the pouch included one of the following features: a fistula or fistulae that occur 6–12 months after IPAA, the presence of a structure in the pre-pouch ileum or pouch inlet, or the presence of pre-pouch ileitis.[10] In these studies, clinical response was generally defined based on physician's global assessment. However, in the assessment of clinical response in patients with a fistula, a marked improvement in fistula drainage was often included in this definition of response as well. Of 288 patients evaluated, the pooled response rate with advanced immunosuppressive therapies for Crohn's-like disease of the pouch was 74% (95% CI, 68–79) (eFigure 5). With a hypothetical spontaneous improvement rate of 30% (range, 20–40%), in patients with Crohn's-like disease of the pouch, patients treated with advanced immunosuppressive therapies were 2.5-fold more likely to achieve clinical response (RR, 2.49; 95% CI, 1.87–3.73). This body of evidence is also supported by the established efficacy of advanced immunosuppressive therapies in patients' luminal and fistulizing CD. The overall body of evidence was rated as very low certainty, derived primarily from observational studies, at high risk of bias with use of non-standard outcome metrics, inconsistency due to diversity of patients evaluated, with varying levels of disease severity and prior treatment exposures, and use of a hypothetical spontaneous improvement rate (Table 11).

Benefits and Harms (Downsides)—The potential benefits of advanced immunosuppressive therapies in the treatment of Crohn's-like disease of the pouch are observed high rates of clinical response, across different classes of therapies in published studies. There is considerable experience with advanced immunosuppressive therapies for Crohn's disease, and borrowing from this body of evidence, these therapies are associated with increase in risk of serious infections, malignancies such as lymphoma and drug-specific

side effects, with risk varying between different therapies. Adverse events unique to the use of these advanced therapies in patients with Crohn's-like disease of the pouch have not been identified.

Rationale—An estimated 10% of patients will develop Crohn's-like disease of the pouch after proctocolectomy with IPAA for UC. Patients do not have to be diagnosed with acute pouchitis (and then chronic pouchitis) to progress to a diagnosis of Crohn's-like disease of the pouch. Some patients may initially present with strictures, fistulae or more advanced disease indicating a Crohn's-like disease phenotype rather than intermittent pouch inflammation typical of pouchitis. Other patients with Crohn's-like disease of the pouch may have concomitant chronic antibiotic-responsive pouchitis who will still respond to antibiotic therapy and require antibiotics intermittently for symptom management while being treated with an advanced therapy. These points highlight our limited understanding of both the disease process and the management of Crohn's-like disease of the pouch. In these patients, akin to luminal CD, advanced immunosuppressive therapies are effective for management. The evidence base supporting the use of advanced therapies is based on case series or cohort studies. No RCTs focusing on patients with Crohn's-like disease of the pouch were identified. This is likely because of limited understanding of this entity, including its pathophysiology, and lack of agreement on nomenclature, definition, endoscopic and other diagnostic features limit standardization of inclusion and outcome measures.

Whether an advanced therapy or mechanism of action that was used pre-colectomy for the treatment of UC can be re-used if a patient develops Crohn's-like disease of the pouch is unknown at this time, and thus it may be reasonable to reconsider those advanced therapies that were not previously effective in the treatment of UC. It is also recognized that in many cases, patients treated for Crohn's-like disease of the pouch will continue to require antibiotic therapy for concomitant pouchitis and symptom control, even when on advanced therapies.

TREATMENT OF CUFFITIS

Question 13. In adult outpatients with cuffitis, what is the effectiveness of pharmacological management?

Recommendation 13. In patients with ulcerative colitis who have undergone IPAA, and develop symptoms due to cuffitis, the AGA suggests using therapies that have been approved for the treatment of ulcerative colitis, including topical 5-aminosalicylates, topical corticosteroids, etc. (*Conditional recommendation, very low certainty of evidence*)

Implementation considerations

- In patients with cuffitis, topical therapies should be the first-line therapy, such as mesalamine suppositories, corticosteroid suppositories or corticosteroid ointment applied directly to the cuff.
- In patients with refractory cuffitis, immunosuppressive therapies approved for treatment of ulcerative colitis may be used, including TNFα antagonists

(infliximab, adalimumab, golimumab, certolizumab pegol), vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib.

Summary and Certainty of the Evidence—There is paucity of direct data on the effectiveness of medical therapies for cuffitis. However, since the cuff is a remnant of the rectal mucosa after colectomy and ileal pouch anal anastomosis creation in UC, we extrapolated data from the prior AGA guidelines on the management of mild-moderate and moderate-severe UC to cuffitis.[96] Based on indirect evidence, therapies approved for UC including topical and oral 5-ASA, topical and oral corticosteroids, thiopurines and advanced immunosuppressive therapies may be effective for the management of cuffitis.

Benefits and Harms (Downsides)—The benefits and harms of each treatment would have to be individualized, considering the severity of cuffitis, impact on quality of life, effectiveness and safety of treatment option and patient preference.

Rationale—Even though there are very limited studies on the management of cuffitis, it is likely similar to UC due to its underlying pathophysiology and is limited to a very short segment of the rectum. Use of oral or topical therapies, including topical corticosteroid cream applied directly to the cuff, besides suppositories may be effective in patients with mild to moderate symptoms of cuffitis. Cuffitis may often co-exist with pouchitis, and hence, treatment approach should be modified depending on predominant source of symptoms, and often requires therapies directed towards both cuffitis and pouchitis.

FUTURE DIRECTIONS

Even though pouchitis is relatively common after IPAA for UC, we observed that most of the evidence informing these guidelines was low to very low quality, derived from case series or small cohort studies, and several knowledge gaps exist. Several initiatives towards improving management of inflammatory pouch disorders are already underway. However, concerted efforts in key domains are central towards improving patient care. Key research and clinical gaps that will inform the field in the future include:

1. **Standardization of disease entities**: Several inflammatory and non-inflammatory disorders of the pouch are poorly defined, and for these guidelines, we relied on functional definitions based primarily on response to existing therapies. A deeper understanding of disease pathophysiology and clinical and endoscopic presentations will allow better controlled studies, and a more optimal categorization of diseases and treatment approaches. These include entities like chronic antibiotic-dependent pouchitis, chronic antibiotic-refractory pouchitis and Crohn’s-like disease of the pouch.
2. **Natural history and risk factors for inflammatory disorders of the pouch**: A deeper understanding of the natural history of pouches in patients with IPAA for UC, as well as evolution of intermittent and chronic pouchitis and Crohn’s-like disease of the pouch is warranted. Risk factors associated with the development of each of these entities may facilitate early intervention to prevent development

of these disorders, or more effective treatment to avoid disability; factors predictive of response to different therapies, likewise, can be very effective. This includes assessing the relevance of persistent inflammation in the pouch, in the absence of symptoms, and non-inflammatory drivers of symptoms in patients with IPAA. Additionally, the role of environmental exposures including diet on the disease course after IPAA remain a relatively unexplored area.

3. **Improving clinical trial design in pouchitis**: There was a marked paucity of well-conducted clinical trials in patients with pouchitis, with inclusion of highly heterogeneous patient groups, variable and non-validated disease activity indices and non-standard outcome definitions (such clinical improvement and clinical remission with or without ongoing use of antibiotics; endoscopic remission, etc.). More recently, with the publication of the pivotal EARNEST trial, there has been a move towards more standardized evaluation of pouchitis, development of disease activity indices (such as the Atlantic Pouchitis Index) and outcome definitions. Besides efficacy trials, large pragmatic trials comparing different therapies such as use of chronic antibiotics vs. advanced immunosuppressive therapies in patients with chronic antibiotic-dependent pouchitis, primary and secondary prevention strategies in patients at high risk of pouchitis, etc. are warranted. In lieu of trials, real-world evidence with well-conducted observational comparative effectiveness studies using prospective registries can also enrich the evidence. Non-invasive monitoring tests of pouch disorders can facilitate effectiveness trials.

What do other societal guidelines say?

There have been no recent societal guidelines published on the management of pouchitis. The most recent European Crohn's and Colitis Organization guidelines covered the management of pouchitis in the "Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis" published in 2017. Consistent with our guidelines, ECCO guidelines recommended the use of ciprofloxacin or metronidazole for acute pouchitis, and combination of two antibiotics, oral budesonide, oral beclomethasone dipropionate, infliximab or adalimumab for management of chronic pouchitis. However, these guidelines did not explicitly provide recommendations on primary or secondary prevention of pouchitis, role of chronic or alternative antibiotic therapy, other advanced immunosuppressive medications, or on the management of Crohn's-like disease of the pouch.

Plans for updating this guideline

Guidelines are living products. To remain useful, they need to be updated regularly as new information accumulates. This document will be updated when major new research is published. The need for update will be determined no later than 2027 and, if appropriate, we will provide rapid guidance updates to incorporate updated recommendations as new evidence, without duplicating or creating a new comprehensive guideline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Focused questions and corresponding PICOs being addressed in the guidelines

Focused question	Patients	Interventions	Comparator	Outcome
PREVENTION OF POUCHITIS				
In patients who undergo ileal pouch anal anastomosis for ulcerative colitis, what is the effectiveness of probiotics or antibiotics for the primary prevention of pouchitis?	Patients who undergo ileal pouch anal anastomosis for ulcerative colitis	• Probiotics • Antibiotics	Placebo/no treatment	Prevention of pouchitis
TREATMENT OF POUCHITIS				
In adult outpatients with pouchitis, what is the effectiveness of antibiotics for treatment of pouchitis?	Adult outpatients with pouchitis	• Ciprofloxacin • Amoxicillin/clavulanic acid • Rifaximin • Metronidazole • Vancomycin • Other antibiotics	Placebo/no treatment, alternative antibiotics	• Symptomatic improvement
In adult outpatients with pouchitis, what is the effectiveness of probiotics for treatment of pouchitis?	Adult outpatients with pouchitis	• Single-strain or multi-strain probiotics	Placebo/no treatment	• Symptomatic improvement
In adult outpatients with pouchitis, what is the effectiveness of probiotics for prevention of recurrent pouchitis?	Adult outpatients with recurrent pouchitis	• Single-strain or multi-strain probiotics	Placebo/no treatment	• Recurrence of pouchitis
In adult outpatients with pouchitis who have adequate response to antibiotics, but relapse shortly after stopping antibiotics, what is the effectiveness of using chronic antibiotic therapy or advanced immunosuppressive therapies to prevent recurrent pouchitis?	Adult outpatients with pouchitis, who have adequate response to antibiotics, but relapse shortly after stopping antibiotics	• Chronic antibiotic therapy • Advanced immunosuppressive therapies (TNF antagonists including infliximab, adalimumab, golimumab, certolizumab pegol, vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib)	Placebo/no treatment	• Symptomatic improvement
In adult outpatients with pouchitis who have inadequate response to antibiotics, what is the effectiveness of advanced immunosuppressive therapies, corticosteroids or mesalamine?	Adult outpatients with pouchitis who have inadequate response to antibiotics	• Advanced immunosuppressive therapies (TNF antagonists including infliximab, adalimumab, golimumab, certolizumab pegol, vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib) • Corticosteroids (budesonide, prednisone or equivalent) • Mesalamine	Placebo/no treatment	• Symptomatic improvement

Focused question	Patients	Interventions	Comparator	Outcome
TREATMENT OF CROHN'S DISEASE OR CROHN'S-LIKE DISEASE OF THE POUCH				
In adult outpatients with Crohn's-like disease of the pouch, what is the effectiveness of corticosteroids, or advanced immunosuppressive therapies?	Adult outpatients with Crohn's-like disease of the pouch	• Corticosteroids (budesonide, prednisone or equivalent) • Advanced immunosuppressive therapies (TNF antagonists including infliximab, adalimumab, golimumab, certolizumab pegol, vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib)	Placebo/no treatment	• Symptomatic improvement
TREATMENT OF CUFFITIS				
In adult outpatients with cuffitis, what is the effectiveness of pharmacological management?	Adult outpatients with cuffitis	Oral and/or rectal mesalamine, rectal corticosteroids, UC-directed therapies including advanced immunosuppressive therapies	Placebo/no treatment	• Symptomatic improvement

Table 2.

Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessment, Development and Evaluation Framework

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with their values and preferences. Use shared-decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will involve various stakeholders. Performance measures should assess whether decision making is appropriate.

Table 3.

Executive summary of recommendations for the management of pouchitis and inflammatory pouch disorders

PREVENTION OF POUCHITIS
1. In patients with ulcerative colitis who undergo IPAA, the AGA makes no recommendation in favor of, or against, the use of probiotics for primary prevention of pouchitis*(No recommendation, very low certainty of evidence)* *Implementation Consideration* • There is a need for better evidence from clinical trials to inform the use of probiotics as a primary prevention strategy for pouchitis, especially given the potential cost and burden of long-term use with limited data on potential benefits.
2. In patients with ulcerative colitis who undergo IPAA, the AGA suggests against using antibiotics for the primary prevention of pouchitis*(Conditional recommendation, very low certainty of evidence)* *Implementation Consideration* • There is a need for better evidence from clinical trials to inform the use of antibiotics as a primary prevention strategy for pouchitis, especially given the potential side effects and burden of long-term use with limited data on potential benefits.
TREATMENT OF POUCHITIS
3. In patients with ulcerative colitis who have undergone IPAA and experience symptoms of pouchitis, the AGA suggests using antibiotics for treatment of pouchitis*(Conditional recommendation, very low certainty of evidence)* *Implementation Considerations* • Based on available evidence, ciprofloxacin and/or metronidazole are the preferred antibiotics for treatment of pouchitis. • The typical duration of antibiotic therapy for the treatment of pouchitis is 2–4 weeks. • An approach using a combination of antibiotics may be more effective in patients who do not respond to single antibiotic therapy. • Alternative antibiotic regimens, such as oral vancomycin, may be considered in patients who do not respond to initial course of antibiotics, or have allergies or intolerance to ciprofloxacin and/or metronidazole.
4. In patients with ulcerative colitis who have undergone IPAA and experience symptoms of pouchitis, the AGA makes no recommendation in favor of, or against, the use of probiotics for the treatment of pouchitis*(No recommendation, very low certainty of evidence)*
5. In patients with ulcerative colitis who have undergone IPAA and experience episodes of recurrent pouchitis that responds to antibiotics, the AGA suggests using probiotics for preventing recurrent pouchitis*(Conditional recommendation, very low certainty of evidence)* **Comment**: Patients, particularly those with infrequent episodes of recurrent pouchitis or where the burden of long-term probiotic treatment is excessive, may reasonably choose avoiding any treatment to prevent recurrence of pouchitis. *Implementation consideration* • De Simone formulation of multi-strain probiotics was used in clinical trials of prevention of pouchitis
6. In patients with ulcerative colitis who have undergone IPAA, and experience recurrent pouchitis which responds to antibiotics but relapses shortly after stopping antibiotics (commonly referred to as *chronic antibiotic-dependent pouchitis*), the AGA suggests using chronic antibiotic therapy to treat recurrent pouchitis*(Conditional recommendation, very low certainty of evidence)* *Implementation consideration* • The panel suggests endoscopic evaluation of the pouch with confirmation of inflammation and ruling out alternative etiologies in patients with recurrent pouchitis.

- Lowest effective dose of antibiotics (for example, ciprofloxacin 500mg daily or 250mg twice daily) with intermittent gap periods (such as approximately one week/month), or use of cyclical antibiotics (such as rotating between ciprofloxacin, metronidazole, vancomycin, etc. every 1–2 weeks) may be considered to decrease risk of antimicrobial resistance.

7. In patients with ulcerative colitis who have undergone IPAA, and experience recurrent pouchitis which responds to antibiotics but relapses shortly after stopping antibiotics (commonly referred to as *chronic antibiotic-dependent pouchitis*), the AGA suggests using advanced immunosuppressive therapies to treat recurrent pouchitis*(Conditional recommendation, low certainty of evidence for vedolizumab and very low certainty of evidence for other advanced immunosuppressive therapies)*
Implementation consideration

- The panel suggests endoscopic evaluation of the pouch with confirmation of inflammation and ruling out alternative etiologies in patients with recurrent pouchitis.
- Advanced immunosuppressive therapies approved for treatment of UC or CD may be used, including TNF antagonists (infliximab, adalimumab, golimumab, certolizumab pegol), vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib.
- Advanced immunosuppressive therapies may be used in lieu of chronic, continuous antibiotic therapy, particularly in patients who are intolerant to antibiotics or where patients and/or providers are concerned about risks of long-term antibiotic therapy.
- Advanced immunosuppressive therapies that patients have used prior to colectomy may be reconsidered

8. In patients with ulcerative colitis who have undergone IPAA, and experience recurrent pouchitis with inadequate response to antibiotics (commonly referred to as *chronic antibiotic-refractory pouchitis*), the AGA suggests using advanced immunosuppressive therapies*(Conditional recommendation, low certainty of evidence for vedolizumab and very low certainty of evidence for other advanced immunosuppressive therapies)*
Implementation considerations

- The panel suggests endoscopic evaluation of the pouch with confirmation of inflammation and ruling out alternative etiologies in patients with recurrent pouchitis.
- Immunosuppressive therapies approved for treatment of ulcerative colitis or Crohn's disease may be used, including TNF antagonists (infliximab, adalimumab, golimumab, certolizumab pegol), vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib.
- Advanced therapies that patients have used prior to colectomy may be reconsidered.
- A subset of patients may continue to derive partial symptomatic benefit from antibiotics and may benefit from ongoing use of antibiotics besides advanced immunosuppressive therapies.

9. In patients with ulcerative colitis who have undergone IPAA, and experience recurrent pouchitis with inadequate response to antibiotics (commonly referred to as *chronic antibiotic-refractory pouchitis*), the AGA suggests using corticosteroids*(Conditional recommendation, very low certainty of evidence)*
Implementation considerations

- The panel suggests endoscopic evaluation of the pouch with confirmation of inflammation and ruling out alternative etiologies in patients with recurrent pouchitis.
- Controlled ileal-release budesonide is the preferred corticosteroid formulation
- Corticosteroids should generally be used for a short duration (<8 weeks) with consideration of steroid-sparing therapies for long-term use

10. In patients with ulcerative colitis who have undergone IPAA, and experience with recurrent pouchitis with inadequate response to antibiotics (commonly referred to as *chronic antibiotic-refractory pouchitis*), the AGA suggests against the use of mesalamine for treatment of pouchitis*(Conditional recommendation, very low certainty of evidence)*
Implementation considerations

- While sulfasalazine may be effective in patients with infrequent episodes of pouchitis, its effectiveness in patients with chronic antibiotic-refractory pouchitis is unknown.

TREATMENT OF CROHN'S-LIKE DISEASE OF THE POUCH

11. In patients with ulcerative colitis who have undergone IPAA and develop symptoms due to Crohn's-like disease of the pouch, the AGA suggests using corticosteroids*(Conditional recommendation, very low certainty of evidence)*
Implementation considerations

- The panel suggests endoscopic evaluation of the pouch to confirm Crohn's-like disease of the pouch.

- Controlled ileal-release budesonide is the preferred corticosteroid formulation.
- Corticosteroids should generally be used for a short duration (<8 weeks) with consideration of steroid-sparing therapies for long-term use

12. In patients with ulcerative colitis who have undergone IPAA and develop symptoms due to Crohn's-like disease of the pouch, the AGA suggests using advanced immunosuppressive therapies*(Conditional recommendation, very low certainty of evidence)*

Implementation considerations

- The panel suggests endoscopic evaluation of the pouch to confirm Crohn's-like disease of the pouch.
- Immunosuppressive therapies approved for treatment of ulcerative colitis or Crohn's disease may be used, including TNFα antagonists (infliximab, adalimumab, golimumab, certolizumab pegol), vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib.
- Advanced therapies that patients have used prior to colectomy may be reconsidered.
- A subset of patients may continue to require chronic antibiotics for associated pouchitis and ongoing symptom management despite the use of advanced immunosuppressive therapies.

TREATMENT OF CUFFITIS

13. In patients with ulcerative colitis who have undergone IPAA, and develop symptoms due to cuffitis, the AGA suggests using therapies that have been approved for the treatment of ulcerative colitis, including topical 5-aminosalicylates, topical corticosteroids, etc.*(Conditional recommendation, very low certainty of evidence)*

Implementation considerations

- In patients with refractory cuffitis, topical therapies should be the first approach to management.
- In patients with refractory cuffitis, immunosuppressive therapies approved for treatment of ulcerative colitis may be used, including TNF antagonists (infliximab, adalimumab, golimumab, certolizumab pegol), vedolizumab, ustekinumab, risankizumab, ozanimod, tofacitinib and upadacitinib.

Table 4.

Key overarching considerations in the management of patients with pouchitis and inflammatory disorders of the pouch

1. Normal bowel function after IPAA for UC, and symptoms suggestive of pouchitis: After an initial period of postoperative adjustment, patients can expect to average 4–8 bowel movements per day and 1–2 bowel movements per night. Symptoms of pouchitis typically include increased stool frequency, urgency, abdominal pain or cramping, or pelvic discomfort. Clinical symptoms of pouchitis do not necessarily correlate with findings on endoscopy or histology.
2. Endoscopic evaluation in patients with pouch disorders: • Endoscopic evaluation of the pouch should be performed in patients experiencing frequent recurrent episodes of pouchitis (suspected chronic antibiotic-dependent pouchitis), in patients with inadequate response to antibiotics before considering other therapies (suspected chronic antibiotic-refractory pouchitis), in patients experiencing atypical symptoms of pouchitis, and when the diagnosis of Crohn's-like disease of the pouch is being considered. • Routine endoscopic evaluation of the pouch to confirm pouch inflammation in patients experiencing typical symptoms of pouchitis, prior to initiation of antibiotics, or in patients who experience infrequent episodes of pouchitis that respond to typical management, may not be required, although it may provide additional information on disease severity in this setting
3. **Treatment goals and targets in patients with pouch disorders:** The overall goal of treating patients with pouchitis is resolution of symptoms. Endoscopic and/or histologic resolution of inflammation was not considered a critical treatment goal at this time due to lack of data on the additional benefits of achieving these goals. By extension, asymptomatic patients who have endoscopic evidence of inflammation of the pouch may not routinely warrant treatment.
4. **Alternative etiologies for patients with pouch disorders:** In patients with atypical symptoms of pouchitis, or with inadequate response to conventional therapy or recurrent symptoms of pouchitis, alternative etiologies of symptoms should be considered. These include: *Clostridioides difficile* infection of the pouch, mechanical obstructions such as strictures at the ileo-anal anastomosis or the pouch inlet or stoma takedown site (about 20–40cm proximal to pouch inlet), non-relaxing pelvic floor dysfunction, etc.

Table 5.

Pragmatic definitions of inflammatory pouch disorders.

A. Intermittent pouchitis was defined as isolated and infrequent episodes of typical pouchitis symptoms that improved with therapy (most commonly, antibiotics) or spontaneously, followed by resolution of symptoms and periods of normal pouch function.
B. Chronic antibiotic-dependent pouchitis was defined recurrent episodes of pouchitis that responds to antibiotic therapy but relapses shortly after stopping antibiotics (typically within days to weeks), and often require recurrent or continuous antibiotic therapy or other advanced therapies to achieve symptom control. We did not define this entity based on a specific number of pouchitis episodes within a 12-month time period, since this is a continuum (some patients require 3–4 courses of antibiotics per year, and others require almost continuous antibiotics) and patients' and providers' preferences for treatment approach vary depending on their disease.
C. Chronic antibiotic-refractory pouchitis was defined as relapsing-remitting or continuous symptoms of pouchitis with inadequate response to typical antibiotic therapy, often needing escalation to other therapies.
D. Crohn's-like disease of the pouch was defined based on the most common and accepted diagnostic criteria for this condition, recognizing variability in prior literature. These diagnostic criteria included presence of a perianal or other fistula that developed at least 12 months postoperatively, stricture of the pouch body or pre-pouch ileum, and the presence of pre-pouch ileitis. Pouchitis may often co-exist in patients with Crohn's-like disease of the pouch.

Table 6.

GRADE Evidence Profile for PICO #1, comparing (A) probiotics and (B) antibiotics for primary prevention of pouchitis

A. PROBIOTICS compared with placebo for primary prevention of pouchitis

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With probiotics	Relative effect (95% CI)	Risk with placebo	Risk difference with probiotics
Prevention of pouchitis (follow-up: range 6 months to 12 months)											
70 (3 RCTs)	serious[1]	not serious	not serious	very serious[2]	publication bias strongly suspected[3]	⨁◯◯◯ Very low	14/34 (34.1%)	4/36 (8.5%)	**RR 0.18** (0.05 to 0.62)	412 per 1,000	**338 fewer per 1,000** (from 391 fewer to 156 fewer)

CI: confidence interval; **RR:** risk ratio
1-Unclear risk of bias in >2/6 domains in 2/3 RCTs
2-Very low event rate, <35 events, rate down twice for lack of optimal information size
3-Suspected publication bias, given 2/4 trials have only been published as conference proceedings

B. ANTIBIOTICS compared with placebo for primary prevention of pouchitis

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With probiotics	Relative effect (95% CI)	Risk with placebo	Risk difference with probiotics
Prevention of pouchitis (follow-up: 12 months)											
38 (1 RCT)	serious[1]	not serious	not serious	very serious[2]	publication bias strongly suspected[3]	⨁◯◯◯ Very low	5/13 (38.5%)	2/25 (8.0%)	**RR 0.21** (0.05 to 0.93)	385 per 1,000	**304 fewer per 1,000** (from 365 fewer to 27 fewer)

CI: confidence interval; **RR:** risk ratio
1-Unclear risk of bias across 4/6 domains, published only as abstract
2-Very low event rate, <35 events, rate down twice for lack of optimal information size
3-Suspected publication bias, trial only published as conference proceeding

Table 7.

GRADE Evidence Profile for PICO #2, comparing antibiotics vs. no treatment for treatment of pouchitis

Antibiotics compared with no treatment for pouchitis

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**With placebo**	**With probiotics**	**Relative effect (95% CI)**	**Risk with placebo**	**Risk difference with probiotics**
Treatment of pouchitis (follow-up: 8–16 weeks)											
239 (12 cohorts)	Serious[1]	Serious[2]	Not serious[3]	Not serious	None	⨁◯◯◯ Very Low	40% (30% −50%)	160/239	**RR 1.67** (1.34–2.01)	400 per 1,000	**268 more per 1,000** (from 136 more to 404 more)

CI:confidence interval; **RR:**risk ratio

1- Risk of bias due to non-standard outcome metrics (usually physician global assessment), selective inclusion of patients

2- high statistical and clinical heterogeneity (diverse patients, with varying level of disease severity/antibiotic-refractoriness)

3- No clear control group for comparison, hence using hypothetical placebo/spontaneous response rates

Table 8.

GRADE Evidence Profile for PICO #3 and #4, evaluating probiotics for (A) treatment of pouchitis, and (B) prevention of recurrent pouchitis

Probiotics compared with no treatment for treatment and secondary prevention of pouchitis

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no treatment	With probiotics	Relative effect (95% CI)	Risk with placebo	Risk difference with antibiotics
Treatment of acute pouchitis (follow-up: 4–12 weeks)											
84 (2 cohorts + 1 RCT)	Serious[1]	Serious[2]	Not serious[3]	Serious[3]	Serious[4]	⨁◯◯◯ Very low	40% (30–50%)	47/84	**RR 1.40** (1.12 to 1.86)	400 per 1,000	**160 more per 1,000** (from 48 more to 344 more)
Preventing relapse of pouchitis after response to antibiotics (follow-up: 6–12 months)											
3 RCTs	Not serious	Not serious	Not serious	Serious[5]	Serious[4]	⨁⨁◯◯ Low	36/41	6/45	**0.17** (0.09–0.34)	887 per 1000	**729 fewer per 1000** (from 799 fewer to 580 fewer)

CI:confidence interval; **RR:**risk ratio

[1]-Risk of bias due to non-standard outcome metrics (usually physician global assessment), selective inclusion of patients

[2]-high statistical and clinical heterogeneity (differences in probiotics, outcome measures)

[3]-No clear control group for comparison, hence using hypothetical placebo/spontaneous response rates; low event rate, <220 events, rate down once for lack of optimal information size

[4]-Clinical experience does not match what is observed in published studies, significant paucity of published data – high suspicion of publication bias

[5]-Low event rate, <220 events, rate down once for lack of optimal information size

Table 9.

GRADE Evidence Profile for PICO #5 and #6, evaluating advanced immunosuppressive therapies for treatment of antibiotic-dependent and antibiotic-refractory pouchitis

ADVANCED THERAPIES compared to no treatment for antibiotic-dependent or antibiotic-refractory pouchitis

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With advanced therapies	Relative effect (95% CI)	Risk with placebo	Risk difference with advanced therapies
Treatment of recurrent pouchitis (follow-up: range 8–16 weeks)											
560 (31 cohorts)	Serious[1]	Serious[2]	Not serious[3]	Not serious	None	⨁◯◯◯ Very Low	30% (20% −40%)	287/560	**RR 1.71** (1.28 to 2.56)	300 per 1,000	**213 more per 1,000** (from 84 more to 468 more)
102 (1 RCT of vedolizumab)	Not serious	Not serious	Not serious	Very serious[4]	None	⨁⨁◯◯ Low	10% (5/51)	18/51	**RR 3.60** (1.45 to 8.96)	10 per 1,000	**255 more per 1,000** (from 44 more to 780 more)

CI:confidence interval; **RR:**risk ratio

[1]-Risk of bias due to non-standard outcome metrics

[2]-high statistical and clinical heterogeneity (diverse patients, with varying level of disease severity/antibiotic-refractoriness)

[3]-No clear control group for comparison, hence using hypothetical placebo/spontaneous response rates

[4]-Very low event rate (n=23)

Table 10.

GRADE Evidence Profile for PICO #6, evaluating (A) corticosteroids and (B) mesalamine for treatment of antibiotic-dependent and antibiotic-refractory pouchitis

A. Corticosteroids compared with no treatment for antibiotic-dependent or antibiotic-refractory pouchitis

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no treatment	With corticosteroids		Risk with placebo	Risk difference with corticosteroids
Treatment of recurrent pouchitis (follow-up: 4–12 weeks)											
30 (2 case series of budesonide)	Serious[1]	Not serious	Serious[2]	Serious[3]	None	⨁◯◯◯ Very Low	30% (20% −40%)	23/30	**RR 2.30** (1.91–3.83)	300 per 1,000	**390 more per 1,000** (from 273 more to 849 more)

1-Risk of bias due to non-standard outcome metrics
2-No clear control group for comparison, hence using hypothetical placebo/spontaneous response rates
3-low event rate, <220 events, rate down once for lack of optimal information size

B. 5-ASA compared with no treatment for antibiotic-dependent or antibiotic-refractory pouchitis

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no treatment	With 5-ASA		Risk with placebo	Risk difference with 5-ASA
Treatment of pouchitis (follow-up: 8 weeks)											
11 (1 case series of sulfasalazine)	Serious[1]	Not serious	Very serious[2]	Serious[3]	None	⨁◯◯◯ Very Low	30% (20% −40%)	11/11	**RR 3.33** (2.50–5.00)	300 per 1,000	**699 more per 1,000** (from 450 more to 1000 more)

1-Risk of bias due to non-standard outcome metrics
2-Patient population consisted of patients with acute pouchitis, not patients with antibiotic-dependent or antibiotic refractory pouchitis; only sulfasalazine was studied which may have antibiotic-like effects; No clear control group for comparison, hence using hypothetical placebo/spontaneous response rates
3-low event rate, <220 events, rate down once for lack of optimal information size

Table 11.

GRADE Evidence Profile for PICO #6, evaluating advanced immunosuppressive therapies for treatment of Crohn's-like disease of the pouch

ADVANCED THERAPIES compared with no treatment for Crohn's like disease of the pouch

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With advanced therapies	Relative effect (95% CI)	Risk with placebo	Risk difference with advanced therapies
Treatment **of CD or CDL of pouch (follow-up: range post-induction)**											
288 (10 cohorts)	Serious[1]	Serious[2]	Serious[2]	Not serious	None	⨁◯◯◯ Very Low	30% (20% −40%)	215/288	**RR 2.49** (1.87–3.73)	300 per 1,000	**447 more per 1,000** (from 261 more to 819 more)

CI:confidence interval; **RR:**risk ratio

[1]-Risk of bias due to non-standard outcome metrics

[2]-high clinical heterogeneity (diverse patients, with varying level of disease severity/antibiotic-refractoriness)

[3]-No clear control group for comparison, hence using hypothetical placebo/spontaneous response rates