GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

September 2023 Volume 19, Issue 9, Supplement 4

Highlights in Gastrointestinal Disorders From the GI ReConnect Conference 2023

Positioning Therapies in Gastrointestinal Disorders

June 1-3, 2023 • Huntington Beach, California

- Irritable Bowel Syndrome and Chronic Idiopathic Constipation
- Food Intolerance and Congenital Sucrase-Isomaltase Deficiency
- Eosinophilic Esophagitis
- *Clostridioides difficile* Infection
- Ulcerative Colitis
- Crohn's Disease

THIRD ANNUAL GI ReConnect
CONNECT: Communicate • Network • Educate

This activity is jointly provided by the University of Cincinnati and the Gi Health Foundation.

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A CME Activity
Approved for 1.0
AMA PRA
Category 1 Credit™

Release Date: September 8, 2023
Expiration Date: September 8, 2024
Estimated time to complete activity: 1.0 hour

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Target Audience

This activity has been designed to meet the educational needs of healthcare providers involved in the care of patients with gastrointestinal disorders.

Goal Statement

This supplement summarizes the key points of each discussion, with the aim of providing a snapshot of best practices for managing GI disorders in real world practice in the context of evolving clinical guidelines and an ever-expanding therapeutic landscape.

Educational Objectives

Upon completion of this activity, participants should be able to:

- Describe evolving patient management and treatment strategies for CLD and GI disorders
- Integrate significant advances in therapeutic and diagnostic modalities into clinical practice
- Apply the latest clinical research, including future therapies and their role in the context of the current clinical paradigm

Accreditation Statement

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Positioning Therapies in Gastrointestinal Disorders

In June 2023, as part of the GI ReConnect conference, a series of discussions was held on the contemporary management and positioning of therapies in key gastrointestinal (GI) conditions. Nearly 100 clinical experts from across the United States representing multiple specialties contributed to these discussions. This supplement summarizes the key points of each discussion to provide a snapshot of the best practices for managing GI disorders in the real world in the context of evolving clinical guidelines and an ever-expanding therapeutic landscape.

Irritable Bowel Syndrome (IBS) and Chronic Idiopathic Constipation (CIC)

Both the American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA) have recently updated clinical guidelines for the management of IBS.[1-3] Recognizing differences in the guideline recommendations of these 2 organizations, the expert panel (Table 1) noted that the committees used slightly different methodologies and outcomes to grade evidence and support their recommendations. Importantly, the key objective of the guidelines is to review and summarize the scientific evidence rather than discuss the nuances needed to inform treatment decision making for individual patients.

A clinical decision support tool for IBS was developed in conjunction with the AGA clinical guidelines to summarize the treatment options that were reviewed for the updates (Figure 1).[4] The experts noted that this tool is not intended to be a prescriptive algorithm for determining the sequencing of treatments, but rather a practical tool for summarizing the various approaches to management. Importantly, the clinical guidelines and clinical decision support tool are not intended to guide payers in determining the appropriateness of and coverage for various treatments. Clinicians, as well as payers, must bear in mind that every patient deserves an individualized approach and that treating IBS is not conducive to a one-size-fits-all paradigm.

Despite a tendency to rush to pharmacologic treatment, the experts emphasized the importance of the initial approaches specified in the clinical decision support tool for most patients with IBS. Establishing a solid provider-patient relationship is critical for managing IBS effectively, as patients are unlikely to have confidence in their treatment or return for follow-up visits without such a rela-

Table 1. IBS/CIC Expert Panel

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CIC, chronic idiopathic constipation; IBS, irritable bowel syndrome.

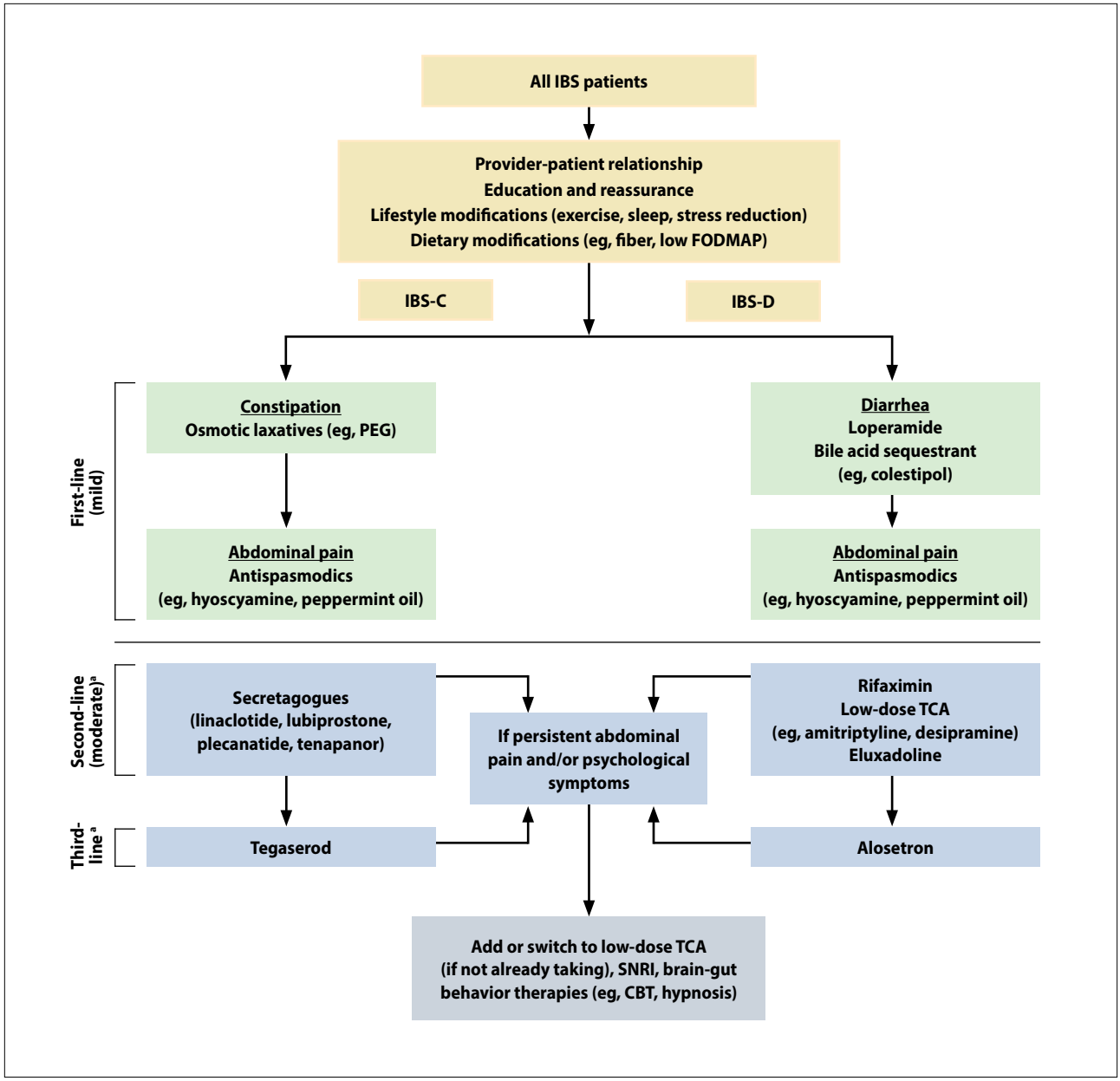

Figure 1. AGA clinical decision support tool for IBS.

[a]Selection of the medication should be based on the clinical features and needs of the patient.

AGA, American Gastroenterological Association; CBT, cognitive behavioral therapy; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; PEG, polyethylene glycol; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

tionship. An important aspect of this relationship is that providers validate patients' symptoms and demonstrate to them that they understand not only the symptoms but also their impact on patients' lives. Because much of this relationship is developed in the first visit, clinicians need to spend time listening to patients during this visit to elicit their key symptoms, explore potential causes of those symptoms, and determine what patients most want from evaluation and treatment. It is also important to set up realistic expectations with patients, reassuring them that treatments are available that will relieve their symptoms but also that the symptoms are likely to wax and wane throughout their lives.

Similarly, the importance of approaching patients from a holistic perspective that incorporates dietary, lifestyle, and behavioral interventions should not be underestimated in IBS management. Acknowledging that these approaches are among the most effective interventions for IBS, patients should be educated about the brain-gut connection in the context of their symptoms and be involved in

shared decision making to determine which approaches may be beneficial for them. Many experts are now engaging psychologists and behavioral interventions, traditionally relegated to last-line treatments, earlier in the treatment algorithm. Although such interventions require time and ideally a multidisciplinary approach, the experts opined that some patients are not likely to experience optimal relief without them.

Digital Health Technologies. Despite the growing use of behavioral interventions, the lack of access to psychologists specializing in GI disorders has been a barrier to their use in clinical practice. To that end, multiple behavioral digital therapeutics have been developed to extend the reach of these interventions for patients with IBS.[5] Although some require a prescription, the interventions can be viewed as self-management tools that teach some of the skills and concepts associated with cognitive behavioral therapy (CBT) and gut-directed hypnotherapy (GDH) that have achieved successful outcomes. Despite a general lack of awareness and limited uptake of these tools in the community,[6] the experts believe that such interventions may be beneficial in selected patients who are motivated and driven to address their treatment from an integrative perspective. Some experts recommend the interventions so that patients can have active treatment while waiting for an appointment with a GI psychologist, which can take many months. More complicated patients with severe symptoms may be better prioritized by a GI psychologist or general mental health provider. Although some patients who use these tools fail to complete the entire program, patients are more likely to complete the treatment if it is initiated by a gastroenterologist and if they are engaged in active follow-up with the practice. The experts also noted that failure to respond to a digital therapeutic does not equate to failing behavioral intervention as a class, and alternative delivery methods should be considered for willing and motivated patients.

The evolving field of virtual reality (VR)-mediated education and therapy provides an immersive experience for patients that is designed to engage the limbic system and motion centers of the brain in ways that 2-dimensional media do not. These systems can trigger learning through emotional valence. A VR app is currently in development that provides a virtual clinic incorporating elements of diaphragmatic breathing, GDH, and CBT. Studies are currently underway to evaluate the effects of this tool in combination with linaclotide for IBS.

VR allows patients to sense that they are literally present in an environment, engaging the limbic system and motion centers of the brain in ways that 2-dimensional media do not. These systems can trigger learning through emotional valence. A VR app is currently in development that provides a virtual clinic incorporating elements of diaphragmatic breathing, GDH, and CBT. Studies are currently underway to evaluate the effects of this tool in combination with linaclotide for IBS.

Pharmacologic Therapies. Pharmacologic therapies are generally directed toward the predominant symptoms of IBS in the context of patient preference, expectations, and experience with prior therapies. Although therapies that relieve abdominal pain and bowel symptoms (ie, global response or adequate relief response) may be favored, the experts noted that this goal may be more pertinent to clinical trials and not always achievable in real-world practice. In such cases, most experts choose to prioritize the symptom(s) most bothersome to the patient. Alternatively, multiple treatments can be combined simultaneously to address multiple symptoms.

Moderate- to high-quality evidence supports the use of the secretagogues (lubiprostone, linaclotide, plecanatide, and tenapanor) for patients with constipation.[1,2] Tenapanor, a medication for IBS with constipation (IBS-C) that was recently approved by the US Food and Drug Administration (FDA), inhibits dietary sodium absorption from the GI tract. Although polyethylene glycol relieves bowel symptoms of constipation, it is not effective in relieving pain for IBS.[2,3] The experts consider the recently approved and marketed vibrating capsule to be a potentially effective option for technologically savvy patients who prefer not to take pharmaceutical laxatives long term. Additionally, this treatment does not appear to be associated with urgency and diarrhea, which is a priority for many patients.

Antispasmodics continue to play a role for patients with cramping abdominal pain and provide an option for as-needed use for symptoms, although limited evidence is available to characterize their efficacy. Tricyclic antidepressants (TCAs) have pain-modulating properties and are useful in patients with evidence of visceral hypersensitivity, but they act slowly, and careful dose titration is often required. Experts use selective serotonin reuptake inhibitors (SSRIs) if they perceive that a mood disorder is driving patients' symptoms, but these agents are not effective for relieving pain and are generally not recommended for IBS. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are also used for pain, but they have not been extensively studied in patients with IBS. Rifaximin has demonstrated efficacy in IBS with diarrhea (IBS-D)[2,3] and may be particularly useful for patients who want a short-term treatment rather than committing to long-term therapy. Alosetron has demonstrated robust efficacy in patients with IBS-D,[2,3] but access to this agent is challenging. Eluxadoline is another effective alternative in IBS-D provided that potential candidates have been screened for alcohol misuse disorder and pancreaticobiliary disorders, as well as cholecystectomy. Additionally, bile acid sequestrants may have a role for patients with suspected bile acid diarrhea.

Food Intolerance and Congenital Sucrase-Isomaltase Deficiency (CSID)

Dietary Management of Disorders of Gut-Brain Interaction (DGBI)

Patients have long acknowledged food as a trigger for their GI symptoms, and dietary intervention is now recognized as a cornerstone treatment option for DGBI.[7,8] However, the increasing prevalence of eating disorders and their high rate of overlap with DGBI[9] can complicate the use of dietary therapies in this population. Given that exclusion or restrictive diets may conceptually conflict with eating disorders,[9] the experts (Table 2) emphasized the importance of screening patients before dietary therapies are implemented. Patients must be carefully screened not only for a history of eating disorders centered on shape and weight concerns but also for disordered eating behaviors such as avoidant/restrictive food intake disorder (ARFID). The latter is particularly concerning in light of recent data highlighting the significant rate of comorbid ARFID and DGBI.[8-10] Other patients who are poor candidates for diet interventions include those at risk for malnutrition, those who are food insecure, those who consume few culprit foods, and those with uncontrolled psychiatric disorders.[8]

The experts emphasized the importance of partnering with a dietitian with GI expertise to implement the dietary treatment of DGBI successfully. The AGA recommends referral to a registered dietitian nutritionist (RDN) to optimize the quality of teaching and clinical response.[8] Recognizing that access to such specialists is limited in many settings, clinicians who do not involve an RDN in treatment are encouraged to use reliable patient education resources and digital tools to help implement dietary modifications. The experts also encouraged clinicians to acknowledge the substantial impact that diet interventions can have on patient's lives and to offer reassurance and validate their patients' concerns when these therapies are implemented.

Table 2. Food Intolerance Expert Panel

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Dietary Interventions for IBS. A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) is among the most common and best-studied dietary interventions for patients with IBS.[7,8] The experts have found this diet to be most effective at targeting abdominal pain and bloating in their patients. The mechanisms for the effects of the low-FODMAP diet are not completely understood, but the initial benefit is usually attributed to a reduction in the osmotic load produced by poorly absorbed FODMAP sugars in the gut. Longer-term effects are likely related to alterations in the microbiome that lead to changes in mast cell activation, colonic barrier function, and visceral hypersensitivity.

Approaches to initiating a low FODMAP diet vary considerably among experts in clinical practice. Whereas some clinicians educate patients on the diet themselves, others require that patients see a dietitian before initiating the diet. Patients and their families must be evaluated to assess if they have the dedication, time, and energy to comply with the diet. Regardless of the approach, patients should understand that the low-FODMAP diet is a 3-phase process that begins with a reduction of foods rich in FODMAPs for a limited time, followed by the reintroduction of FODMAP subtypes to identify FODMAP triggers and ultimately the implementation of a personalized, long-term maintenance plan (Figure 2).[7,8]

Other dietary interventions that have been studied in patients with IBS include the Mediterranean diet and a gluten-free diet, although more data are needed to characterize their efficacy in this population.[7] The experts noted that when excluding celiac disease in these patients, it is essential to assess gluten intake prior to diagnostic testing as a gluten-free diet could lead to false negative results.

Functional Foods. Functional foods, or foods that offer health benefits beyond basic nutrition, may be useful as natural laxatives in some patients with functional constipation.[7] Such foods include prunes, prune juice, figs, kiwifruit, aloe, and rhubarb. Although the experts have found these foods to be effective in adult patients, they are used less in toddlers and young children because constipation is often behavioral in these age groups. However, natural laxatives can be useful in older children and adolescents, provided that the family is willing to apply these approaches. Although some children are unlikely to eat prunes, they may find kiwifruit, aloe, or chia seeds more acceptable. Additionally, blending kiwifruit or other natural laxatives into smoothies may improve acceptability in this population.

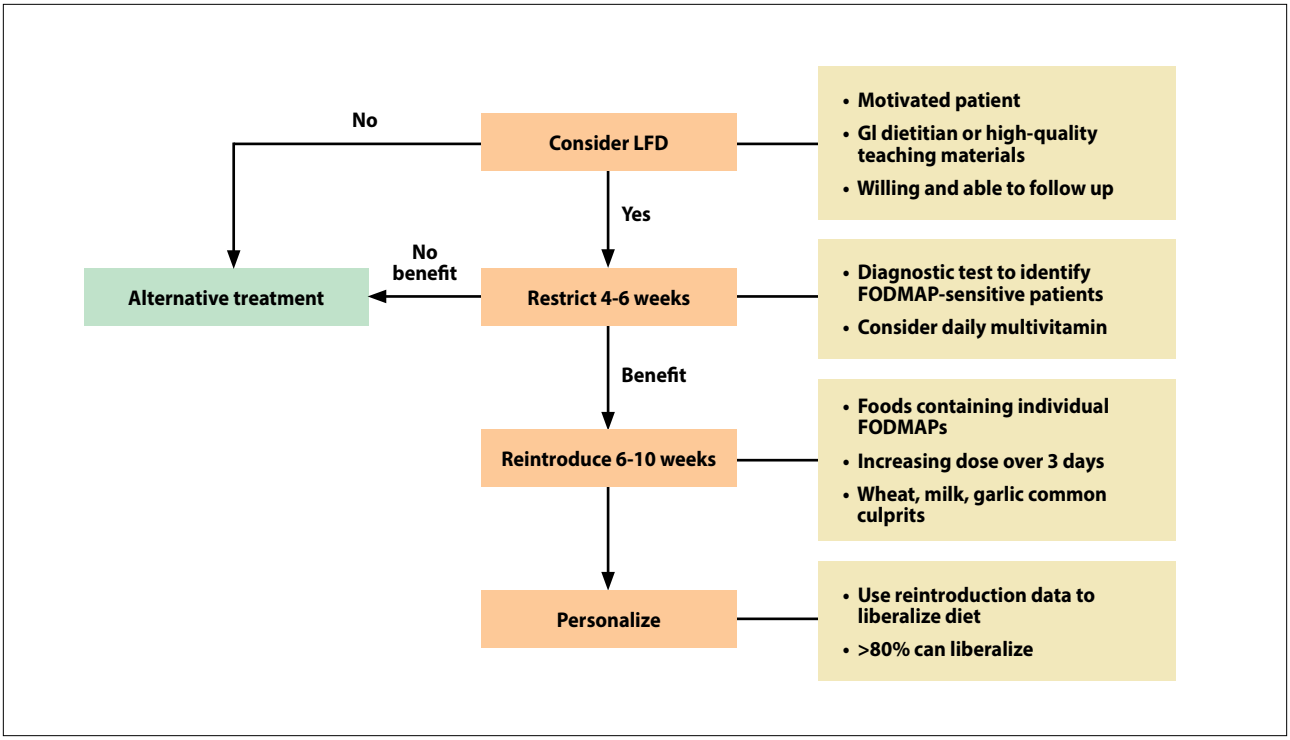

Figure 2. Low-FODMAP diet for patients with IBS.
FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI, gastrointestinal; LFD, low-FODMAP diet.

Congenital Sucrase-Isomaltase Deficiency

CSID results when an individual inherits 2 defective copies of the sucrase-isomaltase (*SI*) gene as a consequence of either recessive homozygous or compound heterozygous mutations that reduce or abolish enzymatic activity.[12] Although symptoms usually appear early in life, the clinical presentation and severity vary considerably depending on the nature and position of the mutations, as well as the homozygous or heterozygous combinations.[12,13] In addition to congenital forms of the disorder, acquired or secondary forms of sucrase-isomaltase deficiency have been observed in patients with chronic diarrhea owing to other causes, such as villous atrophy, infection, and rapid-transit syndromes.[14]

The experts noted that CSID is a more common problem than was initially believed, but they acknowledged that awareness of the condition in the community is low. The diagnosis of CSID may be delayed or even missed because the symptoms are incorrectly attributed to other causes of recurrent diarrhea, particularly IBS.[15] To that end, recent studies have found that sucrase deficiency is found in approximately 7% of adults with diagnosed IBS-D or functional diarrhea who undergo small-bowel biopsy for disaccharidase analysis[16] and in more than 20% of those who undergo ^{13}C-sucrose breath testing.[17]

The experts agreed that the absence of a simple, reliable, and noninvasive test makes diagnosing CSID challenging in clinical practice. Sucrose breath testing is an appropriate first step for evaluating patients with symptoms suggestive of the disorder because it is simple and can be performed at home. However, this test has not been well validated in clinical practice and may not correlate well with a disaccharidase enzyme assay, which is considered the gold standard for diagnosing CSID.[18] Although a disaccharidase assay provides the activities of all the disaccharidases (lactase, sucrase, maltase, and palatinase), the thresholds used to establish normal activities for these assays are based on data from infants with homozygous *SI* mutations and classic severe clinical presentations of CSID. Accordingly, the applicability of these thresholds across various combinations of *SI* mutations and clinical phenotypes requires further study.

The dietary management of CSID, which requires sucrose restriction and possibly starch reduction, is a complex process that can be challenging for patients and their providers.[18,19] A sucrose-restricted diet should not be confused with a low-FODMAP diet, which eliminates non-sucrose sugars (eg, lactose) and poorly absorbed short-chain carbohydrates and is less effective in patients with pathogenic *SI* mutations than in those with IBS.[20] Many experts use enzyme replacement with commercially available sacrosidase to treat CSID[21]; this is taken orally and allows patients to follow a more liberal diet. However, because this enzyme does not replace isomaltase, patients may still have to modify their starch intake. Patients are

encouraged to work with a dietitian, when available, to learn which foods require enzyme supplementation and which foods they can tolerate without supplementation. Previously available in multidose bottles that must be refrigerated, the recent availability of single-dose containers of sacrosidase has made enzyme supplementation much easier for patients, particularly school-age children and persons who are traveling or away from home.

Eosinophilic Esophagitis (EoE)

During the past 2 decades, EoE has evolved from the subject of a series of case reports to a leading cause of food impaction, a dominant cause of dysphagia, and a condition associated with significant healthcare costs.[22-24] Treatment of EoE is directed not only at relieving clinical symptoms but also at reducing mucosal inflammation, managing complications, and preventing disease progression.[25,26] To that end, multiple guidelines and consensus statements have been published and/or updated to define more clearly the diagnostic pathway and potential treatment options for EoE.[24,27-29] According to the 2020 AGA Institute and Joint Task Force (AGA/JTF) on Allergy-Immunology Practice Parameters Clinical Guidelines, options for EoE include dietary therapies, proton pump inhibitors (PPIs), topical corticosteroids, and esophageal dilation (Figure 3).[24] Additionally, the monoclonal interleukin 4/interleukin 3 (IL-4/IL-13) antibody dupilumab was approved for treating EoE following the publication of the AGA/JTF guidelines.[30] In light of the prevalence of anxiety and depression among patients with EoE,[31] the expert panel (Table 3) suggested that psychological approaches also be incorporated when appropriate.

Recognizing the lack of evidence comparing the available therapies and the absence of a true first-line treatment, the expert panel underscored the importance of shared decision making when therapies for patients with EoE are chosen. As part of this process, it is essential to explain the rationale for treatment, emphasizing that difficulty swallowing is not normal and offering encouragement that therapy can relieve symptoms. Clinicians should counsel patients on the benefits and limitations of the various medical and dietary treatment options so that patients can make an educated decision regarding their preferred therapy. Another key aspect of management is educating patients on the importance of follow-up and setting appropriate expectations around the need for repeat endoscopy. Patients should understand that their symptoms may not accurately reflect the underlying disease process and that routine endoscopic follow-up after treatment implementation or change is needed to monitor response to therapy, regardless of which treatment is chosen.

Table 3. EoE Expert Panel

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EoE, eosinophilic esophagitis.

Medical Therapies. The AGA/JTF Clinical Guidelines on EoE conditionally recommend PPIs for patients with symptomatic disease based on an analysis of 23 observational studies reporting a 42% reduction in histologic features of the disease.[24,26] PPIs are typically well tolerated by patients and often used as first-line treatment in clinical practice because of their ease of use, low cost, and established safety profile.[24,28,32] However, the experts noted that clinicians should be prepared to discuss the benefits and purported risks of PPIs as many patients are aware of the increasing safety concerns associated with these agents in observational studies.[33]

The AGA/JTF Clinical Guidelines strongly recommend swallowed topical corticosteroids in preference to no treatment with a moderate certainty of evidence.[24] This recommendation is based on a meta-analysis of 8 randomized controlled trials demonstrating histologic remission in 64.9% of patients treated with topical corticosteroids vs 13.8% of placebo-treated patients.[34] Despite their efficacy, the expert panel noted that the use of these agents, which were developed for asthma, may be challenging, especially for those with poor health literacy, because of the need for education on their administration and potential adherence issues. Additionally, patient counseling is important when these therapies are initiated to optimize delivery of the formulation and minimize adverse effects (eg, eating or drinking immediately after administration).[35]

Dietary Therapy. Dietary approaches to managing EoE include elemental or amino acid–based diets, allergen testing–directed elimination diets, and empiric elimination diets.[36] Given the findings suggesting that conventional allergy testing is unreliable in identifying food triggers, empiric elimination strategies are favored over diets based on allergy tests. Elimination diets are successful in a variable proportion of patients, but they are limited by challenges with long-term adherence

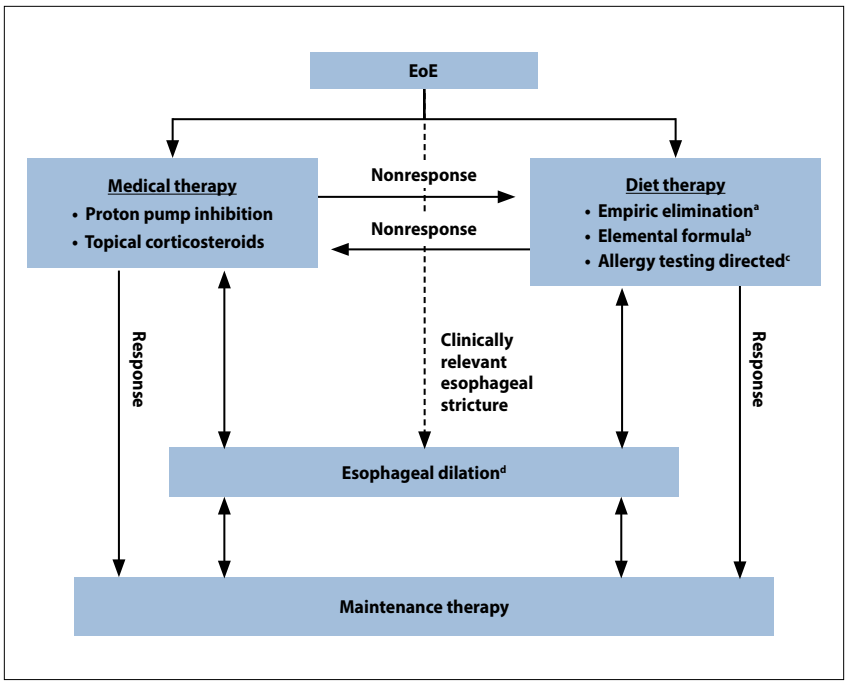

Figure 3. AGA clinical decision support tool for EoE.

[a]Recommendation in favor of empiric elimination diets is based on the published experience with the six-food elimination diet. Patients who put a higher value on avoiding the challenges of adherence to diet involving elimination of multiple common food staples and the prolonged process of dietary reintroduction may reasonably decline this treatment option. Emerging data on less restrictive diets (4-food, milk elimination, 2-4-6 step-up diet) may increase both provider and patient preference for diet therapy.

[b]Patients who put a higher value on avoiding the challenges of adherence to an elemental diet and the prolonged process of dietary reintroduction may reasonably decline this treatment option.

[c]Due to the potential limited accuracy of the currently available, allergy-based testing for the identification of specific food triggers for EoE, patients may prefer alternative medical or dietary therapies to an exclusively testing-based elimination diet.

[d]Esophageal dilation does not address the esophageal inflammation associated with EoE.

AGA, American Gastroenterological Association; EoE, eosinophilic esophagitis.

and the need for repeated endoscopic biopsy assessment during the food reintroduction process.[24,28,36,37] Additionally, the use of dietary approaches in clinical practice is complicated by a lack of access to dietitians in many settings, including both the community and academic centers. The expert panel noted that dietary treatment can be labor-intensive and requires family commitment, particularly for pediatric patients. Some experts initiate dietary treatment with PPIs to identify offending foods and eventually discontinue PPI therapy.

Endoscopic Therapy. Esophageal dilation is effective in a majority of patients for managing dysphagia resulting from strictures.[24] Although approaches to esophageal dilation vary in clinical practice, the expert panel agreed that dilation should be performed with a slow, steady technique and may best be reserved for patients who are symptomatic despite appropriate medical treatment. Further, dilation is not acceptable to all patients, particularly those who have experienced a traumatic dilation. Although dilation is a practical strategy for relieving symptoms, patients must understand that managing EoE is a long-term process and that dilation does not obviate the need to continue therapy to control the underlying inflammation that drives remodeling and stricture formation.

Dupilumab. In 2022, dupilumab became the first FDA-approved treatment for EoE. Administered as a weekly subcutaneous injection, this agent is indicated for treating EoE in adults and pediatric patients aged 12 years and older.[30] Consistent with clinical trial data,[38] the expert panel described a favorable clinical experience with dupilumab, with very strong patient responses and few tolerability issues. However, the cost of dupilumab mandates careful consideration in patient selection, as well as routine endoscopic follow-up to ensure efficacy. Although the labeled indication does not restrict the use of dupilumab to patients who have failed PPIs or topical corticosteroids,[30] access to this treatment is often driven by insurance coverage and payer-driven stepped-care policies. Although its optimal positioning has not been defined,[32,39] the expert panel considers dupilumab to be appropriate for patients with disease refractory to medical or dietary therapies, as well as those with significant comorbid atopic conditions (eg, asthma, atopic dermatitis requiring corticosteroids) that may also be responsive to therapy.

Clostridioides difficile Infection (CDI)

Clostridioides difficile (formerly *Clostridium difficile*) has long been recognized as a major cause of antibiotic-associated diarrhea and is now appreciated as the most common healthcare-associated infection in the United States.[41-45] Although the incidence of CDI in the healthcare setting is declining,[46] it has been increasingly reported outside acute care facilities, and community-associated CDI has emerged as a growing problem over the last decade.[42,44,47-49]

Guidelines for preventing and managing CDI have been updated by the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA)[50,51] and the ACG (Table 4).[52] Notable changes in the current IDSA/SHEA

Table 4. IDSA/SHEA and ACG Recommendations for Treatment of CDI in Adults[50-52]

	IDSA/SHEA 2021[50]	ACG[52]
Initial CDI episode		
Nonsevere	**Fidaxomicin** PO 200 mg BID × 10 d (preferred) **Vancomycin** PO 125 mg QID × 10 d (alternative) **Metronidazole** 500 mg TID PO × 10-14 d (if above agents unavailable and WBC <15,000/mL^3 and SeCr <1.5 mg/dL)	**Vancomycin** PO 125 mg QID × 10 d **Fidaxomicin** PO 200 mg BID × 10 d **Metronidazole** PO 500 mg TID in low risk patients (younger with minimal comorbidities)
Severe	**Fidaxomicin** PO 200 mg BID × 10 d (preferred) **Vancomycin** PO 125 mg QID × 10 d (alternative)	**Vancomycin** PO 125 mg QID × 10 d **Fidaxomicin** PO 200 mg BID × 10 d
Recurrent CDI episodes		
First CDI recurrence	**Fidaxomicin** PO 200 mg BID × 10 d or BID for 5 d followed by once every other day for 20 d (preferred) **Vancomycin** PO in a tapered and pulsed regimen or vancomycin PO 125 mg QID for 10 d (alternative) **Bezlotoxumab** 10 mg/kg IV once during administration of SOC antibiotics[a,b] (adjunctive treatment)	**Tapered-pulsed vancomycin** if vancomycin/fidaxomicin/metronidazole used initially **Fidaxomicin** 200 mg BID × 10 d if vancomycin or metronidazole used initially **Bezlotoxumab** for recurrence prevention can be considered
Second or subsequent recurrence	**Fidaxomicin** PO 200 mg BID × 10 d or BID for 5 d followed by once QOD for 20 d, or **Vancomycin** in a tapered and pulsed regimen, or **Vancomycin** PO 125 mg QID for 10 d followed by rifaximin 400 mg TID for 20 d, or **FMT** (adjunctive treatment) **Bezlotoxumab** 10 mg/kg IV once during administration of SOC antibiotics[a,b] (adjunctive treatment)	**Vancomycin** 125 mg PO QID for 10 d, or **Fidaxomicin** 200 mg for 7-10 d, followed by **FMT** via colonoscopy or capsule **Repeat FMT** for recurrences within 8 wk of FMT (adjunctive treatment) **Antibiotic regimens** if FMT not available (long-term suppressive vancomycin)

[a]Bezlotoxumab may also be considered for patients with other risks for CDI recurrence, but implementation depends upon available resources and logistics for IV administration, particularly for patients with an initial CDI episode. Additional risk factors for CDI recurrence include age >65 years, immunocompromised host (per history or use of immunosuppressive therapy), and severe CDI on presentation.
[b]The FDA warns that bezlotoxumab should be reserved for use when the benefits outweigh the risks in patients with a history of CHF.
ACG, American College of Gastroenterology; BID, twice daily; CDI, *Clostridioides difficile* infection; CHF, congestive heart failure; FDA, US Food and Drug Administration; FMT, fecal microbiota transplant; IDSA, Infectious Diseases Society of America; IV, intravenous(ly); PO, orally; QID, 4 times daily; SeCr, serum creatinine; SHEA, Society for Healthcare Epidemiology of America; SOC, standard of care; TID, 3 times daily; WBC, white blood cell.

guidelines include the addition of fidaxomicin as a preferred agent over vancomycin, with metronidazole a less favored option and considered only for those with mild CDI.[50,51] Fidaxomicin, a targeted macrolide antibiotic approved in 2011, is as effective as vancomycin for initial treatment response and superior to vancomycin with regard to short-term recurrence.[53-55] Although oral metronidazole historically was used as a first-line treatment for CDI, the IDSA/SHEA guidelines recommend it as an alternative for non-severe disease only if either vancomycin or fidaxomicin is unavailable or contraindicated. This change stems from studies demonstrating the superior efficacy of oral vancomycin, as well as the potential for oral metronidazole to cause cumulative and potentially irreversible neurotoxicity with repeated or prolonged use.[41,51,56]

For recurrent CDI, the IDSA/SHEA guidelines recommend either 10 days of fidaxomicin or a 5-day course of fidaxomicin followed by a pulse of this antimicrobial as the preferred treatment. An alternative is vancomycin in a tapered and/or pulsed regimen or 10 days of vancomycin if metronidazole was used initially (Table 4).[50-52] Antibiotic treatment options for patients with more than one recurrence include a fidaxomicin regimen, a tapered and pulsed oral vancomycin regimen, or a standard course of oral vancomycin followed by rifaximin. As part of the guideline updates, bezlotoxumab, a monoclonal antibody directed against *C difficile* toxin B, was added to the treatment algorithm as a one-time infusion in those at greatest risk for recurrence. Fecal microbial transplant (FMT) after a standard-of-care antimicrobial course is recommended as an alternative for patients with 2 or more recurrences who have failed appropriate antibiotic-only treatments.[50] Despite the extensive use of probiotics in clinical practice, neither the ACG

Table 5. CDI and Microbiome Expert Panel

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CDI, *Clostridioides difficile* infection.

nor the IDSA/SHEA guidelines consider the current evidence sufficient to recommend these agents for the primary prevention of CDI.[51,52]

First-Line Fidaxomicin? Acknowledging that fidaxomicin is associated with a lower recurrence rate than vancomycin,[57,58] the expert panel (Table 5) prefers using fidaxomicin as first-line treatment in patients with a first episode or first recurrence of CDI in either the recommended 10-day regimen[50,52] or an extended 20-day regimen. Given concerns about adherence to the extended regimens, however, it is important to provide patients with written instructions and/or other tools as needed to help clarify the dosing schedule.

Despite the preference for fidaxomicin, cost, and access issues are key challenges to its use in clinical practice. In addition to wide variability in access, co-pays may be prohibitively high, even for commercially insured patients. Given these challenges, hospitalized patients are often treated with vancomycin in anticipation that they will not have access to fidaxomicin as outpatients. Alternatively, some experts initiate the prior authorization process at the time fidaxomicin treatment is started in the hospital to expedite access upon discharge.

Stratifying Disease Severity. Unlike the IDSA/SHEA guidelines, the ACG guidelines stratify treatment recommendations for CDI by disease severity, as defined by white blood cell count and serum creatinine level.[50,52] However, in clinical practice, most experts stratify treatment recommendations based on patients' risk for recurrence rather than disease severity. Therefore, patients who have multiple risk factors for recurrence should be treated in the first-line setting with fidaxomicin rather than vancomycin. Despite this trend, evaluating the severity of CDI is important to ensure that metronidazole is not used in patients with severe disease, given the data demonstrating lower rates of cure with metronidazole than with vancomycin in this clinical presentation.[59,60]

Bezlotuxumab. Bezlotuxumab was approved in the United States in 2016 as adjunctive therapy to reduce the risk for recurrence in persons aged 18 years or older who are receiving treatment for high-risk CDI.[61] Although the expert panel expressed varied levels of success with the use of this agent in clinical practice, specific patient populations may be particularly suited for add-on treatment with bezlotuxumab. Patients for whom bezlotuxumab may be appropriate include those with IBD who are immunocompromised, those who have undergone stem cell transplant, patients with risk factors for recurrence, and those who either have contraindications to or prefer not to be treated with a live biotherapeutic product (LBP) or capsule-based FMT. Bezlotuxumab may also have a role as a single outpatient infusion in patients without access to fidaxomicin who are treated with vancomycin for the initial episode. Additionally, the experts noted that further durability data and data regarding the effects of bezlotuxumab are needed to better define the role of this agent in current treatment paradigms for CDI management.

Microbiota Restoration Therapies. Microbiota restoration, which aims to restore a gut with persistent dysbiosis to a healthy state, is now the cornerstone for preventing recurrent CDI.[62,63] The most common modality of restoring the microbiota is FMT, which is regarded by the experts as a safe and effective treatment option for recurrent CDI. Delivery of FMT via colonoscopy or capsules is recommended by both the IDSA/SHEA and ACG in patients with multiple recurrences not responding to appropriate antibiotic regimens.[50,52] Although it was not used during the COVID-19 pandemic, experts are using FMT again with excellent results consistent with the high efficacy seen in clinical trials,[64] and often with greater access than to fidaxomicin or bezlotuxumab. FMT has traditionally been safe, with the most common adverse effects being abdominal pain, diarrhea, and bloating.[65] Infectious complications reported to date have been rare, although the potential long-term complications are currently unknown.[51] Despite its efficacy and generally good patient acceptance, FMT remains a heterogeneous practice, with a lack of standardization in donor screening and stool processing, patient preparation, and the administration process.[63,65]

LBPs are standardized microbiome therapies that have been developed under the auspices of pharmaceu-

Table 6. Treatment Options for Microbiome Restoration

	FMT[64,66]	Rebyota[67] (formerly RBX2660)	Vowst[68] (formerly SER-109)
Composition	Varies by donor	Each 150-mL dose of Rebyota contains between 1×10^8 and 5×10^{10} CFU/mL of fecal microbes, including $>1 \times 10^5$ CFU/mL of *Bacteroides* per milliliter	Purified live Firmicutes bacterial spores
Source	Healthy human donor	Human fecal matter sourced from qualified donors	Healthy human donor stool
FDA-approved indication	Experimental	Prevention of rCDI in patients ≥18 y following antibiotic treatment for rCDI	Prevention of rCDI in patients ≥18 y following antibiotic treatment for rCDI
Administration	Can be administered by colonoscopy, capsules, enema, or NG tube	Single 150 mL rectal enema suspension 1-3 days after last dose of antibiotics	• Complete antibiotic treatment for rCDI 2-4 days before initiation of VOWST • 10 oz of magnesium citrate day before or ≥8 h before first dose of VOWST • 4 capsules VOWST orally once daily on empty stomach for 3 consecutive days
Most common AEs	Abdominal pain, diarrhea, postinfectious IBS	Abdominal pain, diarrhea, abdominal distension, flatulence, nausea	Abdominal distension, fatigue, constipation, chills, diarrhea
Other considerations	Lack of standardization in donor screening, feces and patient preparation, and administration procedures		• Potential impact of delayed gastric emptying (eg, gastroparesis) • Potential impact of accelerated gastric transit (eg, concomitant GLP-1 agonist therapy)

AE, adverse event; CFU, colony-forming unit; FDA, US Food and Drug Administration; FMT, fecal microbial transplantation; GLP-1, glucagon-like peptide-1; IBS, irritable bowel syndrome; NG, nasogastric; rCDI, recurrent *Clostridioides difficile* infection.

tical companies and the FDA.[62] Since the IDSA/SHEA and AGA guideline updates were last published,[50,52] 2 LBPs have been approved by the FDA to prevent recurrent CDI[66,67] (Table 6) and another is entering late-stage investigation.[62,65] Rebyota™ (formerly RBX2660), a commercially prepared, microbiota-based enema suspension, consists of a broad consortium of live microbes prepared from human stool collected from rigorously screened healthy donors.[66,68] The expert panel noted that in-office administration of Rebyota has been simple, with nurses or advanced practitioners administering the product and observing patients for the following 15 minutes. Because patients are treated with a standard-of-care antimicrobial before microbiota restoration, they should be stooling at or close to their baseline, so there should be no risk for transfer of *C difficile* with the administration of this LBP in the office. VOWST™ (formerly SER-109) is an oral formulation of approximately 50 species of purified Firmicutes spores derived from the stool of healthy donors.[67] This agent is administered as an oral capsule within 2 to 4 days of antibiotic treatment for recurrent CDI, and an initial 10 ozs of magnesium citrate is required as a bowel washout before 4 capsules are taken daily for 3 consecutive days.

Given the cost of LBPs, the expert panel agreed that the first recurrence of a CDI in a young, otherwise healthy patient can be managed with fidaxomicin or vancomyin taper. Although either treatment is appropriate in younger patients who are likely to recover, the cost of fidaxomicin may not be appropriate for patients who are likely to need a microbiome-based product. Such patients include older adults and those with comorbidities or other risk factors for recurrence, with an incomplete response to fidaxomicin or vancomycin, or with a history of severe or fulminant disease.

Multiple factors influence the choice of therapies from among the available microbiome-based products. Unlike traditional FMT, which is considered experimental and delivers an unknown microbiota composition, Rebyota delivers a known composition and is FDA-regulated, a difference that could have implications for medical liability. Other key factors driving treatment decisions include patient preference, cost, and availability. Although some patients may prefer taking oral capsules (ie, VOWST) rather than an enema formulation, others may find the requirement for a bowel washout with this agent to be a disadvantage. VOWST, like Rebyota, delivers a known consortium of microorganisms.

Inflammatory Bowel Disease (IBD)

Multiple international and national clinical practice guidelines are available to guide clinicians in the various aspects of IBD management.[69-72] With the introduction of new treatment options, including new classes of therapies and biosimilars, treatment decisions in patients with IBD are becoming increasingly complex. Indeed, more than 20 treatment options are now available for managing IBD, and new approvals are anticipated in the next several years.

With this situation in mind, the experts (Tables 7 and 8) emphasized that clinical guidelines should serve as a framework for evaluating evidence rather than discourage clinicians from making the nuanced decisions necessary to optimize care for individual patients with IBD. Clinical guidelines should be broad enough to allow clinicians flexibility in decision making and not perceived as absolute guardrails to limit the use of potentially useful therapies. Additionally, given the rapidly expanding therapeutic landscape in IBD, the experts suggested that approaching clinical guidelines as online "living" documents would allow more frequent updates, minimizing publication delays and facilitating rapid access to new evidence as it becomes available.

Table 7. Ulcerative Colitis Expert Panel

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UC, ulcerative colitis.

Expert Guidance for the Management of Ulcerative Colitis (UC)

Mild Ulcerative Proctitis. Various approaches to managing mild ulcerative proctitis are used in clinical practice. Whereas some experts initiate treatment with twice-daily mesalamine suppositories for a limited duration, others start with a combination of oral and rectal mesalamine to taper the rectal formulation after a short period (ie, 2-8 weeks). Other strategies include compounded suppositories that contain tacrolimus for severe proctitis or a combination of mesalamine and budesonide. Patient preference is essential when therapies are chosen in this setting because acceptance of rectal therapies is not universal, particularly among younger patients, who may be less likely to adhere to their regimens. In contrast, some patients may prefer rectal therapies, given that they reach the site of action immediately and may relieve symptoms more rapidly than oral therapies do.

Once patients are in clinical and endoscopic remission, therapy can be tapered to a maintenance regimen. In the absence of evidence to guide regimen tapering, clinicians use varying approaches (eg, switching administration to every other day for 2 weeks and then every third day for 2 weeks). Many experts prescribe twice-weekly mesalamine suppositories to maintain remission, although providers often need to negotiate with patients as many prefer to discontinue rectal therapies rather than continue with the minimum frequency necessary to maintain remission.

Mildly Active UC. Patients with mildly active left-sided UC are often treated with a combination of oral and rectal 5-aminosalicylate (5-ASA) enemas. Most providers initiate mesalamine at 4.8 g/d, but some start at 2.4 g/d to allow room for titration. When treatment with 5-ASA enemas is initiated, patients should be counseled to understand that retention usually improves with use and encouraged to continue use until the full dose is

reached. Budesonide foam is an alternative for those who cannot tolerate or retain mesalamine enemas after several days of use. However, rectal enemas for UC are costly and may not be accessible for patients who do not have adequate insurance coverage. With that in mind, the panel emphasized the need for oral therapy in patients who cannot access or retain these therapies.

Although it is acknowledged that mesalamine is very safe and effective for a considerable proportion of patients with mild or mild-to-moderate disease,[72,73] it is important to escalate to more advanced therapies when mesalamine fails to induce remission. Clinicians generally expect a symptomatic response within the first 4 to 8 weeks of mesalamine therapy. Treatment should be continued in patients with symptomatic relief and then assessed subsequently with objective endpoints. Although patients who do not respond within the first 8 weeks may respond eventually, the expert panel emphasized the importance of maintaining a low threshold for moving to advanced therapies rather than allowing patients to remain symptomatic. This concept also holds true for patients with right-sided disease that responds to therapy and a portion of left-sided colitis that does not heal.

Although most experts try to avoid using systemic corticosteroids for induction, treatment with these agents may be more appropriate than waiting 4 to 8 weeks for a mesalamine response in patients with relatively moderate symptoms (eg, 12-15 bowel movements per week). Budesonide MMX is also an option in this setting, although access and cost can limit its use in clinical practice. The choice between budesonide and systemic corticosteroids as bridge therapy depends on symptom severity, with budesonide favored for patients who are likely to be maintained on 5-ASA and systemic corticosteroids possibly more appropriate for those waiting for approval of therapies such as ozanimod or vedolizumab. However, whenever possible, experts prefer to initiate advanced therapy in patients with any extent of disease who fail oral mesalamine rather than repeat courses of oral corticosteroids.

The choice of maintenance therapy for patients with mild UC is a complex decision influenced by symptom severity and patient preference. The expert panel agreed that maintenance dosing of 5-ASA in mild UC should be the dose that induced remission. Maintaining a steroid-free remission is more challenging in patients who have undergone steroid induction than in steroid-naïve patients.

Moderately to Severely Active UC. Patients with moderately to severely active UC who fail to respond to a combination of oral and topical 5-ASA should be switched to advanced therapy (Figure 4).[69] Despite the publication of some head-to-head studies,[74,75] randomized comparative data are insufficient to guide treatment selection in bio-naïve patients. In the absence of such data, treatment selection should be individualized and guided by patient-specific factors, such as medical history, comorbidities, and response to prior therapies. Insurance-driven stepped-care requirements are also key drivers of treatment selection, an unfortunate reality in which insurers often fail to recognize the clinical nuances needed to make informed decisions for individual patients.

Despite the demonstrated efficacy of Janus kinase (JAK) inhibitors as first-line therapy in bio-naïve patients,[76] the experts noted that using these agents in this setting is not consistent with the FDA class labeling restricting their use to patients in the United States who have failed anti–tumor necrosis factor (anti-TNF) therapies.[77,78]

After an advanced therapy is initiated, most experts evaluate patients within 6 to 10 weeks to ensure that their symptoms and fecal calprotectin are decreasing relative to baseline. Although therapy can be extended as needed to achieve remission in patients whose condition is improving, treatment should be optimized as needed or discontinued and changed in those who fail to respond. However, the experts noted that patient response and continued improvement should be assessed over a window of time rather than at a single time point, consistent with STRIDE-II recommendations for evaluating treatment goals in IBD.[79]

Despite the AGA suggestion to combine biologic therapies with an immunomodulator (Figure 4), approaches to using combination therapy in patients with moderate-to-severe UC vary in clinical practice. The UC-SUCCESS trial provides strong evidence for the combination use of infliximab and azathioprine,[80] but few data are available informing other combination therapies in UC. Although combining an immunomodulator with an anti-TNF therapy is recommended in patients with a documented history of immunogenicity with these agents, many experts consider the favorable pharmacokinetic and immunogenicity profiles of the non–anti-TNF biologics to obviate the need for concomitant immunosuppression. More data are needed to better inform decisions regarding combinations of immunomodulators with these newer biologics.

Crohn's Disease

Mild Crohn's Disease. The expert panel (Table 8) defined mild disease as the presence of mild symptoms that do not significantly affect daily activities in the presence of a small burden of inflammation (eg, findings of limited aphthous ulcers) on endoscopic or radiologic assessment. Recognizing that disease activity does not necessarily predict prognosis, however, the panel noted that little evidence is available to determine if patients with mild disease need treatment or if treatment will alter the natural history of the disease.

With this in mind, some clinicians do not treat patients with newly diagnosed mild disease, opting to monitor them with a routine assessment of inflammatory markers (eg, fecal calprotectin) and endoscopy for disease progression. Others practice shared decision making with their

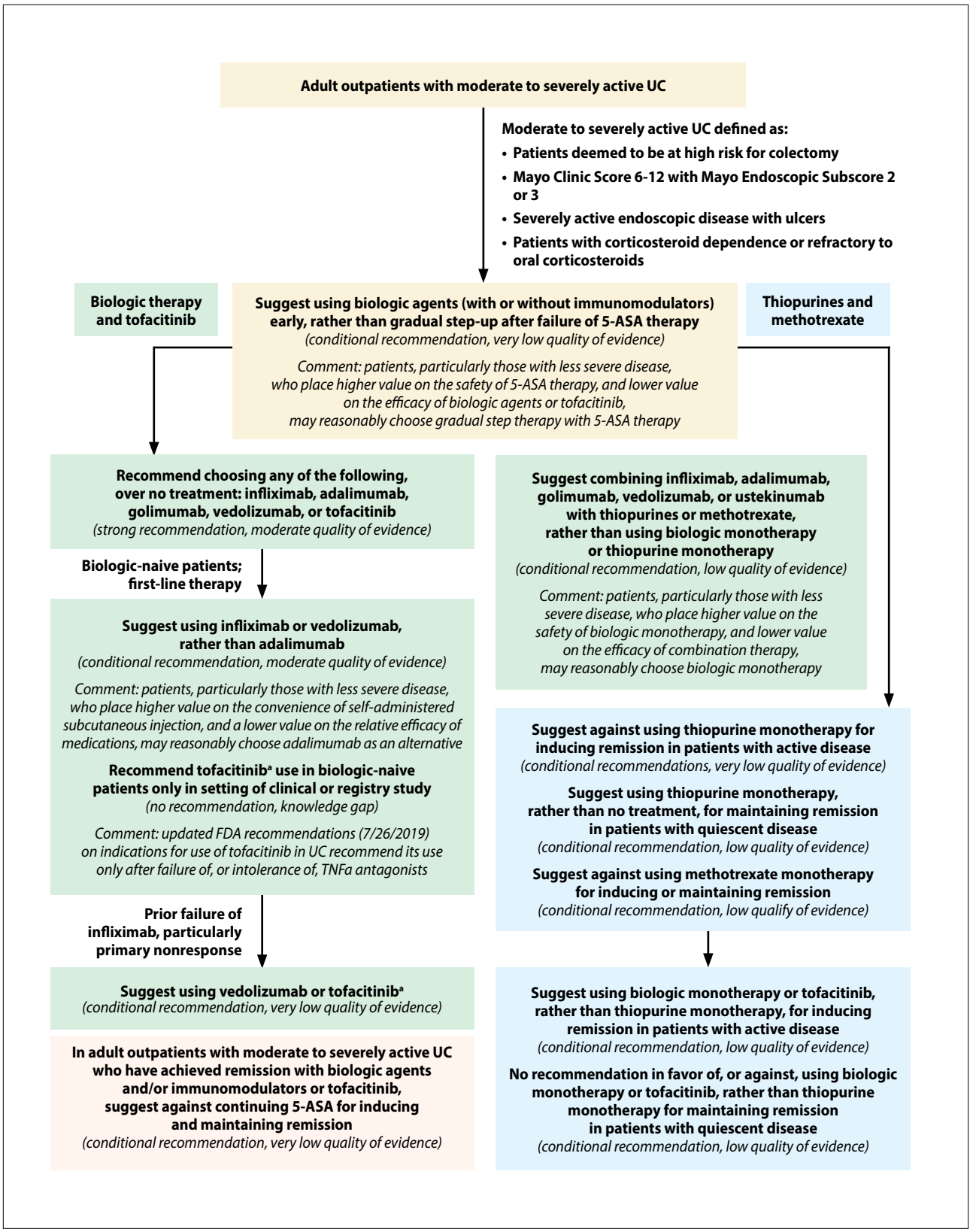

Figure 4. AGA clinical decision support tool for the pharmacologic management of adult patients with moderate to severely active UC. [a]Tofacitinib dose is 10 mg BID for 8 weeks for induction, followed by 5 mg BID for maintenance.

5-ASA, 5-aminosalicylate; BID, twice daily; FDA, US Food and Drug Administration; TFNα, tumor necrosis factor α; UC, ulcerative colitis.

patients to guide treatment decisions. When treatment is warranted, various therapies (mesalamine, controlled ileal-release budesonide, antibiotics) are used to control symptoms.[82] Despite the ACG recommendation against using mesalamine in patients with active Crohn's disease because of a lack of consistently demonstrated efficacy,[82] the expert panel notes that mesalamine can be effective in a select, small group of patients. However, mesalamine has not been shown to achieve mucosal healing in Crohn's disease. Mesalamine should be discontinued if no benefit is observed after 8 to 12 weeks. Although most experts are no longer using antibiotics, a subset of patients with small intestinal bacterial overgrowth or microbiome-related functional symptoms may benefit from antibiotic treatment.

Table 8. Crohn's Disease Expert Panel

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Moderate Crohn's Disease. Patients with symptoms attributed to inflammation that do not respond to first-line interventions are considered to have moderate disease. These patients may have symptoms (eg, fatigue, diarrhea, abdominal pain) that affect their daily activities, laboratory abnormalities (eg, elevated C-reactive protein), and endoscopic and radiologic evidence of inflammation that is more than mild. Extraintestinal manifestations may be present as well.

Given the lack of correlation between clinical and endoscopic findings in Crohn's disease, it is critical to evaluate and incorporate a patient's inflammatory burden in decision making. This may be particularly important in a patient with mild or no symptoms in the face of moderate-to-severe endoscopic activity. These types of patients may be especially vulnerable to undertreatment and disease progression as their symptoms do not appear to warrant treatment escalation. Additionally, because only symptomatic patients are enrolled in clinical studies, this population is not represented in current clinical guidelines.

The expert panel recommended that patients with a diagnosis of moderate-to-severe luminal Crohn's disease be started on an FDA-approved therapy for this indication without delay. Although the short-term use of prednisone is acceptable for inducing clinical improvement or remission, it should not preclude the use of an FDA-approved treatment, nor should it be continued long term. If oral corticosteroids are initiated, the experts recommend discussing and implementing an exit strategy with patients. However, it is preferable to avoid oral corticosteroids and initiate advanced therapy when possible. Treatment decisions regarding the addition of a thiopurine (azathioprine, 6-mercaptopurine) should be considered on a case-by-case basis. Despite some evidence of efficacy, most experts do not use methotrexate as induction therapy for Crohn's disease. Additionally, the experts agreed that mesalamine has no role in treating patients with moderate-to-severe Crohn's disease.

Bio-naïve Patients. The expert panel agreed that the biologics noted in the AGA guidelines for moderate-to-severe Crohn's disease[83] are effective in inducing remission. In the absence of head-to-head trials comparing these agents, treatment decisions are driven by patient-related factors such as age, comorbidities, contraindications, prior malignancy, extraintestinal manifestations, and preference.

Bio-exposed Patients. When bio-exposed patients are evaluated, it is essential to understand the treatment history and reasons for the failure of prior therapies. Clinicians should consider if the prior therapy was optimized, a process that relies on therapeutic drug monitoring for

some agents, especially the anti-TNF agents. Noting that underdosing and inadequate duration of treatment are common mistakes with biological use, the experts emphasized that higher drug levels are generally needed for relatively severe disease. Another key consideration in this setting is to evaluate whether surgery rather than medical treatment is needed, and the experts emphasized the need to consider at every juncture whether the patient is best served by switching to a different biologic or small-molecule therapy or surgery.

When patients fail a treatment despite its optimization, most experts choose to switch to a therapy with a different mechanism. An exception may be switching to another biologic in the same class, such as an anti-TNF agent in a patient who has failed infliximab, owing to immunogenicity. However, such patients should be considered for treatment with an immunomodulator in combination to minimize the development of immunogenicity with the alternative agent. After the reason for treatment failure has been evaluated, decisions are generally guided by considerations of patient-related factors, as they are in bio-naïve patients.

Although not addressed in the latest clinical guidelines for Crohn's disease,[82,83] experts consider risankizumab an appropriate first-line therapy for moderate-to-severe Crohn's disease and upadacitinib an appropriate second-line therapy in patients with anti-TNF exposure. Some data have suggested that prior failure with ustekinumab does not preclude the use of risankizumab,[84] although switching to therapy with an alternate mechanism is preferred by some experts in this scenario.

Severe Crohn's Disease. Signs of severe Crohn's disease include weight loss, inability to work, and laboratory abnormalities (anemia, low albumin level). When evaluating such patients, clinicians should carefully assess whether symptoms are due to Crohn's disease or to other factors such as CDI, cytomegalovirus infection, enteric pathogens, mesenteric thrombosis, or strictures. The management of patients with severe Crohn's disease requires a multidisciplinary approach that may involve medical therapy along with nutritional interventions, surgical consultation, and interventional radiology. Although treatment decisions in these patients are complex, appropriate options may include intravenous corticosteroids and various combinations of biological therapies.

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Notes


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