Gastroenterology 2019;156:748–764

CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis

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This document presents the official recommendations of the American Gastroenterological Association (AGA) on the management of mild-to-moderate ulcerative colitis (UC). The guideline was developed by the AGA Institute's Clinical Guidelines Committee and approved by the AGA Institute Governing Board. It is accompanied by a technical review[1] that is a compilation of the clinical evidence on which these recommendations were formulated. Development of this guideline and the accompanying technical review was fully funded by the AGA Institute without additional outside funding.

UC is a chronic inflammatory bowel disease with onset most frequently in young adulthood. Most patients with UC have a mild-to-moderate course characterized by periods of activity or remission. More than 90% of patients with UC are treated with 5-aminosalicylates (5-ASA) shortly after disease diagnosis, and most who achieve clinical remission with these medications continue them for maintenance of remission.[2] The minority of patients with UC require immunomodulators or biologic therapies for disease control.[2]

The severity of UC is generally classified as mild-to-moderate or moderate-to-severe. The definition of mild-to-moderate disease activity in UC varies in clinical practice and the medical literature. For this guideline and the accompanying technical review, mild–moderate UC was defined as patients with <4–6 bowel movements per day, mild–moderate rectal bleeding, absence of constitutional symptoms, low overall inflammatory burden, and absence of features suggestive of high inflammatory activity, based upon Truelove and Witt's criteria[3] and the Mayo Clinic score.[4] Although disease activity exists on a spectrum, patients in the mild–moderate category who have more frequent bowel movements, more prominent rectal bleeding, or greater overall inflammatory burden should be considered to have moderate disease. Patients with mild–moderate disease activity generally are at low risk of requiring colectomy. However, certain disease features, even in patients who present initially with mild–moderate disease activity, may predict an aggressive disease course.[5] These include age younger than 40 years at diagnosis, extensive disease, severe endoscopic activity (presence of deep ulcers), extra-intestinal manifestations, and elevated inflammatory markers.[5] Clinicians should be aware of these high-risk features to identify patients who may benefit from more aggressive initial therapy or who might need more rapid intensification of therapy if symptoms are not adequately controlled. In addition, clinicians should avoid repeated courses of corticosteroids, even in those with mild–moderate disease, and consider escalation of therapy in patients who frequently need corticosteroids for disease control.

Patients with UC may have variable anatomic extent of their disease. Conventionally, patients are defined as having extensive disease if inflammation extends proximal to the splenic flexure, left-sided disease if inflammation extends proximal to the rectum but not past the splenic flexure (or <50 cm from the anus), and proctitis if inflammation is limited to the rectum (or <15–20 cm from the anus). Both disease severity and anatomic extent are important in choosing appropriate treatment.

The mainstay of therapy for mild–moderate UC is the 5-ASA class of medications, including sulfasalazine, mesalamine, and diazo-bonded 5-ASA (Table 1). Sulfasalazine, the oldest medication in this class, consists of 5-ASA bonded to sulfapyridine. Sulfasalazine is converted to the sulfapyridine and 5-ASA moieties by colonic bacteria. The 5-ASA moiety is believed to be the active compound for treatment of UC, while sulfapyridine is thought to contribute to adverse effects. Mesalamine is available in a variety of formulations designed to deliver the active compound to different parts of the small or large intestine. Diazo-bonded 5-ASAs, including balsalazide and olsalazine, are prodrugs converted to 5-ASA by colonic bacteria. Systemic exposure to 5-ASA is similar for all oral mesalamine preparations and diazo-

Abbreviations used in this paper: **AGA, American Gastroenterological Association; 5-ASA, 5-aminosalicylates; CIR, controlled ileal release; FMT, fecal microbiota transplantation; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, relative risk; UC, ulcerative colitis.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2018.12.009

Table 1. Characteristics of Available 5-Aminosalicylates and Sulfasalazine

Mesalamine	Diazo-bonded 5-ASAs	Sulfasalazine
Chemical structure		
5-ASA	Prodrug converted to 5-ASA in the colon Olsalazine consists of two 5-ASA moieties joined by an azo bond Balsalazide consists of one 5-ASA moiety linked to an inert carrier molecule	Prodrug consisting of 5-ASA linked to sulfapyridine Converted to 5-ASA and sulfapyridine moieties in the colon The 5-ASA moiety is believed to be the active compound for treatment of ulcerative colitis, while sulfapyridine is thought to contribute to most adverse effects
Availability		
Delayed-release enteric-coated tablet: pH-sensitive to allow release in distal ileum and colon	Olsalazine	Enteric or non-enteric–coated tablets
Controlled release: delivery beginning in duodenum and continuing into lower bowel	Balsalazide	
MMX-delayed and extended delivery throughout the lower bowel		
Capsule containing delayed enteric-coated granules		
Dosage		
Low dose: <2 g/d mesalamine Standard dose: 2–3 g/d mesalamine High dose: >3 g/d mesalamine	6.75 g balsalazide provides approximately 2.4 g 5-ASA	4 g sulfasalazine provides approximately 1.6 g 5-ASA
Adverse effects		
Uncommon idiosyncratic worsening of colitis, presumed hypersensitivity syndrome Uncommon: interstitial nephritis	Secretory diarrhea (primarily with olsalazine) Rare idiosyncratic worsening of colitis, presumed hypersensitivity syndrome Rare: interstitial nephritis	Interferes with folate metabolism Male infertility Rare serious cutaneous side effects, such as Stevens-Johnson syndrome Anemia, leukopenia, and thrombocytopenia Pneumonitis Hepatitis
Monitoring		
Monitor renal function periodically	Monitor renal function periodically	Monitor complete blood count and liver function tests periodically Patients should take folic acid supplement

bonded 5-ASAs.[6] Therapeutic efficacy and safety are also similar with different 5-ASA formulations.[7] Therefore, comparability of the different commercial formulations of mesalamine at equivalent doses was assumed for purposes of this guideline.

This guideline addresses the medical management of patients with mild–moderate UC, focusing on use of both oral and topical 5-ASA medications, rectal corticosteroids, and oral budesonide. Unless otherwise specified, we do not present separate recommendations for induction and maintenance of remission, as patients who receive induction therapy with 5-ASAs most commonly remain on these agents to maintain remission. The guideline first discusses appropriate therapy for patients with extensive disease, with additional specific recommendations for patients with proctosigmoiditis or isolated proctitis. The guideline also covers less-conventional therapies, including probiotics, curcumin, and fecal microbiota transplantation (FMT). While this guideline is intended to assist in management of patients with mild–moderate UC, some patients will not respond adequately to the therapies outlined here, and may need to escalate therapy to systemic corticosteroids, immunomodulators, or biologic therapies for induction and maintenance of remission. The use of biologic therapies and immunomodulators is not specifically addressed in this guideline.

In the recommendations presented here and the accompanying technical review,[1] estimates of the effects of different medications are presented as the risk for failure to induce or maintain remission. Therefore, a relative risk (RR) <1 indicates that the agent under evaluation is more effective than the comparison medication or placebo for inducing or maintaining remission; RR >1 indicates that the agent under evaluation is less effective.

This guideline was developed using a process described elsewhere.[8] Briefly, the AGA process for developing

Table 2. Grading of Recommendations Assessment, Development, and Evaluation Definitions of Quality and Certainty of the Evidence

Quality grade	Definition
High	We are very confident that the true effect lies close to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low	Our confidence in the estimate is limited. The true effect may be substantially different from the estimate of effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
Evidence gap	Available evidence is insufficient to determine true effect.

clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[9] and best practices as outlined by the Institute of Medicine.[10] GRADE methodology was used to prepare the background information for the guideline and the accompanying technical review. Optimal understanding of the guideline will be enhanced by reading the applicable portions of the technical review. The guideline panel and the authors of the technical review met face to face on March 4, 2018 to discuss the findings from the technical review. The guideline authors subsequently formulated the recommendations. Although the quality of evidence (Table 2) was a key factor in determining the strength of the recommendations (Table 3), the panel also considered the balance between benefit and harm of interventions, patients' values and preferences, and resource utilization. The recommendations, quality of evidence, and strength of recommendations are summarized in Table 4.

Recommendation 1. In patients with extensive mild–moderate UC, the AGA recommends using either standard-dose mesalamine (2–3 g/d) or diazo-bonded 5-ASA rather than low-dose mesalamine, sulfasalazine, or no treatment. *Strong recommendation, moderate quality evidence.*
Comment: Patients already on sulfasalazine in remission or patients with prominent arthritic symptoms may reasonably choose sulfasalazine 2–4 g/d if alternatives are cost-prohibitive, albeit with higher rate of intolerance.

The AGA recommends treating patients with extensive mild–moderate UC with either standard-dose mesalamine or diazo-bonded 5-ASA. Eighteen randomized controlled trials (RCTs) comparing different doses of mesalamine or placebo were identified and reviewed. For purposes of this guideline and the technical review, low-dose mesalamine was defined as a total daily dose <2 g, standard dose as 2–3 g/d, and high dose as >3 g/d. High-dose,[4,11–15] standard-dose,[11,13,14,16–19] and low-dose mesalamine[4,11,16,18] were all superior to placebo for induction of remission (RR, 0.75; 95% confidence interval [CI], 0.66–0.86 for high dose; RR, 0.84; 95% CI, 0.78–0.91 for standard dose; RR, 0.88; 95% CI, 0.82–0.94 for low dose), and all doses were well tolerated. Both high-dose[4, 11,20–23] and standard-dose[11,15,16,18,20–24] mesalamine were superior to low-dose mesalamine for induction of remission (RR, 0.81; 95% CI, 0.71–0.92 for high dose; RR, 0.88; 95% CI, 0.79–0.99 for standard dose), with a trend favoring a modest benefit of high-dose over standard-dose mesalamine (RR, 0.94; 95% CI, 0.88–1.01).[11,13–15,20–23,25–28] For maintenance of remission, both standard-dose[29,30] and low-dose mesalamine[31–33] were superior to placebo (RR, 0.55; 95% CI, 0.43–0.70 for standard dose; RR, 0.63; 95% CI, 0.51–0.78 for low dose), and

Table 3. Grading of Recommendations Assessment, Development, and Evaluation Definitions on Strength of Recommendation and Guide to Interpretation

Strength of recommendation	Wording in the guideline	For the patient	For the clinician
Strong	"The AGA recommends…"	Most individuals in this situation would want the recommended course and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests…"	The majority of individuals in this situation would want the suggested course, but many would not.	Different choices would be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
No recommendation	"The AGA makes no recommendation…"	—	The confidence in the effect estimate is so low that any effect estimate is speculative at this time.

Table 4. Summary of Recommendations of the American Gastroenterological Association Clinical Guidelines Committee for the Management of Mild-to-Moderate Ulcerative Colitis

Recommendations	Strength of recommendation	Quality of evidence
1. In patients with extensive mild–moderate UC, the AGA recommends using either standard-dose mesalamine (2–3 g/d) or diazo-bonded 5-ASA rather than low-dose mesalamine, sulfasalazine, or no treatment.	Strong	Moderate
Comment: Patients already on sulfasalazine in remission or patients with prominent arthritic symptoms may reasonably choose sulfasalazine 2–4 g/d if alternatives are cost-prohibitive, albeit with higher rate of intolerance		
2. In patients with extensive or left-sided mild–moderate UC, the AGA suggests adding rectal mesalamine to oral 5-ASA.	Conditional	Moderate
3. In patients with mild–moderate UC with suboptimal response to standard-dose mesalamine or diazo-bonded 5-ASA or with moderate disease activity, the AGA suggests using high-dose mesalamine (>3 g/d) with rectal mesalamine.	Conditional	Moderate (induction of remission) Low (maintenance of remission)
4. In patients with mild–moderate UC being treated with oral mesalamine, the AGA suggests using once-daily dosing rather than multiple times per day dosing.	Conditional	Moderate
5. In patients with mild–moderate UC, the AGA suggests using standard-dose oral mesalamine or diazo-bonded 5-ASA, rather than budesonide MMX or controlled ileal release budesonide for induction of remission.	Conditional	Low
6. In patients with left-sided mild–moderate ulcerative proctosigmoiditis or proctitis, the AGA suggests using mesalamine enemas (or suppositories) rather than oral mesalamine.	Conditional	Very low
Comment: patients who place a higher value on convenience of oral medication administration and a lower value on effectiveness could reasonably choose oral mesalamine.		
7. In patients with mild–moderate ulcerative proctosigmoiditis who choose rectal therapy over oral therapy, the AGA suggests using mesalamine enemas rather than rectal corticosteroids.	Conditional	Moderate
Comment: Patients who place a higher value on avoiding difficulties associated with mesalamine enemas and a lower value on effectiveness may reasonably select rectal corticosteroid foam preparations.		
8. In patients with mild–moderate ulcerative proctitis who choose rectal therapy over oral therapy, the AGA recommends using mesalamine suppositories.	Strong	Moderate
9. In patients with mild–moderate ulcerative proctosigmoiditis or proctitis being treated with rectal therapy who are intolerant of or refractory to mesalamine suppositories, the AGA suggests using rectal corticosteroid therapy rather than no therapy for induction of remission.	Conditional	Low
10. In patients with mild–moderate UC refractory to optimized oral and rectal 5-ASA, regardless of disease extent, the AGA suggests adding either oral prednisone or budesonide MMX.	Conditional	Low
11. In patients with mild–moderate UC, the AGA makes no recommendation for use of probiotics.	No recommendation	Knowledge gap
12. In patients with mild–moderate UC despite 5-ASA therapy, the AGA makes no recommendation for use of curcumin.	No recommendation	Knowledge gap
13. In patients with mild–moderate UC without *Clostridium difficile* infection, the AGA recommends fecal microbiota transplantation be performed only in the context of a clinical trial.	No recommendation for treatment of UC	Knowledge gap

standard-dose was superior to low-dose mesalamine[34–37] (RR, 0.63; 95% CI, 0.55–0.78). No benefit of high-dose over standard-dose mesalamine was seen for maintenance of remission[38,39] (RR, 0.93; 95% CI, 0.71–1.17).

Six RCTs comparing diazo-bonded 5-ASA with placebo for induction[40–45] and 2 trials of olsalazine[46,47] for maintenance of remission were identified. No trials of balsalazide for maintenance of remission were found. Diazo-bonded 5-ASA was significantly better than placebo for both induction (RR, 0.86; 95% CI, 0.76–0.98) and was numerically, but not statistically, better for maintenance of remission (RR, 0.71; 95% CI, 0.41–1.21). Olsalazine was less well tolerated than both placebo and balsalazide due to the adverse effect of watery diarrhea.[1] There was also a trend toward superiority of diazo-bonded 5-ASA over standard-dose mesalamine for induction of remission[48–52] (RR, 0.81; 95% CI, 0.60–1.08). Diazo-bonded 5-ASA was more effective than mesalamine for maintenance of remission[53–55] (RR, 0.69; 95% CI, 0.51–0.98), though only low-dose mesalamine was used for comparison in these trials. Rates of treatment discontinuation were higher for olsalazine than placebo, but not for balsalazide vs placebo.

Evidence for sulfasalazine comes from 2 RCTs conducted in the 1960s. In these studies, sulfasalazine was given at

doses of 2–6 g/d and was more effective than placebo for induction of remission[56,57] (RR, 0.62; 95% CI, 0.45–0.87). There was large heterogeneity in the effect estimate, with a larger effect size observed in the trial using doses of 4–6 g/d. Sulfasalazine 2 g/d was more effective than placebo for maintenance of remission[58–61] (RR, 0.45; 95% CI, 0.23–0.89). However, sulfasalazine was not well tolerated, with a high rate of treatment discontinuation in the induction trials (RR for treatment discontinuation, 5.14; 95% CI, 0.95–27.93). In trials of maintenance therapy enrolling patients who entered remission on sulfasalazine, tolerability was better with modestly increased rates of treatment discontinuation compared to placebo[58–61] (RR, 2.22; 95% CI, 0.67–7.35).

Pooled analysis of 4 trials comparing sulfasalazine to standard-dose mesalamine strongly suggested superiority of mesalamine[21,24,62,63] (RR, 1.27; 95% CI, 0.94–1.73). For maintenance of remission, pooled estimates from 6 RCTs, most of which used low-dose mesalamine, showed that sulfasalazine was not statistically inferior to mesalamine[64–69] (RR, 1.13; 95% CI, 0.91–1.40). Like mesalamine, diazo-bonded 5-ASA was more effective than sulfasalazine for inducing remission[70–77] (RR, 0.77; 95% CI, 0.61–0.96) with similar effectiveness for maintenance of remission[76,78–82] (RR, 1.07; 95% CI, 0.98–1.16). Overall, mesalamine and diazo-bonded 5-ASA were better tolerated than sulfasalazine in the induction but not the maintenance trials.

Systemic exposure to 5-ASA is similar for all oral mesalamine preparations and diazo-bonded 5-ASA.[6] Mesalamine and balsalazide are generally well tolerated without significant adverse events, except for the rare occurrence of interstitial nephritis (Table 1). Olsalazine is generally less well tolerated than either mesalamine or balsalazide, with up to a 20% risk of secretory diarrhea necessitating treatment discontinuation. Although many different preparations of mesalamine are commercially available, there is little evidence to suggest differences in efficacy between them.[7] Therefore, we do not recommend switching between mesalamine preparations in search of more effective treatment. Balsalazide is the preferred diazo-bonded 5-ASA due to its better tolerability.

Conversely, sulfasalazine is often poorly tolerated due to side effects, such as headache, nausea, diarrhea, and rash (Table 1). Patients often need to start at lower-dose sulfasalazine with gradual dose escalation as tolerated. In addition, sulfasalazine interferes with folic acid metabolism, and patients are recommended to take folate supplementation. Rare but serious cutaneous side effects, allergic reactions, hepatitis, and hematologic toxicity are also possible. Because of these side effects, laboratory monitoring of complete blood counts and liver function tests is needed. Overall, sulfasalazine may be more difficult to incorporate routinely into clinical practice because of its adverse effects and need for laboratory monitoring. However, sulfasalazine is commonly prescribed for rheumatologic disorders, including spondyloarthropathies, rheumatoid arthritis, and psoriatic arthritis,[83–85] and patients with concomitant arthritic symptoms may benefit from its use.

Overall, standard-dose mesalamine and diazo-bonded 5-ASA are effective for both induction and maintenance of remission. There may be a small benefit for high-dose mesalamine over standard-dose mesalamine for induction of remission, but not necessarily maintenance. Balsalazide is the better-tolerated diazo-bonded 5-ASA, with similar effectiveness to standard-dose mesalamine for induction and better efficacy for maintenance. Therefore, either standard-dose mesalamine or balsalazide are appropriate for treatment of extensive mild–moderate UC. Sulfasalazine is potentially an acceptable alternative in patients who can tolerate it or in patients with prominent arthritic symptoms.

The overall quality of evidence for this recommendation was moderate for both induction and maintenance of remission (Tables 3–7 in accompanying technical review). Evidence for high or standard-dose mesalamine vs placebo or low-dose mesalamine was rated as high quality; evidence for use of high-dose over standard-dose mesalamine for induction was rated as moderate quality. The quality of evidence for diazo-bonded 5-ASA vs placebo for induction of remission was rated high. However, the evidence for maintenance of remission was low quality due to imprecision and indirectness. In particular, no trials of balsalazide vs placebo for maintenance of remission were identified. Only low-quality evidence supported a benefit of diazo-bonded 5-ASA over standard-dose mesalamine for induction and maintenance of remission because the maintenance trials used low-dose, rather than standard-dose, mesalamine. Evidence supporting use of sulfasalazine over placebo was rated down due to imprecision for induction, and due to imprecision and indirectness for maintenance.

Recommendation 2. In patients with extensive or left-sided mild–moderate ulcerative colitis, the AGA suggests adding rectal mesalamine to oral 5-ASA. *Conditional recommendation, moderate quality evidence*.

The AGA suggests adding rectal mesalamine to oral 5-ASA therapy for patients with extensive mild–moderate UC. Four RCTs comparing combined oral and topical 5-ASA vs oral sulfasalazine or standard-dose mesalamine for induction of remission were identified. Combination therapy was significantly more effective for induction of remission[86–89] (RR, 0.68; 95% CI, 0.49–0.94), and was superior to oral 5-ASA alone for maintenance of remission in 2 RCTs[90,91] (RR, 0.45; 95% CI, 0.20–0.97). In the maintenance trials, enemas were used twice per week or for 1 week per month. Both oral and topical mesalamine were well tolerated.

Combined oral and rectal therapy may allow a higher effective dose of 5-ASA to be delivered to the involved area of the colon. The strategy of combining oral and topical therapy allows optimization of 5-ASA regimens to achieve higher rates of induction and maintenance of remission, potentially avoiding escalation of therapy to corticosteroids or immunosuppression. A potential drawback to a combined strategy is low patient acceptance of topical therapy and suboptimal adherence. Patients may prefer to try oral therapy first, with addition of rectal therapy in the event of inadequate response. Although trials did not compare

optimized combination therapy with oral and rectal 5-ASA vs corticosteroids and/or immunosuppressive therapy in the subset of patients with persistent mild–moderate disease activity, combination therapy may be able to salvage some patients with inadequate response to oral 5-ASA, and may be more acceptable to patients who wish to avoid corticosteroids or immunosuppression.[92]

The overall evidence for this recommendation was rated as moderate quality. The event rates in both the induction and maintenance trials were low, leading to imprecision. In the maintenance studies, the oral mesalamine groups received low-dose mesalamine, but the oral and rectal treatment groups received >2 g mesalamine in total, leading to indirectness because of differences in the total doses of medications received.

Recommendation 3. In patients with mild–moderate UC with suboptimal response to standard-dose mesalamine or diazo-bonded 5-ASA or with moderate disease activity, the AGA suggests using high-dose mesalamine (>3 g/d) with rectal mesalamine. *Conditional recommendation, moderate-quality evidence [induction of remission], low-quality evidence (maintenance of remission).*

The AGA suggests using combined high-dose oral mesalamine with rectal 5-ASA in patients with suboptimal response to standard-dose mesalamine or diazo-bonded 5-ASA or in patients with moderate disease activity, as defined above. High-dose oral mesalamine may have a modest benefit over standard-dose for induction of remission[11,13–15,20–23,25–28] (RR, 0.94; 95% CI, 0.88–1.01), and is similar for maintenance of remission[38,39] (RR, 0.93; 95% CI, 0.73–1.17). Escalating to high-dose over standard-dose mesalamine may have a modest benefit for achieving and maintaining remission. As discussed in Recommendation 2, addition of rectal therapy may provide some additional benefit over oral therapy alone, although some patients prefer to avoid rectal therapy.[92,93] Optimization of 5-ASA therapy by using high-dose oral therapy combined with rectal therapy may allow some patients to avoid corticosteroids or immunosuppression.

If patients are experiencing progressively worsening symptoms and increasing disease severity (eg, extra-intestinal manifestations or constitutional symptoms such as weight loss or fevers), escalation to high-dose oral mesalamine with rectal therapy may not be effective. These patients should be considered for use of systemic corticosteroids, biologic therapies, or immunomodulators to induce disease remission. Continuing 5-ASA–based therapy in these patients may delay more effective therapy and place patients at risk for worsening disease and complications.

The overall quality of evidence was rated as moderate for induction of remission and low for maintenance. Evidence was rated down for imprecision as confidence intervals for the effect estimates contained the possibility of no effect. Because no trials of high-dose oral and rectal mesalamine were identified, the evidence for this recommendation was considered indirect. However, as mentioned, combined oral and rectal therapy will effectively deliver a higher dose of mesalamine to the involved area of colon and optimize use of 5-ASA–based therapy before escalating treatment.

Recommendation 4. In patients with mild–moderate UC being treated with oral mesalamine, the AGA suggests using once-daily dosing rather than multiple times per day dosing. *Conditional recommendation, moderate quality evidence*.

The AGA suggests using once-daily dosing rather than multiple times per day dosing for patients with mild–moderate UC being treated with oral mesalamine. In 4 RCTs comparing equivalent doses of mesalamine administered once daily vs multiple times daily, there was no significant difference in the rate of induction of remission[13,14,94,95] (RR, 0.96; 95% CI, 0.85–1.08), while similar rates of maintenance of remission were seen in 11 trials comparing once or multiple times daily dosing[34,36,96–104] (RR, 0.96; 95% CI, 0.85–1.07). Within these clinical trials, adherence to the different dosing schedules, defined as taking >80% of recommended doses, was similar (pooled adherence 92.4% with once-daily vs 93.6% with multiple daily doses). However, medication adherence in clinical trials is typically better than seen in clinical practice. A meta-analysis of observational studies in patients with various chronic diseases demonstrated better adherence with once-daily dosing of medications compared to more complex dosing regimens.[105] With maintenance treatment, non-adherence to mesalamine is common and is associated with higher risk of disease relapse.[106–108] Because clinical effectiveness is similar with different dosing schemes, use of once-daily dosing will likely improve adherence, allow patients to achieve a higher daily dose of mesalamine, and improve overall disease control.

This conditional recommendation is intended to apply to all available formulations of mesalamine, as there are not demonstrable differences in efficacy between the different mesalamine products.[7] With formulations that require a large daily pill burden, taking the total recommended daily dose at one time may be challenging for patients; with such formulations, it is reasonable to simplify the recommended regimen into as few doses per day to maintain adherence. Comparative studies of diazo-bonded 5-ASA or sulfasalazine with different dosing schemes have not been conducted, so the panel did not make specific recommendations for these medications.

The quality of evidence supporting this recommendation was rated as moderate quality (Table 9 in accompanying technical review). Evidence was rated down due to imprecision with wide CIs for the effect estimates.

Recommendation 5. In patients with mild–moderate UC, the AGA suggests using standard-dose oral mesalamine or diazo-bonded 5-ASA, rather than budesonide MMX or controlled ileal-release budesonide for induction of remission. *(Conditional recommendation, low quality of evidence)*.

The AGA suggests using standard-dose oral mesalamine or diazo-bonded 5-ASA over budesonide preparations for induction of remission. Budesonide is a high-potency corticosteroid with low systemic activity due to first pass metabolism by the liver. Two oral preparations of budesonide are currently available. Budesonide MMX is designed for release throughout the colon and is approved by the US Food and Drug Administration for treatment of UC, while controlled ileal release (CIR) budesonide is primarily released in the distal ileum and right colon and has not been specifically approved for UC. Evidence for use of CIR-budesonide was derived from a 4-arm RCT comparing different doses of budesonide MMX to placebo, in which CIR-budesonide was used as an active comparator.[19] There are few long-term efficacy or safety data for use of budesonide for maintenance of remission and, therefore, budesonide is unsuitable for maintenance therapy, given the potential for corticosteroid-related adverse effects.

In pooled analysis of 3 RCTs, budesonide MMX 9 mg/d was more effective than placebo in inducing remission[19,109,110] (RR, 0.88; 95% CI, 0.83–0.94). In 1 RCT, CIR-budesonide was modestly more effective than placebo for this same indication[110] (RR, 0.93; 95% CI, 0.87–0.99). The 4-arm CORE-I trial compared budesonide MMX 6 mg or 9 mg daily, mesalamine 2.4 g daily, and placebo, finding no significant difference between budesonide MMX 9 mg/d and mesalamine in inducing remission[19] (RR, 0.94; 95% CI, 0.85–1.04) with similar tolerability. A separate RCT showed CIR-budesonide to be less effective than high-dose mesalamine for inducing remission[111] (RR, 1.34; 95% CI, 1.09–1.64) with higher discontinuation rates. In the CORE-II trial, budesonide MMX and CIR-budesonide were similarly effective in inducing remission[110] (RR, 0.95; 95% CI, 0.86–1.04) with comparable tolerability. Overall, the budesonide preparations are not superior to mesalamine for induction of remission. The lack of superiority over 5-ASA for induction of remission, and the lack of long-term efficacy and safety data for maintenance of remission with budesonide, make oral 5-ASAs the preferred treatment for most patients with mild–moderate UC.

The quality of evidence for budesonide MMX vs placebo was moderate and was rated down for imprecision due to low event rates. Evidence for CIR-budesonide vs placebo and for budesonide MMX vs mesalamine was rated as low quality due to imprecision and high risk of bias in the available studies. Evidence comparing CIR-budesonide to mesalamine was rated as moderate and was rated down due to low event rates (Tables 10 and 11 in accompanying technical review).

Recommendation 6. In patients with mild–moderate ulcerative proctosigmoiditis or proctitis, the AGA suggests using mesalamine enemas (or suppositories) rather than oral mesalamine. *Conditional recommendation, very-low-quality evidence*.
Comment: Patients who place a higher value on convenience of oral medication administration and a lower value on effectiveness could reasonably choose oral mesalamine.

The AGA suggests using mesalamine enemas (or suppositories) rather than oral mesalamine in patients with mild–moderate ulcerative proctosigmoiditis or proctitis. Pooled analysis of 4 RCTs showed a trend favoring rectal mesalamine over oral mesalamine for induction[88,112–114] (RR, 0.43; 95% CI, 0.14–1.31), but with considerable heterogeneity. After excluding 1 trial comparing high-dose MMX-release mesalamine vs mesalamine enemas, topical 5-ASA was significantly more effective than oral therapy (RR, 0.28; 95% CI, 0.14–0.56). For maintenance of remission, pooled effect estimates from 3 single-blinded trials showed a trend for increased effectiveness of topical 5-ASA vs oral therapy[115–117] (RR, 0.69; 95% CI, 0.41–1.17). In these studies, oral therapy consisted of sulfasalazine 2 g/d or low-dose mesalamine, while topical 5-ASA consisted of mesalamine enemas 4 g 2–3 times per week or 1 week per month.

Studies of topical mesalamines for UC have used varying definitions of left-sided disease. Some have defined left-sided disease as inflammation extending up to the splenic flexure, while others have used a definition of inflammation extending <50 cm from the anus. However, enema preparations are unlikely to reach proximal to the sigmoid colon. Patients with inflammation extending into the descending colon may be more appropriately treated with combined oral and topical therapy, as discussed in Recommendation 2.

Clinicians recognize that many patients prefer oral over topical therapy, and that adherence to rectal therapy may be inadequate. An additional limitation of rectal therapy is that patients with active disease may have difficulty retaining enemas adequately due to discomfort and urgency. Given these limitations and the uncertainty in the effect estimates, patients with mild–moderate ulcerative proctitis or proctosigmoiditis who place higher value on convenience of oral medication administration may reasonably choose oral 5-ASA over rectal therapy. Some patients with left-sided UC may choose to use combined oral and rectal therapy, as outlined in Recommendation 2.

The overall quality of evidence was rated very low due to high risk of bias and imprecision with wide CIs crossing 1 (Table 14 in accompanying technical review). Evidence for induction therapy was also rated down for inconsistency. Trials for maintenance therapy were rated down for indirectness as the oral comparator was low-dose and not standard-dose 5-ASA.

Recommendation 7. In patients with mild–moderate ulcerative proctosigmoiditis who choose rectal therapy over oral therapy, the AGA suggests using mesalamine enemas rather than rectal corticosteroids. *Conditional recommendation, moderate-quality evidence*.
Comment: Patients who place a higher value on avoiding difficulties associated with mesalamine enemas and a lower value on effectiveness may reasonably select rectal corticosteroid foam preparations.

If patients with ulcerative proctosigmoiditis are being treated with rectal therapy, the AGA suggests using

mesalamine enemas rather than rectal corticosteroids. Pooled results from 4 RCTs showed that mesalamine enemas (4 g nightly) are more effective than placebo for induction of remission[118–121] (RR, 0.50; 95% CI, 0.35–0.73). Only 1 small study of mesalamine enemas 1 g/d for maintenance of remission was identified, showing superiority to placebo[122] (RR, 0.30; 95% CI, 0.11–0.81). Rectal corticosteroid therapy is also effective for inducing remission, with a pooled RR, comparing rectal corticosteroids with placebo of 0.73 (95% CI, 0.66–0.80).[123–125] All the trials used rectal budesonide; 2 used foam preparations, and 1 used enemas.

Meta-analysis of 13 trials comparing rectal 5-ASA and rectal corticosteroids shows that topical 5-ASA (enemas 1–4 g/d or suppositories 1 g/d) is superior to topical corticosteroids for inducing remission (RR, 0.74; 95% CI, 0.61–0.90).[126–138] The topical corticosteroids studied in these RCTs included hydrocortisone, prednisolone, or budesonide enemas, and hydrocortisone or beclomethasone foam preparations. No head-to-head trials comparing budesonide foam to rectal 5-ASA were identified. Similar effects were seen when limiting the analysis to standard-dose 5-ASA enemas (4 g/d)[129,131,133,138] (RR, 0.39; 95% CI, 0.19–0.82). No trials of maintenance rectal corticosteroids were identified, and their long-term effectiveness and safety are unknown.

Overall, rectal 5-ASA is superior to rectal corticosteroids for induction of remission, and both are superior to placebo. Given potential safety concerns with long-term rectal corticosteroids and superiority of rectal 5-ASA for inducing remission, topical 5-ASAs are preferred. In general, rectal 5-ASA and corticosteroids are both well tolerated. However, some patients, particularly those with active disease, experience discomfort with enemas or are unable to retain them adequately. Patients may prefer corticosteroid foam preparations over enemas because of ease of delivery, better tolerability and improved retention, and foam and enema preparations of the same medication have similar efficacy.[136,139] Thus, patients on rectal therapy who place a higher value on ease and tolerance of medication administration may reasonably choose corticosteroid foam preparations over mesalamine enemas.

The quality of evidence comparing rectal 5-ASA to placebo for induction was moderate due to imprecision from low event rates, while evidence for rectal corticosteroids vs placebo for induction was rated as high (Tables 15–17 in accompanying technical review). The evidence supporting rectal 5-ASA over corticosteroids for induction was moderate, and was rated down for heterogeneity in the effect size. The evidence for maintenance rectal 5-ASA was rated as low quality because only 1 small study was available.

Recommendation 8. In patients with mild–moderate ulcerative proctitis who choose rectal therapy over oral therapy, the AGA recommends using mesalamine suppositories. *Strong recommendation, moderate-quality evidence*.

The AGA recommends using mesalamine suppositories in patients with mild–moderate ulcerative proctitis who opt for rectal therapy. Pooled analysis of 4 RCTs showed that mesalamine suppositories (1–1.5 g/d) are more effective than placebo in inducing remission (RR, 0.44; 95% CI, 0.34–0.56).[104,118,119,140] Maintenance therapy with mesalamine suppositories (0.5–1 g administered once per day to 3 times per week) is also superior to placebo (RR, 0.50; 95% CI, 0.32–0.79).[87,90,115,141] Mesalamine suppositories are generally well tolerated, with few treatment-related adverse effects and better retention than enemas.

No RCTs or cohort studies of corticosteroid suppositories for management of ulcerative proctitis were identified. Benefit may be indirectly inferred from studies of corticosteroid foams or enemas in patients with proctitis and left-sided colitis, although the quality of evidence is low. In addition, rectal corticosteroids have not been studied for maintenance of remission in ulcerative proctitis. Given concerns about long-term safety and effectiveness of corticosteroids for this indication, use of mesalamine suppositories is preferred for treatment of mild–moderate ulcerative proctitis.

The quality of evidence for mesalamine suppositories for induction of remission was rated as moderate, and was rated down for imprecision due to low event rates in the available studies (Table 18 in accompanying technical review). The evidence for mesalamine suppositories for maintenance of remission was rated as low quality due to imprecision and risk of bias.

Recommendation 9. In patients with mild–moderate ulcerative proctosigmoiditis or proctitis being treated with rectal therapy who are intolerant of or refractory to mesalamine suppositories, the AGA suggests using rectal corticosteroid therapy rather than no therapy for induction of remission. *Conditional recommendation, low-quality evidence*.

The AGA suggests using rectal corticosteroid therapy in patients with ulcerative proctitis who are refractory to or intolerant of mesalamine suppositories. Although there are no RCTs of corticosteroid suppositories in this population, indirect evidence from patients with ulcerative proctosigmoiditis suggests a benefit of rectal corticosteroids, as noted.[123–125] Additionally, some patients with prominent proctitis symptoms may tolerate a foam preparation with less discomfort and improved retention compared to a suppository. Therefore, a trial of a rectal corticosteroid is reasonable for patients with inadequate response or tolerance to mesalamine suppositories. Patients with refractory symptoms could also be considered for oral 5-ASAs or systemic corticosteroids.

The overall quality of evidence for this recommendation was low, and was rated down for indirectness because trials were not performed specifically in ulcerative proctitis patients.

Recommendation 10. In patients with mild–moderate UC refractory to optimized oral and rectal 5-ASA, regardless of disease extent, the AGA suggests adding either oral prednisone or budesonide MMX. *Conditional recommendation, low-quality evidence*.

The AGA suggests adding either oral prednisone or budesonide MMX in patients with symptoms refractory to optimized 5-ASA therapy. A single RCT in patients with mild–moderate disease activity despite 5-ASA therapy found that adding budesonide MMX to 5-ASA was only modestly more effective than placebo with 5-ASA for induction of remission[142] (RR, 0.95; 95% CI, 0.89–1.00). No trials directly comparing budesonide MMX with systemic corticosteroids such as prednisone were identified. We reviewed 3 studies comparing second-generation corticosteroids (CIR-budesonide, beclomethasone, and fluticasone) to oral prednisone or prednisolone for induction of remission.[143–145] Pooled results from these 3 trials showed no significant difference for inducing remission (RR, 1.04; 95% CI, 0.96–1.13). Rates of steroid-related adverse events were significantly lower with second-generation corticosteroids (RR, 0.32; 95% CI, 0.16–0.64). Thus, the evidence for comparable efficacy of budesonide MMX and systemic corticosteroids is indirect and in large part inferred from studies of other second-generation corticosteroids.

Patients may fail to achieve clinical remission despite optimized use of 5-ASA therapy, as outlined in the preceding recommendations. Management of these patients requires escalation of therapy, most commonly consideration of a course of corticosteroids to achieve disease control. Some patients with high-risk features as outlined in the introduction may also need earlier consideration of corticosteroids. Second-generation corticosteroids and oral prednisone appear to be equally effective for induction of remission in this situation, although in one study comparing prednisolone to fluticasone, symptoms improved more rapidly with prednisolone.[145] Second-generation corticosteroids appear to have fewer corticosteroid-related side effects, but are significantly more costly than oral prednisone. Therefore, the choice between budesonide MMX and oral prednisone primarily involves trading-off costs and potential for adverse events. Patients who place higher value on avoidance of side effects and lower value on avoiding costs can reasonably choose budesonide MMX in this situation. Lastly, patients who require repeated or prolonged corticosteroid courses should be considered for escalation to biologic therapies and/or immunomodulators.[146]

The overall quality of evidence for this recommendation was rated as low due to imprecision of the effect estimates (Tables 12 and 13 in accompanying technical review). It was also rated down for indirectness, as other second-generation corticosteroids and not budesonide MMX were used in the available RCTs.

Recommendation 11. In patients with mild–moderate ulcerative colitis, the AGA makes no recommendation for use of probiotics. *No recommendation, knowledge gap*.

The AGA makes no recommendation for use of probiotics in patients with mild–moderate UC. Seven RCTs enrolling 585 patients were identified, and probiotics were not more effective than placebo for inducing remission[147–153] (RR, 0.88; 95% CI, 0.69–1.12), with considerable heterogeneity. Notably, these studies used several different probiotic formulations, including *Bifidobacterium* species, *Lactobacillus acidophilus*, VSL #3, and *Escherichia coli Nissle* 1917. Only 1 single small trial compared a probiotic (*E coli Nissle 1917)* vs standard-dose mesalamine for induction, finding no significant difference in remission rates[154] (RR, 1.24; 95% CI, 0.70–2.22). There was no difference in rates of maintaining remission in 2 RCTs comparing probiotics to placebo[155,156] (RR, 0.82; 95% CI, 0.63–1.06) or in 2 RCTs comparing probiotics and mesalamine[157,158] (RR, 1.01; 95% CI, 0.84–1.22).

Although probiotics are popular among patients with UC, their benefit for either inducing or maintaining remission is unclear. In general, probiotics are well-tolerated with low rates of adverse effects. However, if they are used instead of other proven therapy, patients are at risk for progressive symptoms and disease complications. Thus, given their lack of proven efficacy, probiotics should not be used instead of therapies known to be effective. The effectiveness of probiotics added on to proven therapies, such as oral or rectal 5-ASA is unknown.

The identified RCTs were inconsistent in studying several different probiotic formulations and with heterogeneous results. Additional research in this area is needed to identify patient populations for whom probiotics might be beneficial, to identify specific bacterial strains with the greatest therapeutic potential, and to determine appropriate doses.

The quality of evidence comparing probiotics and placebo was rated as very low for several reasons (Table 19 in accompanying technical review). There was inconsistency in the type of probiotic formulations used and in the summary effect estimates. The RCTs were at high risk of bias, with unclear allocation concealment and methods of randomization. Estimates of effect were imprecise with wide CIs crossing 1. The evidence comparing probiotics and mesalamine was rated as very low quality for very serious imprecision and high risk of bias.

Recommendation 12. In patients with mild–moderate ulcerative colitis despite 5-ASA therapy, the AGA makes no recommendation for use of curcumin. *No recommendation, knowledge gap*.

Due to limited evidence, the AGA makes no recommendation for adding curcumin in patients with mild–moderate UC despite 5-ASA therapy. Pooled results from 3 RCTs enrolling 169 patients with mild–moderate symptoms despite standard-dose mesalamine showed a trend to a benefit for oral curcumin over placebo[159–161] (RR, 0.70; 95% CI, 0.48–1.03), with considerable heterogeneity. These 3 studies used widely varying doses of curcumin (150 mg to 3 g/d). The only strongly positive study had an exceptionally low placebo response (12.5%) and remission rates (0%).[161] A single small trial of maintenance therapy in patients also taking mesalamine showed benefit of adding oral curcumin over placebo in maintaining remission[162] (RR, 0.30; 95% CI, 0.11–0.85).

Curcumin has immunomodulatory, pro-apoptotic, and anti-angiogenic properties that have sparked interest in its use for immune-mediated diseases.[163] Because of curcumin's taste and color, it is difficult to develop true placebos for RCTs, and studies of its efficacy are at risk of bias due to inadequate blinding. Curcumin is generally well tolerated without significant harmful effects. The potential risk of using curcumin is delaying more effective therapy with potential for symptom progression. Larger well-designed studies of curcumin are needed to define its role in patients who do or do not respond to proven therapy, such as oral or topical 5-ASA and to evaluate its effectiveness for maintenance.

The overall body of evidence for curcumin in induction of remission was rated as very low quality due to high risk of bias, inconsistency, and imprecision due to low event rates and wide CIs for the effect estimates (Table 20 in accompanying technical review). The evidence for maintenance of remission was rated as very low quality due to serious imprecision because only 1 small trial was identified.

Recommendation 13. In patients with mild–moderate UC without *Clostridium difficile* infection, the AGA recommends fecal microbiota transplantation be performed only in the context of a clinical trial. *No recommendation for treatment of ulcerative colitis, knowledge gap*.

The AGA recommends that FMT be performed only in the context of a clinical trial for patients with mild–moderate UC who do not have *Clostridium difficile* infection. Pooled analysis of 4 RCTs enrolling 281 patients with active symptoms showed that FMT was more effective in inducing clinical remission (RR, 0.80; 95% CI, 0.71–0.89) and endoscopic remission[164–167] (RR, 0.77; 95% CI, 0.63–0.93). FMT and placebo were similarly well tolerated. No RCTs of FMT for maintenance of remission were identified. However, a meta-analysis of 5 non-comparative cohort studies was identified, including 44 patients who received 1–5 FMTs.[164] Of the 44 patients, 22 had clinical response, 16 were unchanged, and 3 patients deteriorated over 4–72 months of follow-up.

The RCTs of FMT were quite heterogeneous in route of administration and inclusion criteria. FMT was variously delivered by colonoscopy followed by 2 enemas,[168] enemas administered 5 days per week for 8 weeks,[166] weekly enemas for 6 weeks,[165] or 2 nasoduodenal tube infusions separated by 3 weeks.[167] The source and quantity of transplanted stool differed between studies, as did the comparator (autologous stool in 2 trials, water in 2 trials). Because of this heterogeneity, there is no evidence to guide practitioners in terms of appropriate donors, dose, route, or schedule of administration for FMT.

FMT is generally well-tolerated, with few serious adverse events in the RCTs for UC. A meta-analysis of 50 studies of FMT for UC or other indications (primarily recurrent *C difficile* infection) showed serious adverse events in 9.2%, including death (3.5%) and infection (2.5%).[169] Another potential adverse effect is the theoretic risk for transmission of infections or chronic diseases, such as obesity and autoimmune conditions.[170] Large studies with long-term follow-up are needed to help understand these risks.

The use of FMT for treatment of UC should be considered experimental at this time, and the Food and Drug Administration does not currently allow FMT for indications other than *C difficile* infection unless conducted as part of a clinical trial. The use of FMT also risks delay in initiation of proven therapy, with possible ongoing or worsening disease activity. Further mechanistic and clinical studies are needed to determine whether FMT will be beneficial in this patient population.

The overall evidence for FMT in induction of remission was rated as low due to inconsistency in the interventions studied and imprecision from low event rates (Table 21 in accompanying technical review). The quality of evidence for FMT in maintenance of remission was rated as very low because only small, non-comparative cohort studies of heterogeneous patients were available.

Summary

These practice recommendations for the management of mild–moderate UC were developed using the GRADE framework and in adherence to the standards set forth by the Institute of Medicine for creation of trustworthy guidelines.[9,10] They are intended to reduce practice variation and promote high-quality, high-value care for patients with mild–moderate UC.

The current evidence supports use of standard-dose mesalamine or diazo-bonded 5-ASAs for induction and maintenance of remission in patients with extensive mild–moderate UC. Use of combined oral and rectal 5-ASA in patients with extensive disease may improve rates of induction of remission, as may escalation to high-dose oral with rectal 5-ASA in patients with suboptimal response to standard-dose therapy. Those with moderate symptoms may benefit from early use of combined oral and rectal 5-ASA. Patients with proctosigmoiditis or proctitis can be treated with topical mesalamines rather than oral 5-ASA. Those patients with suboptimal response or intolerance to rectal mesalamine may opt to use rectal corticosteroids enemas or foams. Patients with inadequate response to optimized 5-ASA require escalation of therapy to oral prednisone or budesonide MMX.

We identified several knowledge gaps and areas for future research in this patient population. Due to evidence gaps, the AGA makes no recommendation for use of probiotics, curcumin, or FMT in patients with mild–moderate UC. Although these modalities appear to be safe, their use risks delaying proven effective therapy with the potential for worsening symptoms or complications. Thus, further studies of their efficacy and safety compared to those of the therapies recommended here are urgently needed. Development and validation of risk-stratification tools to identify patients who have mild–moderate symptoms but who are at high risk of progression to moderate–severe disease and/or

colectomy are needed. Better understanding of optimal dosing regimens, in particular, which patients might benefit from initial use of high-dose mesalamine or topical mesalamine, is also required. We also identified a need to better understand the relative effectiveness and side effects of budesonide and systemic corticosteroids in patients who do not respond adequately to 5-ASAs. Finally, studies to identify the appropriate patient and timing for escalation to immunomodulators and/or biologics would help with targeting therapy appropriately.

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Acknowledgments
The American Gastroenterological Association Clinical Guidelines Committee included Seth Crockett, University of North Carolina at Chapel Hill, NC; Yngve Falck-Ytter, Veterans Affairs and Case Medical Center Cleveland; Joseph Feuerstein, Beth Israel Deaconess Medical Center, Brookline, MA; Steven Flamm, Northwestern University, Chicago, IL; John Inadomi, University of Washington, Seattle, WA; Cynthia Ko, University of Washington, Seattle, WA; Thiruvengadam Muniraj, Yale University, Milford, CT; Robert O'Shea, Cleveland Clinic, University Heights, OH; John Pandolfino, Northwestern University, Chicago, IL; Amit Patel, Duke University, Cary, NC; Ravi Sharaf, North Shore Long Island Jewish Health System, New Hyde Park, NY; Shazia Siddique, University of Pennsylvania, Philadelphia, PA; Grace Su, University of Michigan, Ann Arbor, MI; Kenneth Wang, Mayo Clinic, Rochester, MI; Adam Weizman, Mount Sinai Hospital, Toronto, ON.

At time of publication, litigation between the manufacturer of VSL#3 and Dr. De Simone/ExeGi Pharma over intellectual property claims was ongoing.

Conflicts of interest
All members were required to complete the disclosure statement. These statements are maintained at the American Gastroenterological Association headquarters in Bethesda, Maryland, and pertinent disclosures are published with this report.

This document presents the official recommendations of the American Gastroenterological Association (AGA) on the management of mild-to-moderate ulcerative colitis. The guideline was developed by the AGA's Clinical Practice Guideline Committee and approved by the AGA Governing Board.

Funding
Development of this guideline and its accompanying technical review was fully funded by the AGA Institute with no additional outside funding.