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GUIDELINES

AGA Clinical Practice Guideline on Fecal Microbiota–Based Therapies for Select Gastrointestinal Diseases

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BACKGROUND & AIMS: Fecal microbiota–based therapies include conventional fecal microbiota transplant and US Food and Drug Administration–approved therapies, fecal microbiota live-jslm and fecal microbiota spores live-brpk. The American Gastroenterological Association (AGA) developed this guideline to provide recommendations on the use of fecal microbiota–based therapies in adults with recurrent *Clostridioides difficile* infection; severe to fulminant *C difficile* infection; inflammatory bowel diseases, including pouchitis; and irritable bowel syndrome. **METHODS:** The guideline was developed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework to prioritize clinical questions, identify patient-centered outcomes, and conduct an evidence synthesis. The guideline panel used the Evidence-to-Decision framework to develop recommendations for the use of fecal microbiota–based therapies in the specified gastrointestinal conditions and provided implementation considerations for clinical practice. **RESULTS:** The guideline panel made 7 recommendations. In immunocompetent adults with recurrent *C difficile* infection, the AGA suggests select use of fecal microbiota–based therapies on completion of standard of care antibiotics to prevent recurrence. In mildly or moderately immunocompromised adults with recurrent *C difficile* infection, the AGA suggests select use of conventional fecal microbiota transplant. In severely immunocompromised adults, the AGA suggests against the use of any fecal microbiota–based therapies to prevent recurrent *C difficile*. In adults hospitalized with severe or fulminant *C difficile* not responding to standard of care antibiotics, the AGA suggests select use of conventional fecal microbiota transplant. The AGA suggests against the use of conventional fecal microbiota transplant as treatment for inflammatory bowel diseases or irritable bowel syndrome, except in the context of clinical trials. **CONCLUSIONS:** Fecal microbiota–based therapies are effective therapy to prevent recurrent *C difficile* in select patients. Conventional fecal microbiota transplant is an adjuvant treatment for select adults hospitalized with severe or fulminant *C difficile* infection not responding to standard of care antibiotics. Fecal microbiota transplant cannot yet be recommended in other gastrointestinal conditions.

Keywords: Fecal Microbiota Transplant; *C Difficile* Infection; Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Pouchitis; Irritable Bowel Syndrome.

Fecal microbiota–based therapies include conventional fecal microbiota transplant (FMT) and US Food and Drug Administration (FDA)–approved therapies, fecal microbiota live-jslm and fecal microbiota spores live-brpk. Many clinicians are aware that gut dysbiosis plays a central role in the pathogenesis of *Clostridioides difficile* infections (CDIs) and that conventional FMT is used in the management of recurrent CDIs. There is emerging awareness that dysbiosis may play a role in inflammatory bowel diseases (IBDs), including Crohn's disease (CD), ulcerative colitis (UC), and pouchitis, as well as irritable bowel syndrome (IBS).[1] Trials have investigated conventional FMT in each of these conditions, but there is uncertainty regarding the appropriate use of these therapies.

Objectives

The objective of this American Gastroenterological Association (AGA) guideline is to present clinical recommendations on the use of fecal microbiota–based therapies in adults with recurrent CDI and conventional FMT in severe to fulminant CDI in the hospital setting, IBDs (ie, CD, UC, and pouchitis), and IBS based on the best available evidence.

Target Audience

The target audience for this guideline includes health care professionals, patients, and policy makers. The recommendations in this guideline are intended to provide the basis for rational informed decision making for patient and health care professionals using fecal microbiota–based therapies for adults with recurrent CDI or conventional FMT for severe to fulminant CDI, IBD, and IBS. The recommendations are summarized in Table 1.

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Abbreviations used in this paper: **AGA, American Gastroenterological Association; CD, Crohn's disease; CDI, *Clostridioides difficile* infection; CoE, certainty of evidence; COI, conflict of interest; FDA, US Food and Drug Administration; FMT, fecal microbiota transplant; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; MCID, minimum clinically important difference; PICO, population, intervention, comparator, outcomes; RCT, randomized controlled trial; RR, relative risk; UC, ulcerative colitis.**

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Table 1. Executive Summary of Recommendations and Implementation Considerations

Recommendations
1. **In immunocompetent adults with recurrent *C difficile* infection, the AGA suggests the use of fecal microbiota–based therapies upon completion of standard of care antibiotics over no fecal microbiota–based therapies. *(Conditional recommendation, low certainty evidence)*** The following considerations are specific to immunocompetent adult patients with nonsevere, nonfulminant recurrent CDI in the outpatient setting. Diagnosis of recurrent CDI: • A CDI diagnosis requires acute-onset, clinically significant, new-onset diarrhea (eg, 3 or more unformed stools in 24 hours) and highly sensitive (nucleic acid amplification or glutamate dehydrogenase) in combination with highly specific (toxin enzyme immunoassay) testing plus improvement of diarrhea with *C difficile*–directed antibiotics. A positive nucleic acid amplification test alone in the appropriate clinical context is also reasonable for making a CDI diagnosis. • Recurrent CDI is typically defined as clinically significant diarrhea with a confirmatory positive test within 8 weeks of completing antibiotics for CDI. • In patients who develop recurrent diarrhea after treatment for CDI, it is important to consider not only CDI recurrence, but also alternative diagnoses, especially if there are atypical symptoms, such as diarrhea alternating with constipation or no response in diarrheal symptoms to treatment with vancomycin or fidaxomicin. When to consider fecal microbiota–based therapies: • Fecal microbiota–based therapies include conventional FMT, fecal microbiota live-jslm and fecal microbiota spores live-brpk. • Prevention with fecal microbiota–based therapies can be considered in patients after the second recurrence (third episode) of CDI or in select patients at high risk of either recurrent CDI or a morbid CDI recurrence. Select use includes patients who have recovered from severe, fulminant, or particularly treatment-refractory CDI and patients with significant comorbidities. • Careful consideration before proceeding with fecal microbiota–based therapies is recommended in patients who require frequent antibiotics or long-term antibiotic prophylaxis, because ongoing antibiotics may diminish the efficacy of such therapy. How to administer fecal microbiota–based therapies: • Fecal microbiota–based therapies should be given upon completion of a course of standard of care antibiotics for recurrent CDI. The fecal microbiota–based therapies are to prevent recurrence, not for CDI treatment. • Suppressive anti-CDI antibiotics (eg, vancomycin) should be used to bridge standard of care antibiotics until fecal microbiota–based therapies are given. • Ideally, antibiotics for CDI should be stopped 1–3 days before conventional FMT to allow adequate time for antibiotics to wash out of the system.[16] If a bowel purge is given, FMT can be given 1 day after stopping antibiotics. If no bowel purge is given, 3 days off antibiotics is recommended to allow clearance of oral antibiotics. Rarely, patients will recur rapidly (within 1–2 days of stopping CDI antibiotics), this risk needs to be considered when determining an individual treatment window. When administering fecal microbiota spores live-brpk and fecal microbiota live-jslm, refer to the manufacturer package insert for instructions. • Conventional FMT should be performed with appropriately screened donor stool.[17,18] • Conventional FMT can be delivered via multiple routes. There is insufficient evidence to recommend a specific route. Alternatives to fecal microbiota–based therapies: • A vancomycin taper, tapered-pulsed fidaxomicin, or bezlotoxumab are reasonable alternative therapies to prevent recurrent CDI in patients who are not interested in fecal microbiota–based therapies.
2. **In mildly or moderately immunocompromised adults with recurrent *C difficile* infection, the AGA suggests the use of conventional fecal microbiota transplant upon completion of standard of care antibiotics over no fecal microbiota transplant. *(Conditional recommendation, very low certainty of evidence)*** **In severely immunocompromised adults with recurrent *C difficile* infection, the AGA suggests against the use of fecal microbiota–based therapies upon completion of standard of care antibiotics over no fecal microbiota–based therapies. *(Conditional recommendation, very low certainty of evidence)*** The following considerations are specific to immunocompromised adult patients with nonsevere, nonfulminant recurrent CDI in the outpatient setting. Severely immunocompromised includes patients receiving active cytotoxic therapy for solid tumors and hematologic malignancies, patients who have received chimeric antigen receptor T-cell therapy or hematopoietic cell transplant (only when neutropenic), any neutropenia, patients with severe primary immunodeficiency, patients with advanced or untreated HIV infection (CD4 counts $<200/mm^3$, AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV). Mildly or moderately immunocompromised adults are patients who are immunocompromised but do not meet our definition of severe. • The implementation considerations for the use of fecal microbiota–based therapies in immunocompetent adults with recurrent CDI can be used in the mildly or moderately immunocompetent population, with the exception of using fecal microbiota spores live-brpk or fecal microbiota live-jslm. There is insufficient evidence to recommend fecal microbiota spores live-brpk or fecal microbiota live-jslm in immunocompromised adult patients with recurrent CDI. • Conventional FMT should be performed with appropriately screened donor stool and special testing may be necessary.

Table 1. Continued

Recommendations
3. **In adults hospitalized with severe or fulminant *C difficile* infection not responding to antimicrobial therapy, the AGA suggests the use of conventional fecal microbiota transplant over no fecal microbiota transplant. *(Conditional recommendation, very low certainty of evidence)*** The following considerations are specific to adult patients in the hospital with severe or fulminant CDI refractory to standard of care antibiotics. What is severe or fulminant CDI: • Severe CDI is defined as patients with CDI and a leukocyte count $\geq 15 \times 10^9$ cells/L and/or creatinine $\geq$1.5 mg/dL. • Fulminant CDI presents as severe disease with shock, ileus, or megacolon. When to consider conventional FMT: • Patients with severe or fulminant CDI require multidisciplinary care including critical care, surgery, gastroenterology, and infectious disease. • FMT should be considered in hospitalized patients not responding to standard of care antibiotics, generally within 2–5 days after initiating CDI treatment. • FMT is not advised in patients with a bowel perforation, obstruction, or those who are severely immunocompromised. How to administer conventional FMT: • FMT should be performed with appropriately screened donor stool. There is no evidence for using the FDA-approved fecal microbiota–based therapies as adjuvant treatment in severe or fulminant CDI. • A bowel purge before FMT may not be feasible or safe. In these cases, FMT should be performed without a bowel preparation. • First dose of FMT should be delivered via colonoscopy or flexible sigmoidoscopy. Colonoscopy allows the provider to confirm the diagnosis and determine CDI severity. There is insufficient evidence in severe or fulminant CDI for FMT via enema or capsules. Administration of FMT via nasoenteric tube is discouraged, given the increased risk of fecal aspiration. Follow-up after initial FMT: • Treatment response can be assessed by means of monitoring stool output, white blood cell count, and C-reactive protein. • Most patients with severe or fulminant CDI will need repeat FMT. The exact timing (generally every 3–5 days) should be based on the patient's response to treatment, local protocols, and multidisciplinary care. The route of repeated FMT dosing will depend on local expertise and treatment response.[80,81] • Anti-CDI antibiotics may need to be continued after FMT.[80–82] Most published reports resume anti-CDI antibiotics or continue anti-CDI antibiotics when administering FMT. • After resolution of colitis, suppressive vancomycin should be continued at discharge and a final fecal microbiota–based therapy performed as an outpatient to prevent CDI recurrence. This treatment for prevention of recurrence can be administered via colonoscopy, capsule, or enema. Alternatives to FMT: • Cases of severe CDI not responding to antibiotics, or fulminant CDI, are often considered for colectomy.
4. **In adults with ulcerative colitis, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of clinical trials. *(Conditional recommendation, very low certainty of evidence)*** • Conventional FMT can reasonably be used in the context of clinical trials and potentially outside a clinical trial in cases of expanded access when no comparable or satisfactory alternative therapy options are available. • The recommendation is specific to the use of conventional FMT for the treatment of UC. For patients with recurrent, severe, or fulminant CDI in the settings of UC, please refer to the recommendations of questions 1–3.
5. **In adults with Crohn's disease, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of a clinical trial. *(Conditional recommendation, very low certainty of evidence)*** • The recommendation is specific to the use of conventional FMT for the treatment of CD. For patients with recurrent, severe, or fulminant CDI in the settings of CD, please refer to the recommendations of questions 1–3.
6. **In adults with pouchitis, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of clinical trial. *(Conditional recommendation, very low certainty of evidence)*** • The recommendation is specific to the use of conventional FMT for the treatment of pouchitis. For patients with recurrent, severe, or fulminant CDI in the settings of pouchitis, please refer to the recommendations of questions 1–3.
7. **In adults with irritable bowel syndrome, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of clinical trials. *(Conditional recommendation, very low certainty of evidence)*** • The recommendation is specific to the use of conventional FMT for the treatment of irritable bowel syndrome. For patients with recurrent, severe, or fulminant CDI in the settings of irritable bowel syndrome, please refer to the recommendations of questions 1–3.

Methods

Overview

This document represents the official recommendations of the AGA for use of fecal microbiota–based therapies for management of recurrent CDI, severe to fulminant CDI, IBD, pouchitis, and IBS. The guideline was developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to prioritize clinical questions, identify patient-centered outcomes, and conduct an evidence synthesis. The guideline panel used the Evidence-to-Decision framework to develop recommendations and provided implementation considerations for clinical practice.[2,3] The development of the guideline was fully funded by the AGA without any funding from outside agencies or industry.

Members of the guideline panel were selected on the basis of clinical and methodological expertise and experience and after review of all conflicts of interest in a comprehensive vetting process. The guideline panel included 3 members of the AGA guideline committee (A.F.P., chair of the guideline panel; B.L.; S.S.), a senior methodologist (O.A., co-chair of the guideline panel), a junior methodologist (A.I.), and 3 experts in fecal microbiota–based therapies (C.K., D.K., B.V.). The senior methodologist supervised the evidence synthesis and facilitated discussion among panel members for guideline development. The team reviewed the evidence, contributed to discussion, and participated in the development of guideline recommendations and implementation considerations. A patient representative also participated in the development of recommendations.

AGA adheres to National Academy of Medicine recommendations for managing conflict of interest (COI) disclosures in the development of clinical practice guidelines. All members of the guideline development group, including guideline panel chair, guideline panel members, methodologists, and content experts, completed a disclosure statement before commencing work. Members were expected to update their disclosures in writing as changes occurred throughout the development process. All members of the team were advised not to accept new speaking engagements or consulting arrangements with an honorarium during the guideline development process and until 12 months after publication date. The AGA COI policy is available upon request. All COI disclosure forms are maintained at the AGA National Office in Bethesda, Maryland.

Scope

The guideline panel identified 7 clinically relevant questions to address the use of fecal microbiota–based therapies in adults for the management of recurrent CDI, severe to fulminant CDI, IBD, and IBS. The panel considered addressing use of fecal microbiota–based therapies in other conditions, but decided to focus on the gastrointestinal conditions described in this document.

Formulation of Clinical Questions and Determining Outcomes of Interest

The clinical questions were formulated using the PICO format, which frames a clinical question by defining a specific patient population (P), intervention (I), comparator I, and outcomes (O). The panel selected desirable (benefits) and undesirable (harms) patient-important outcomes and summarized the evidence for each of the questions. The PICO questions are presented in detail in Supplementary Table 1.

The panel rated the Importance of the outcomes and defined thresholds for the minimum clinically important difference (MCID) *a priori* to aid the certainty of evidence (CoE) assessment. The MCID was defined on the basis of published literature, prior AGA clinical guidelines, or, if not available, by surveying the clinical experts separately then reaching consensus.

For the prevention of recurrent CDI in immunocompetent and immunocompromised individuals, the guideline panel determined prevention of recurrent CDI and serious adverse events as critical outcomes. We considered a 15% increase in prevention of recurrent CDI and a 1% increase in serious adverse events as thresholds for MCID.

For individuals with severe or fulminant CDI, the panel determined mortality (MCID 5%), colectomy (MCID 5%), and serious adverse events (MCID 20%) as critical outcomes.

For individuals with IBD, the panel considered induction and maintenance of clinical remission (MCID 10%), serious adverse events (MCID 10%), and change in quality of life (MCID as defined for clinical scoring systems) as critical outcomes.

As for individuals with IBS, the FDA responder end point (MCID 10%) and serious adverse events (MCID 10%) were determined as critical outcomes. If the FDA responder end point was not reported, we used global relief (MCID 10%) as measured by validated scoring systems (eg, IBS symptom severity score) as a critical outcome.

Evidence Review and Synthesis

The guideline panel used recently published systematic reviews when available. For the PICO question addressing recurrent CDI, we identified a recently published Cochrane systematic review, but updated the search and expanded the inclusion criteria to address our PICO question.[4] For the IBD PICO questions, we used a recently published Cochrane systematic review.[5] The panel conducted multiple systematic reviews to summarize and synthesize the evidence regarding the use of fecal microbiota–based therapies in patients with CDI, pouchitis, and IBS. A protocol was developed before the start of evidence synthesis and is registered at the International Prospective Register of Systematic Reviews (PROSPERO) website (CRD42022365147).

Eligibility Criteria

The eligibility criteria were based on the PICO questions (Supplementary Table 1). We included randomized controlled trials (RCTs) to address PICO questions when available. The panel considered observational comparative studies when evidence from RCTs was not available. When no observational comparative studies were available, single-arm observational studies were used. The population of interest was adult patients aged 18 years or older. The intervention of interest was the administration of fecal microbiota–based therapies. We considered studies with conventional FMT using unrelated and minimally manipulated donor stool; FDA-approved fecal microbiota, live-jslm (a donor stool-derived microbiota suspension, formerly RBX2660); FDA–approved fecal microbiota spores, live-brpk

(a donor stool-derived spore suspension, formerly SER-109); and the investigational product CP101 (a lyophilized donor stool–derived product). The panel considered studies with fecal microbiota–based therapies that varied by volume or dose, route of administration (eg, via capsule, colonoscopy, enema, or nasogastric tube), and frequency of administration. We also assessed each fecal microbiota–based therapy separately in a subanalysis. The comparison arms included placebo, standard of care, or autologous fecal microbiota transplantation. The panel considered a different set of outcomes for each of the PICO questions (Supplementary Table 1).

Search Strategy

A literature search was conducted on electronic databases, including Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE, and Embase. The search strategies are available in the Supplementary Document. We searched for ongoing trials at www.ClinicalTrials.gov. We searched the reference sections of eligible published studies, as well as conference abstracts. We updated our searches periodically during the evidence synthesis to look for any new studies that could have been published since the last search. The search strategy was developed by an experienced librarian with input from the methodologists. The last date of the search was March 1, 2023.

Study Selection, Data Collection, and Analysis

At least 2 members of the panel independently screened each relevant title and abstract retrieved from the search using Covidence software.[6] Studies that met criteria for inclusion underwent full text review. At least 2 panel members reviewed the full text for final inclusion for evidence synthesis. Discrepancies at the time of title or full text screening were resolved by means of discussion. Data from included studies were abstracted by at least 2 panel members independently. Conflicts were resolved by means of discussion. The panel extracted eligibility criteria for the study, details of study intervention (eg, donor source, volume, frequency, and route of fecal microbiota–based therapies administration), and information on critical and important outcomes. For outcomes pertaining to the proportion of randomized participants that experienced an event, the data were extracted on an intention-to-treat basis, which accounts for the number of participants originally allocated to each group, and modified Intention to treat, which may have some post-randomization exclusions. In cases when previously conducted reviews were considered for evidence synthesis, the data from all of the included studies in those reviews were extracted by the senior methodologist. If an RCT had multiple arms, the panel combined groups so that the only difference between the intervention and control group was fecal microbiota–based therapies. If an abstract presented updated estimates of effect or unpublished estimates of secondary outcomes, we extracted the additional data from the abstracts. If an abstract of an unpublished clinical trial was identified, we contacted the authors for additional data. We also contacted the corresponding authors of published studies as needed to request additional data (eg, data on immunocompromised individuals).

Risk-of-Bias Assessment

Risk of bias was assessed using the Cochrane risk-of-bias tool (RoB) for RCTs.[7] The ROBINS-I (The Risk of Bias in Non-Randomized Studies of Interventions) tool was used for nonrandomized studies.[8] Risk-of-bias for each study was assessed by both the senior and junior methodologists separately in a blinded manner, and disagreements were resolved by means of discussion. The *robvis* visualization tool was used to produce the traffic-light plots.[9]

Data Analysis

The quantitative data from RCTs and nonrandomized studies with a control arm were combined to obtain a relative risk (RR) for dichotomous outcomes and a mean difference for continuous outcomes and reported with 95% Cis. We used the DerSimonian-Laird random-effects model to pool the relative effects, unless the number of studies was too small to allow precise estimation of a between-study variance, in which case we used the fixed-effects model.[10] For single-arm studies, the proportion of individuals who had the outcome were pooled using the logit transformation and generalized linear mixed models.[11] The statistical heterogeneity in the pooled estimates was assessed by means of visual inspection of the forest plots and the I^2 statistic. Statistical heterogeneity was deemed substantial if I^2 was $>60\%$.[12] When a sufficient number of studies was presented with no substantial heterogeneity, we assessed for publication bias using funnel plot asymmetry tests.[13] We used the package meta 6.1-0 in R, version 4.2.1 to conduct the analyses.[14,15]

Assessments of the Certainty of Evidence

The panel assessed the overall CoE for use of fecal microbiota–based therapies for each of the outcomes using the GRADE framework.[2] The GRADE method rates the overall CoE for use of an intervention for an outcome as high, moderate, low, or very low level. The method considers study design, risk of bias, inconsistency, indirectness, imprecision of the summary estimate, and publication bias. The GRADE evaluations are reported in the evidence profiles for all critical and important outcomes (Supplementary Document). The interpretation of the CoE of effects is summarized in Supplementary Table 2.

Development of Recommendations

The panel used the GRADE approach to make strong or conditional recommendations using the Evidence to Decision framework.[3] The Evidence to Decision framework considers criteria such as balance of benefits and harms of the intervention, CoE, resource use, cost, equity and health disparities, acceptability, and feasibility.[3] The CoE and the strength of recommendation are provided for each clinical question. The recommendations are labeled as “strong” or

"conditional" according to the GRADE approach. The phrase "the guideline panel recommends" is used for strong recommendations, and "the guideline panel suggests" for conditional recommendations. The interpretations of the strength of recommendations are summarized in Supplementary Table 3. GRADE evidence to decision tables are available for each PICO question (Supplementary Document).

Panel members met and developed the recommendations based on the evidence summarized in the evidence to decision tables. For each recommendation, the panel took a population perspective and reached consensus on the following: CoE; balance of benefits and harms; and assumptions about the values and preferences associated with the decision, health equity, acceptability, and feasibility. The panel did not explicitly incorporate cost or cost-effectiveness. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus.

Review Process

Draft recommendations were reviewed by all members of the panel and the guideline and accompanying Supplementary Documents were made available online for a 4-week, open, public comment period. All comments were reviewed and considered carefully. Changes were incorporated in revised documents and when changes were not accepted, an internal response document was created. The document was revised to address pertinent comments and minor changes were made to the recommendations. The guideline also underwent independent peer review and was approved by the AGA Governing Board.

Recommendations

The search strategies identified 7383 references after removal of duplicates. An additional 12 references were identified using a Cochrane systematic review.[5] We included 66 studies in the review that informed this clinical guideline. Details of the screening process are presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart (Supplementary Figure 1).

Question 1: In immunocompetent adults with recurrent *C difficile* infection should fecal microbiota–based therapies be used?

Recommendation 1: In immunocompetent adults with recurrent *C difficile* infection, the AGA suggests the use of fecal microbiota–based therapies upon completion of standard of care antibiotics over no fecal microbiota–based therapies. *(Conditional recommendation, low certainty evidence)*

Implementation Considerations

The following considerations are specific to immunocompetent adult patients with nonsevere, nonfulminant recurrent CDI in the outpatient setting.

Diagnosis of recurrent *Clostridioides difficile* infections.

- A CDI diagnosis requires acute-onset, clinically significant, new-onset diarrhea (eg, 3 or more unformed stools in 24 hours) and highly sensitive (nucleic acid amplification or glutamate dehydrogenase) in combination with highly specific (toxin enzyme immunoassay) testing plus improvement of diarrhea with *C difficile*–directed antibiotics. A positive nucleic acid amplification test alone in the appropriate clinical context is also reasonable for making a CDI diagnosis.
- Recurrent CDI is typically defined as clinically significant diarrhea with a confirmatory positive test within 8 weeks of completing antibiotics for CDI.
- In patients who develop recurrent diarrhea after treatment for CDI, it is important to consider not only CDI recurrence, but also alternative diagnoses, especially if there are atypical symptoms, such as diarrhea alternating with constipation or no response in diarrheal symptoms to treatment with vancomycin or fidaxomicin.

When to consider fecal microbiota–based therapies.

- Fecal microbiota–based therapies include conventional FMT, fecal microbiota live-jslm, and fecal microbiota spores live-brpk.
- Prevention with fecal microbiota–based therapies can be considered in patients after the second recurrence (third episode) of CDI or in select patients at high risk of either recurrent CDI or a morbid CDI recurrence. Select use includes patients who have recovered from severe, fulminant, or particularly treatment-refractory CDI and patients with significant comorbidities.
- Careful consideration before proceeding with fecal microbiota–based therapies is recommended in patients who require frequent antibiotics or long-term antibiotic prophylaxis, because ongoing antibiotics may diminish the efficacy of such therapy.

How to administer fecal microbiota–based therapies.

- Fecal microbiota–based therapies should be given upon completion of a course of standard of care antibiotics for recurrent CDI. The fecal microbiota–based therapies are to prevent recurrence, not for CDI treatment.
- Suppressive anti-CDI antibiotics (eg, vancomycin) should be used to bridge standard of care antibiotics until fecal microbiota–based therapies are given.
- Ideally, antibiotics for CDI should be stopped 1–3 days before conventional FMT to allow adequate time for antibiotics to wash out of the system.[16] If a bowel purge is given, FMT can be given 1 day after stopping antibiotics. If no bowel purge is given, 3 days off antibiotics is recommended to allow clearance of oral antibiotics. Rarely, patients will recur rapidly (within 1–2 days of stopping CDI antibiotics), this risk needs to be considered when

determining an individual treatment window. When administering fecal microbiota spores live-brpk and fecal microbiota live-jslm, refer to the manufacturer's package insert for instructions.

- Conventional FMT should be performed with appropriately screened donor stool.[17,18]
- Conventional FMT can be delivered via multiple routes. There is insufficient evidence to recommend a specific route.

Alternatives to fecal microbiota–based therapies.

- A vancomycin taper, tapered-pulsed fidaxomicin, or bezlotoxumab are reasonable alternative therapies to prevent recurrent CDI in patients who are not interested in fecal microbiota–based therapies.

Summary of the Evidence

We identified 11 RCTs, including 1172 patients with nonsevere, nonfulminant recurrent CDI, that compared fecal microbiota–based therapies with standard of care, placebo, autologous FMT, or rectal bacteriotherapy (ie, 12 bacterial strains isolated from healthy donor stool then administered via enema).[19–34] The panel agreed that the selection of only 12 bacterial strains was not fecal microbiota–based therapy and could be classified with the placebo interventions for the purposes of this analysis. Most trials included adults with a history of multiply recurrent, nonsevere, nonfulminant CDI. The diagnosis of CDI was based on toxin assays and/or nucleic acid amplification tests. One trial included patients with 1 episode of CDI. Trial participants were predominantly older, immunocompetent women. The trial interventions included conventional FMT, fecal microbiota live-jslm, CP101, and fecal microbiota spores live-brpk. Fecal microbiota–based therapies were delivered by means of oral capsules, nasoenteric tube infusion, colonoscopy with lavage, or enema. A summary of the trial characteristics is included in Supplementary Table 4.

Benefits and Harms

Patients randomized to receive fecal microbiota–based therapies were more likely to have recurrent CDI prevented compared with controls (overall: 74.2% vs 51.7%; RR, 1.59; 95% CI, 1.27–2.00; subanalysis: FMT-only RR, 1.97; 95% CI, 1.36–2.86; fecal microbiota spores live-brpk-only RR, 1.46; 95% CI, 1.21–1.75; fecal microbiota live-jslm-only RR, 1.17; 95% CI, 0.99–1.39). The absolute effect estimates showed that 305 more per 1000 patients treated with fecal microbiota–based therapies had recurrent CDI prevented compared with control (95% CI, from 140 to 517 more per 1000). There were trivial to no differences between groups in serious adverse events (10.7% vs 12.6%; RR, 0.93; 95% CI, 0.63–1.36). Quality of life was reported in 1 trials, which showed trivial improvement in total quality of life score after fecal microbiota–based therapies. The pooled mean difference in total Cdiff32 (*Clostridioides difficile* Health-Related Quality-of-Life Questionnaire) score was 7.4 (95% CI, 1.9–12.9), which is below the MCID of 10.[35] A summary of the results, including outcomes of all-cause mortality, hospitalization, and colectomy, as well as subgroup analyses based on treatment, is included in Supplementary Figures 2–8.

Certainty of Evidence

The CoE was rated down due to serious risk of bias (lack of, or poorly described, blinding for subjective outcomes, multiple truncated trials, and use of post-protocol therapies; Supplementary Figure 9) and serious to very serious imprecision (wide CIs spanning multiple effect sizes or small number of events). We were unable to test for publication bias statistically, however, it was not suspected. The overall certainty in evidence of effects for fecal microbiota–based therapies in recurrent CDI was low. The evidence profile, which provides detailed judgments regarding the CoE for each outcome, is included in Table 2. Supplementary Table 5 summarizes the GRADE evidence-to-decision framework judgments.

Discussion

CDI continues to be recognized by the Centers for Disease Control and Prevention as a major health threat, with 462,000 CDI cases in the United States annually.[36] The panel made a conditional recommendation for the use of fecal microbiota–based therapies in immunocompetent adults with recurrent CDI. The recommendation applies to using fecal microbiota–based therapies after standard of care antibiotic treatment (ie, 10 days of vancomycin or fidaxomicin). The effect of fecal microbiota–based therapies on reducing the risk of recurrence was moderate compared with controls. Most trials included in this guideline were limited by small numbers of participants and either a lack of blinding or poorly described blinding. Some of the trials were terminated early and these trials showed a large effect size or no effect. In contrast, completed trials had a small to moderate effect size. The panel suspected that the terminated trials, if completed, could have found different results with smaller magnitude of effect favoring fecal microbiota–based therapies, similar to the completed trials.[37] There was limited evidence for improvement in quality of life. The therapies were well tolerated with no differences in the risk of serious adverse events.

The panel decided that use of fecal microbiota–based therapies in immunocompetent adults with recurrent CDI requires shared decision making and presentation of alternative therapies. The discussion should be individualized to the patient's individual risks, values, and preferences. Although cost of therapy was not considered in recommendations, cost and coverage of fecal microbiota–based therapies may impact access. At the time of this writing, conventional FMT for prevention of recurrent CDI is available via nonprofit stool banks and within select academic centers. FDA-approved fecal microbiota live-jslm and fecal microbiota spores live-brpk are commercially available products. Health care systems and policy makers should consider how material acquisition will affect cost and access.

Multiple guidelines recommend conventional FMT to prevent CDI in patients with a history of 2 or more

Table 2. Grading of Recommendations, Assessment, Development and Evaluation Evidence Profile: Fecal Microbiota–Based Therapies Compared With No Fecal Microbiota–Based Therapies for Treatment of Recurrent *Clostridioides difficile* Infections in Immunocompetent Individuals

		Certainty assessment					No. of patients (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FMT	No FMT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Prevention of recurrent CDI (RR > 1 favors FMT) (follow-up: range, 6–12 wk) 11	Randomized trials	Serious[a]	Not serious[b]	Not serious	Serious[c]	None	452/609 (74.2)	269/520 (51.7)	RR, 1.59 (1.27–2.00)	305 more per 1000 (from 140 more to 517 more)	⨁⨁◯◯ Low	Critical
Serious adverse events (RR < 1 favors FMT) (follow-up: range, 6–24 wk) 11	Randomized trials	Serious[d]	Not serious	Not serious[e]	Serious[f]	None	65/610 (10.7)	66/524 (12.6)	RR, 0.93 (0.63–1.36)	9 fewer per 1000 (from 47 fewer to 45 more)	⨁⨁◯◯ Low	Critical
Improvement in quality of life (MD > 0 favors FMT) (follow-up: mean 8 wk; assessed with Cdiff32; scale from 0 to 100) 2	Randomized trials	Serious[g]	Not serious	Not serious	Very serious[h]	None	229	159	—	MD 7.38 points higher (1.85 higher to 12.91 higher)	⨁◯◯◯ Very low	Important
Improvement in quality of life (RR > 1 favors FMT) (follow-up: mean 8 wk; assessed with Cdiff 32 change by at least 10 points) 1	Randomized trials	Not serious	Not serious	Not serious	Serious[i]	None	59/89 (66.3)	45/93 (48.4)	RR, 1.37 (1.06 to 1.77)	179 more per 1000 (from 29 more to 373 more)	⨁⨁⨁◯ Moderate	Important
All-cause mortality (RR < 1 favors FMT) (follow-up: range, 6–24 wk) 11	Randomized trials	Serious[d]	Not serious	Not serious[e]	Very serious[j]	None	17/610 (2.8)	20/527 (3.8)	RR, 0.78 (0.32–1.90)	8 fewer per 1000 (from 26 fewer to 34 more)	⨁◯◯◯ Very low	Important

Table 2. Continued

Certainty assessment							No. of patients (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FMT	No FMT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
All-cause hospitalization (RR < 1 favors FMT) (follow-up: range, 6–12 wk) 7	Randomized trials	Not serious	Not serious	Not serious	Very serious[k]	None	13/299 (4.3)	13/229 (5.7)	RR, 1.10 (0.53–2.32)	6 more per 1000 (from 27 fewer to 75 more)	⨁⨁◯◯ Low	Important
Colectomy (RR < 1 favors FMT) (follow-up: range, 6–24 wk) 4	Randomized trials	Not serious	Not serious	Not serious	Extremely serious[l]	None	1/243 (0.4)	0/151 (0.0)	RR, 1.45 (0.06–35.44)	4 more per 1000 (from 4 fewer to 12 more)[m]	⨁◯◯◯ Very low	Important

Cdiff32, *Clostridioides difficile* Health-Related Quality-of-Life Questionnaire; MD, mean difference; RR, risk ratio.

[a]We rated down for serious risk of bias. Many of the included studies lacked blinding or did not clearly describe it. As diarrhea was defined as the number of bowel movements usually, this may have led to anticipating lack of effect in patients who did not receive FMT. We also noted that some of the trials were terminated earlier and those trials showed either a large effect or no effect. The completed trials seemed to have mild to moderate effect. We think that the terminated trials, if completed, could have found different results.

[b]We did not rate down for inconsistency because the direction of effect was in favor of FMT in all the studies except 1. We think the observed $I^2 = 69\%$ is because of the difference in the magnitude of the effect and the effect remain meaningful even for the studies that showed conservative effect.

[c]We rated down for serious imprecision because the absolute effect estimate CI included trivial, small, and moderate effect sizes.

[d]We rated down for serious risk of bias. Some of the trials lack blinding and were terminated earlier. Most of the trials offered post-protocol therapies, usually FMT, for patients who failed treatment.

[e]We considered post-protocol therapies as a risk-of-bias issues, although it can be considered an indirectness problem.

[f]We rated down for serious imprecision. There was a small number of events, and the CI around the summary estimate included both clinically important increased and decreased risk of serious adverse events.

[g]We rated down for serious risk of bias. The quality of life data were available from 1 study (Feuerstadt et al[31]) and included 71% of the total patient randomized, hence concerns for significant attrition.

[h]We rated down for very serious imprecision. The CI around the summary estimate was wide and included worsening of quality of life, as well as trivial and mild improvement in quality of life. Also, the number of participants was small.

[i]We rated down for very serious imprecision. The CI around the summary estimate was wide and included a trivial to a moderate effect (Cdiff32 minimal clinically important difference is 10). Also, the pooled sample size was (182 overall) <30% of the optimal information size (240 overall) required to identify a small effect (0.2 SDs, which requires 400 per group).

[j]We rated down for very serious imprecision. There was small number of events, and the CI around the summary estimate included both increased and decreased risk of mortality.

[k]We rated down for very serious imprecision because the number of events was very small and the CI was very wide. The ratio between the upper and lower limits of RR CI was 4 indicating the optimal information size was not met.

[l]We rated down for extremely serious imprecision. There was 1 event in the 4 included studies, and the ratio between the upper and lower limits of the RR CI was very large.

[m]The absolute effects were estimated using the absolute risk difference because the baseline risk in the placebo arm was 0%.

recurrences. This includes guidelines from the American College of Gastroenterology,[38] European Society of Clinical Microbiology and Infectious Disease, [39] Infectious Diseases Society of American and Society for Healthcare Epidemiology of America,[40] and British Society of Gastroenterology and Healthcare Infection Society.[41] Fecal microbiota spores live-brpk and fecal microbiota live-jslm are new products not yet included in guidelines.

The panel intentionally refrains from limiting fecal microbiota–based therapies to after the second recurrence. Some patients are at increased risk of recurrence and/or morbid recurrence and may benefit from fecal microbiota–based therapy after the initial CDI episode or first recurrence. Select patients who may benefit from earlier therapy for prevention include those recovered from severe, fulminant, or CDI more refractory to standard treatment. Patients with significant comorbidities recovered from CDI may also benefit from earlier fecal microbiota–based therapies. However, those with recurrences driven by subsequent antibiotic administration may benefit from an alternative strategy to prevent CDI recurrence.

Future Directions

Conventional FMT poses a challenge for regulatory bodies. In the United States and Canada, FMT is considered a biologic drug. In the United Kingdom, FMT is regulated as a medicinal product and in EU countries it is classified as a tissue.[42] FMT remains unregulated in other counties, such as Finland, China, and India. Conventional FMT use in clinical care and in research in the United States is challenging due to regulatory hurdles, including the requirement for an Investigational New Drug application for clinical trials. Although stool banks have supplied donor material for FMT for more than a decade, updates to FDA guidance now limit the policy of enforcement discretion to establishments under which FMT products are collected or prepared for local treatment of patients. This policy was enacted to "control risks presented by centralized manufacturing," and stool banks now have to maintain an Investigational New Drug in order to continue to supply FMT material for clinical use.[43] Conventional FMT regulations should be revised to make clinical applications and research in this space feasible.

In addition to improving conventional FMT access to both researchers and clinicians, there is a continued need to accurately diagnose CDI and personalize the risk of recurrence. The mechanisms by which fecal microbiota–based therapies are effective in recurrent CDI are complex, poorly understood, and need to be defined. There is a clear need for research on host microbial interactions after these therapies and mechanistic studies using multiomics technology and multidisciplinary expertise. Trials are needed to assess fecal microbiota–based therapies as primary prevention in patients at high risk of CDI, as first-line treatment after short course of anti-CDI therapy, as treatment for CDI (not prevention), and in combination with bezlotoxumab. Comparative effectiveness studies are needed to address the impact of route on CDI outcomes and to compare conventional FMT with FDA-approved fecal microbiota–based therapies. It is unclear whether manipulation of donor fecal microbiota affects the efficacy for preventing recurrent CDI. The potential tradeoffs in safety and efficacy between microbiota therapeutics constitute an important knowledge gap and should be addressed. Future trials should include patient-centered outcomes, including quality of life and defined microbiome therapeutics. Algorithms are needed for CDI treatment, taking into account the efficacy and costs of various approved treatments (eg, bezlotoxumab and fidaxomicin) vs earlier use of fecal microbiota–based therapies.

Question 2: In immunocompromised adults with recurrent *C difficile* infection, should fecal microbiota–based therapies be used?

Recommendation 2: In mildly or moderately immunocompromised adults with recurrent *C difficile* infection, the AGA suggests the use of conventional fecal microbiota transplant upon completion of standard of care antibiotics over no fecal microbiota transplant. *(Conditional recommendation, very low certainty evidence)*

In severely immunocompromised adults with recurrent *C difficile* infection, the AGA suggests against the use of fecal microbiota–based therapies upon completion of standard of care antibiotics over no fecal microbiota–based therapies. *(Conditional recommendation, very low certainty evidence)*

Implementation Considerations

The following considerations are specific to immunocompromised adult patients with nonsevere, nonfulminant recurrent CDI in the outpatient setting. "Severely immunocompromised" includes patients receiving active cytotoxic therapy for solid tumors and hematologic malignancies, patients who have received chimeric antigen receptor T-cell therapy or hematopoietic cell transplantation (only when neutropenic), any neutropenia, patients with severe primary immunodeficiency, patients with advanced or untreated HIV infection (CD4 counts $<200/mm^3$, AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV). Mildly or moderately immunocompromised adults are patients who are immunocompromised but do not meet our definition of "severe."

- The implementation considerations for the use of fecal microbiota–based therapies in immunocompetent adults with recurrent CDI (under Recommendation 1 above) can be used in the mildly or moderately immunocompetent population, with the exception of using fecal microbiota spores live-brpk or fecal microbiota live-jslm. There is insufficient evidence to recommend fecal microbiota spores live-brpk or fecal microbiota live-jslm in immunocompromised adult patients with recurrent CDI.

- Conventional FMT should be performed with appropriately screened donor stool.

Summary of the Evidence

We did not identify any RCTs or comparative observational study that directly compared fecal microbiota–based therapies with placebo or standard of care in immunocompromised adults with nonsevere, nonfulminant recurrent CDI. Some of the published studies and trials included immunocompromised individuals, but we were unable to obtain separate outcomes data for the immunocompromised subgroups. Thus, we identified 25 observational studies of conventional FMT in immunocompromised patients with nonsevere recurrent or severe CDI.[44–68] The type of immunocompromise included patients with malignancy (n = 84), IBD (n = 461), solid organ transplant (n = 115), and a heterogeneous population with variable types of immunocompromise (n = 500). Patients who were severely immunocompromised were generally excluded from these studies. The intervention in the studies was conventional FMT. Although conventional FMT was delivered via colonoscopy in most of the studies, all of the administration routes were observed. A summary of the observational study characteristics is included in Supplementary Table 6.

Benefits and Harms

Data from the observational studies suggest that the rates of prevention of recurrent CDI in immunocompromised individuals that received conventional FMT (85% malignancy, 84% IBD, 67% solid organ transplant, and 79% immunocompromised) were comparable with the pooled estimate of the rate of prevention of recurrent CDI in the FMT arms (83.4%) of the RCTs that evaluated FMT in immunocompetent individuals.[19–33] There was a trivial to no difference in rates of prevention of recurrent CDI in immunocompromised patients compared with immunocompetent patients (RR, 0.96; 95% CI, 0.90–1.02). Data from observational studies also showed that the rates of serious adverse events in immunocompromised individuals who received FMT (3% malignancy, 11% IBD, 4% in solid organ transplant, and 14% in immunocompromised) were comparable with events in the intervention arm of trials in immunocompetent patients with recurrent CDI (11%).[19–33] There were no quality of life or all-cause mortality data available in the immunocompromised population. A summary of the results is included in Supplementary Figures 10–14.

Certainty of Evidence

The CoE was rated down due to serious risk of bias (observational single-arm studies with concern for selection bias), inconsistency (studies showed variable effect sizes), indirectness (there was no comparison group, and we used data from immunocompetent individuals for comparison to estimate the effect size), and imprecision (wide CI) for all critical outcomes. Publication bias was also strongly suspected (the studies were case series).[69] The overall certainty in evidence of effects for conventional FMT in immunocompromised adults with recurrent CDI was very low. The evidence profile is included in Supplementary Table 7. Supplementary Table 8 summarizes the GRADE evidence-to-decision framework judgments.

Discussion

The panel made a conditional recommendation for the use of conventional FMT in mildly or moderately immunocompromised adults with recurrent CDI. The effect of FMT on reducing the risk of recurrence was similar to the immunocompetent adults with recurrent CDI. There were no quality of life data available. FMT appears to be well tolerated with no differences in the risk of serious adverse events. Use of FMT in immunocompromised adults with recurrent CDI requires shared decision making, acknowledgment of the very low certainty evidence, and discussion of alternative therapies. The discussion should be individualized to the patient's individual risks, values, and preferences.

Some key considerations for immunocompromised people include the pathogenesis of recurrent CDI, diagnosis, and risks. Clinically significant diarrhea is common in many conditions that compromise the immune system, making the diagnosis of CDI more challenging. In addition, *C difficile* colonization rates are higher in many immunocompromised populations. Therefore, a lack of response to anti-CDI antibiotics could suggest symptomatic colonization, and alternative etiologies of diarrhea should be considered. Furthermore, the driver of dysbiosis in immunocompromised individuals may not be ameliorated after FMT. Thus far, the safety of FMT in mildly or moderately immunocompromised adults is reassuring, although the observational nature of the data limits the certainty in the evidence.

There is insufficient evidence to recommend fecal microbiota spores live-brpk or fecal microbiota live-jslm in immunocompromised adult patients with recurrent CDI. The FDA Clinical Review Memoranda for both FDA-approved products reported the data to be insufficient to assess for difference in safety and efficacy in immunocompromised individuals.[70,71] In addition, the guideline panel has concerns over the stool donor process used for these FDA-approved products. The concern is whether the financial incentive to donate creates an incentive for stool donors to inaccurately report their health or risk behaviors. Similar concerns are well described in the blood donation literature.[72–74] Evidence suggests that paid and professional blood donors are more likely to have an infectious disease compared with voluntary donors. The World Health Organization states "An adequate and reliable supply of safe blood can be assured by a stable base of regular, voluntary, unpaid blood donors. These donors are also the safest group of donors as the prevalence of bloodborne infections is lowest among this group."[75] Furthermore, many consider voluntary blood donation the safest way to avoid new blood-borne infectious. We have similar concerns about emerging infections that may be carried in stool. The screening process for these products is not publicly available and how they will adapt to emerging infections is unclear.

In severely immunocompromised adults, the panel made a conditional recommendation against the use of any fecal microbiota–based therapy to prevent recurrent CDI. Severely immunocompromised adults are at increased risk

of serious or life-threatening infections with the use of fecal microbiota–based therapy.[76] These patients were largely excluded from the observational studies we reviewed. The evidence to date was limited by observational studies in heterogeneous populations. The benefits and harms of fecal microbiota–based therapy may vary by type of immunocompromising condition. Extended or suppressive antibiotic therapy until immune recovery is likely a safer option.

FMT in immunosuppressed populations for recurrent CDI is inconsistently discussed in guidelines. Immune status was not addressed in the European Society of Clinical Microbiology and Infectious Disease guideline,[39] or the Infectious Diseases Society of American and Society for Healthcare Epidemiology of America guideline.[40] The American College of Gastroenterology guideline noted that conventional FMT is considered the best treatment option for multiply recurrent CDI and that rigorous donor screening is critical in immunocompromised populations.[38] The authors of the British Society of Gastroenterology and Healthcare Infection Society guideline recommend that FMT be offered with caution to immunosuppressed CDI patients, in whom FMT appears efficacious without significant additional adverse effects.[41]

Future Directions

The panel suggested similar considerations for future research for use of fecal microbiota–based therapies for mildly or moderately immunocompromised adults with recurrent CDI, as detailed above for immunocompetent adults. Future studies should include controlled trials in select immunocompromised populations. Patients with IBD are at higher risk of CDI, which increases risks of mortality and colectomy in hospitalized patients with both IBD and CDI compared with those with IBD alone.[77,78] Studies are needed to accurately determine CDI diagnosis vs colonization in patients with active IBD, given the complex nature of dysbiosis and colitis. A prospective study found that conventional FMT is effective for treatment of CDI in patients with IBD with favorable IBD-related outcomes.[79] However, it remains uncertain whether escalation of IBD therapy should proceed before or after FMT in those with active IBD. Further studies in this population, in whom immunosuppressive drugs and alterations in the microbiome contribute to both CDI risk and IBD disease activity, are needed. Furthermore, data are lacking on effectiveness and particularly the safety of recently FDA-approved fecal microbiota–based therapies in immunocompromised patients.

Question 3: In adults hospitalized with severe or fulminant *C difficile* infection, should conventional fecal microbiota transplant be used?

Recommendation 3: In adults hospitalized with severe or fulminant *C difficile* infection not responding to antimicrobial therapy, the AGA suggests the use of conventional fecal microbiota transplant over no fecal microbiota transplant. *(Conditional recommendation, very low certainty evidence)*

Implementation Considerations

The following considerations are specific to adult patients in the hospital with severe or fulminant CDI refractory to standard of care antibiotics.

What is severe or fulminant CDI?

- Severe CDI is defined as patients with CDI and a leukocyte count $\geq 15 \times 10^9$ cells/L and/or creatinine ≥ 1.5 mg/dL.
- Fulminant CDI presents as severe disease with shock, ileus, or megacolon.

When to consider conventional fecal microbiota transplant.

- Patients with severe or fulminant CDI require multidisciplinary care, including critical care, surgery, gastroenterology, and infectious disease.
- FMT should be considered in hospitalized patients not responding to standard of care antibiotics, generally within 2–5 days after initiating CDI treatment.
- FMT is not advised in patients with a bowel perforation, obstruction, or those who are severely immunocompromised.

How to administer conventional fecal microbiota transplant.

- FMT should be performed with appropriately screened donor stool. There is no evidence for using fecal microbiota spores live-brpk or fecal microbiota live-jslm as adjuvant treatment in severe or fulminant CDI.
- A bowel purge before FMT may not be feasible or safe. In these cases, FMT should be performed without a bowel preparation.
- First dose of FMT should be delivered via colonoscopy or flexible sigmoidoscopy. Colonoscopy allows the provider to confirm the diagnosis and determine CDI severity. There is insufficient evidence in severe or fulminant CDI for FMT via enema or capsules. Administration of FMT via nasoenteric tube is discouraged, given the increased risk of fecal aspiration.

Follow-up after initial fecal microbiota transplant.

- Treatment response can be assessed by monitoring stool output, white blood cell count and C-reactive protein.
- Most patients with severe or fulminant CDI will need repeat FMT. The exact timing (generally every 3–5 days) should be based on the patient's response to treatment, local protocols, and multidisciplinary care. The route of repeated FMT dosing will depend on local expertise and treatment response.[80,81]
- Anti-CDI antibiotics may need to be continued after FMT.[80–82] Most published reports resume anti-CDI antibiotics or continue anti-CDI antibiotics when administering FMT.
- After resolution of colitis, suppressive vancomycin should be continued at discharge and a final fecal microbiota–

based therapy performed as an outpatient to prevent CDI recurrence. This treatment for prevention of recurrence can be administered via colonoscopy, capsule, or enema.

Alternatives to FMT.

- Cases of severe CDI not responding to antibiotics, or fulminant CDI, are often considered for colectomy.

Summary of the Evidence

We identified 5 observational studies in 647 patients with severe or fulminant CDI that compared conventional FMT (n = 333; only 179 received FMT) with standard of care, including colectomy (n = 314).[83–87] Most studies included hospitalized adults with severe or fulminant CDI. One study included only patients with fulminant CDI.[86] Study participants were predominantly older adults with a high Charlson Comorbidity Index. Some of the studies included individuals with at least mild immunocompromise. The intervention in all of the studies was conventional FMT delivered via nasogastric tube, small bowel enteroscopy, flexible sigmoidoscopy, or colonoscopy. A small number of patients in 1 study had FMT via enema. Some of the studies repeated FMT every 3–5 days until resolution of pseudomembranes. A summary of the study characteristics is included in Supplementary Table 9.

Benefits and Harms

Patients hospitalized with severe or fulminant CDI treated with conventional FMT had a reduced risk of mortality compared with standard of care (RR, 0.37; 95% CI, 0.23–0.59). Treatment with FMT was associated with a reduced risk of mortality in a subgroup analysis by disease severity (severe: OR, 0.21; 95% CI, 0.03–1.58; fulminant: OR, 0.46; 95% CI, 0.26–0.81). There were no differences between groups in serious adverse events; however, this outcome was only reported in 2 studies (OR, 0.29; 95% CI, 0.07–1.11; n = 62). A summary of the results is included in Supplementary Figures 15–20.

Certainty of Evidence

The CoE was rated down due to very serious risk of bias (due to confounding and selection in most of the studies; Supplementary Figure 21), serious indirectness (studies combined both severe and fulminant CDI, which probably have different outcomes), and very serious imprecision (due to small sample size and number of events). We were unable to test for publication bias statistically, however, it was not suspected. The overall CoE of effects for FMT in patients hospitalized with severe or fulminant CDI was very low. The evidence profile is included in Supplementary Table 10. Supplementary Table 11 summarizes the GRADE evidence-to-decision framework judgments.

Discussion

Severe or fulminant CDI can be fatal.[83–89] The panel made a conditional recommendation for the use of conventional FMT in adults hospitalized with severe or fulminant CDI not responding to antimicrobial therapy. Treatment with FMT was associated with a reduced risk of mortality compared with standard of care. FMT was not associated with an increased risk of serious adverse events. Use of FMT in hospitalized adults with severe or fulminant CDI not responding to antimicrobial therapy requires shared decision making with a multidisciplinary team, acknowledgment of the very low CoE, and discussion of alternative therapies. Cases of severe CDI not responding to antibiotics, or fulminant CDI, are often considered for colectomy. However, in the case of fulminant CDI, mortality rates after colectomy are near 50%, thus limiting surgical options.[90] It is notable that FMT has a benefit when patients are not candidates for surgery. It is critical for a care team to include surgical colleagues to accurately portray the surgical risk on an individual basis.

Adjuvant treatment of severe or fulminant CDI with FMT is different than preventing recurrent CDI. The evidence to date used conventional FMT. There is no evidence for using the FDA-approved fecal microbiota–based therapies as adjuvant treatment in severe or fulminant CDI. Per the package insert, each 150-mL dose of fecal microbiota live-jslm contains between 1×10^8 and 5×10^{10} colony-forming units/mL of fecal microbes. The microbial content of fecal microbiota live-jslm is less than that in 1 g of stool. All published FMT studies used far greater dosing.

Although controlled studies of FMT protocols are lacking, some general themes for use of FMT in severe or fulminant CDI exist. Cessation of other nonessential antibiotics is essential when possible and highlights the importance of multidisciplinary care with infectious disease consultants. FMT earlier in the course of severe or fulminant CDI is likely to be more successful than delaying. Response to antibiotics should be assessed at 48–72 hours. A single FMT is likely to be insufficient and multiple FMTs are generally needed.[82] Most published reports also resume anti-CDI antibiotics or continue anti-CDI antibiotics when administering FMT.

FMT treatment in patients with severe or fulminant CDI is inconsistently addressed in guidelines. FMT was recommended for patients with severe and fulminant CDI refractory to antibiotics by the authors of the American College of Gastroenterology guideline.[38] A guideline by the European Society of Clinical Microbiology and Infectious Diseases noted that FMT may be a rescue therapy for patients with fulminant CDI that have deteriorated, despite CDI antibiotic treatment and for whom surgery is not feasible.[39] FMT in severe and fulminant CDI was not addressed in guidelines by the Infectious Diseases Society of American and Society for Healthcare Epidemiology of America or the British Society of Gastroenterology and Healthcare Infection Society.[40,41,91]

Future Directions

Severe and fulminant CDI are relatively uncommon, but associated with significant risk of morbidity and mortality. Research in this space is limited and needs urgent attention. Future multicenter studies should better define which patients with severe or fulminant CDI benefit from FMT, timing of FMT treatment, management of concomitant anti-

CDI antibiotics, ideal number of FMT treatments, route of FMT treatments, biomarkers to determine improvement, and whether such an approach reduces colectomy and/or mortality, or whether aforementioned FMT derivatives have a similar impact. Of note, the AGA National FMT Patient Registry is initiating a substudy to focus on detailed clinical outcomes after FMT in severe and fulminant CDI.

Question 4: In adults with ulcerative colitis should conventional fecal microbiota transplant be used?

Recommendation 4: In adults with ulcerative colitis, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of clinical trials. *(Conditional recommendation, very low certainty of evidence)*

Implementation Considerations

- Conventional FMT can reasonably be used in the context of clinical trials and potentially outside a clinical trial in cases of expanded access when no comparable or satisfactory alternative therapy options are available.
- The recommendation is specific to the use of conventional FMT for the treatment of UC. For patients with recurrent, severe, or fulminant CDI in the settings of UC, please refer to the recommendations of questions 1–3.

Summary of the Evidence

Induction of remission. We identified 9 RCTs in 447 patients with active UC that compared conventional FMT with standard of care (2 trials), placebo (4 trials), autologous FMT (2 trials), or UC exclusion diet (1 trial).[92–100] The trials included adults with active (median Mayo scores 5–10 or Simple Clinical Colitis Activity Index 7–10) UC and either left-sided disease or pancolitis. Some of the studies excluded patients with a history of biologic treatment exposure, and others included patients on stable biologic therapy. Some of the trials pretreated both arms with a course of antibiotics. Some of the trials use single donor and others used pooled donors. Trials required that patients be on stable doses of concomitant UC therapies. The route (eg, enema, capsules, colonoscopy, or nasoduodenal tube), number of treatments (1–82), and duration (1 time treatment to multiple treatments over 8 weeks) of FMT varied markedly among the RCTs. The 9 RCTs had 6–12 weeks of follow-up. There was variation in the definition of remission among the studies. A summary of the trials is included in Supplementary Table 12.

Maintenance of remission. We identified 2 RCTs in 71 patients with UC in remission.[96,101] The first RCT contributed data for induction of remission in active UC. At baseline, most patients (70%–73%) had left-sided disease and a total Mayo score of 5–7 before induction. In this RCT, patients who received FMT during the induction phase and went into clinical remission were re-randomized to receive FMT vs FMT withdrawal. Patients randomized to receive FMT in this RCT (n = 10) received FMT capsules daily for 48 weeks. Stable doses of concomitant medications were allowed and included oral mesalamine, thiopurines, methotrexate, oral prednisolone, and first-line biologic therapy. In the second RCT, patients with active UC (Mayo score 4–10, 73%–80% left-sided disease) were treated with 7 sessions of FMT in combination with standard of care UC therapies (no randomization) for induction of clinical remission. Patients who achieved clinical remission (n = 61) were then randomized to receive FMT vs placebo. Patients randomized to receive FMT, received FMT from a single donor via colonoscopy at week 0, 8, 16, 24, 32, 40, and 48 (total 7 doses). Both the intervention and comparison groups also received standard of care therapy (mesalamine with or without azathioprine or mercaptopurine). None of the patients in this RCT were on biologic therapy during the study. Almost one-quarter of patients (22%–23%) in this RCT had previous exposure to biologics. The 2 RCTs had 48–56 weeks of follow-up. A summary of the trials is included in Supplementary Table 12.

Benefits and Harms

Induction of remission. Patients randomized to receive FMT were more likely to achieve induction of clinical remission compared with control (32.8% vs 16.3%; RR, 1.95; 95% CI, 1.17–3.26). The data were very uncertain for the outcomes of serious adverse events (7.3% vs 5.1%; RR, 1.55; 95% CI, 0.74–3.27), quality of life scores (mean difference, 7.57 higher on the IBD questionnaire in the FMT group vs control; 95% CI, 3.9–19.1 higher) and induction of endoscopic remission (15.6% vs 9.6%; RR, 1.46; 95% CI, 0.65–3.28). A summary of the results is included in Supplementary Figures 22–25.

Maintenance of remission. The data from the 2 RCTs showed a very uncertain effect of FMT on maintenance of clinical remission (88.6% vs 55.6%; RR, 2.97; 95% CI, 0.26–34.4), serious adverse events (no events in either of the group), quality of life scores (mean difference, 38.2 points higher on the IBD questionnaire in the FMT group vs control), and maintenance of endoscopic remission (62.9% vs 22.2%; RR, 3.28, 95% CI, 0.73–14.7).[5]

Certainty of Evidence

Induction of remission. The CoE was rated down for serious risk of bias (due to concerns related to lack of blinding and attrition; Supplementary Figure 26) and imprecision (wide CI and/or small number of events). We were unable to test for publication bias statistically, however, it was not suspected. The overall CoE was very low. The evidence profile is included in Table 3. Supplementary Table 14 summarizes the GRADE evidence-to-decision framework judgments.

Maintenance of remission. The CoE was very low for all of the outcomes due to serious risk of bias (lack of blinding; Supplementary Figure 26), inconsistency, and very serious imprecision (very small sample size). We were unable to test for publication bias statistically, however, it was not suspected. The evidence profile is included in Supplementary Table 13.

Table 3. Grading of Recommendations, Assessment, Development and Evaluation Evidence Profile: Fecal Microbiota Transplantation Compared With No Fecal Microbiota Transplantation for Induction of Remission in Ulcerative Colitis

Certainty assessment							No. of patients (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FMT	No FMT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Induction of clinical remission in UC (follow-up: range, 6–12 wk) 9	Randomized trials	Serious[a]	Not serious[b]	Not serious	Serious[c]	None	76/232 (32.8)	35/215 (16.3)	RR, 1.95 (1.17–3.26)	155 more per 1000 (from 28 more to 368 more)	⨁⨁◯◯ Low	Critical
Serious adverse events in UC patients (follow-up: range, 6–12 wk) 9	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[d]	None	17/232 (7.3)	11/215 (5.1)	RR, 1.55 (0.74–3.27)	28 more per 1000 (from 13 fewer to 116 more)	⨁◯◯◯ Very low	Critical
Change in quality of life score (follow-up: range, 8–12 wk; assessed with IBDQ) 5	Randomized trials	Serious[e]	Not serious	Not serious	Very serious[f]	None	98	99	—	MD 7.57 IBDQ points higher (3.92 higher to 19.07 higher)	⨁◯◯◯ Very low	Critical
Induction of endoscopic remission in UC (follow-up: range, 8–12 wk) 5	Randomized trials	Serious[e]	Not serious	Not serious	Very serious[g]	None	24/154 (15.6)	13/135 (9.6)	RR, 1.46 (0.65–3.28)	44 more per ,000 (from 34 fewer to 220 more)	⨁◯◯◯ Very low	Important

IBDQ, Inflammatory Bowel Disease Questionnaire; MD, mean difference; RR, risk ratio.

[a]We rated down for serious risk of bias because 2 of the included studies were at high risk of bias due lack of blinding of participants or outcome assessors, and 1 study had significant attrition.

[b]We did not rate down for inconsistency although the I^2 was 49%. The direction of effect was in favor of intervention in all the included studies except 1 study. This probably contributed to the wide CI, and we rated down for imprecision.

[c]We rated down for serious imprecision because the CI was wide and included an absolute effect as low as 2.8%, which might not be clinically meaningful. We considered an absolute effect of 10% as minimal clinically important difference. We acknowledge that point estimate of the absolute effect was 155 per 1000 (15.5%) higher for FMT, which is clinically meaningful.

[d]We rated down for very serious imprecision because the number of events was very small (total 28 in both groups) and the 95% CI around the summary estimate was very wide. The ratio of upper limit of CI to lower limit of CI exceeded 4, indicating the current pooled sample size is lower than optimal information size.

[e]We rated down for serious risk of bias. One of the included study had high attrition.

[f]We rated down for very serious imprecision because the CI around the summary estimate was wide, including the minimally important difference (change by 16 points), and almost included a null effect. Also, the pooled sample size was (197 overall) <30% of the optimal information size (240 overall) required to identify a small effect (0.2 SDs which requires 400 per group).

[g]We rated down for very serious imprecision because the CI around the summary estimate was very wide and almost included a null effect. Also the ratio of upper CI to lower interval exceeded 3 indicating that optimal information size was not achieved.

Discussion

The panel made a conditional recommendation against the use of conventional FMT in adults with UC except in the context of clinical trials. This recommendation supersedes a prior recommendation around FMT in UC.[102] Although there is promising evidence in this area, at this time, it is unclear which patients with UC may benefit from FMT and how they should be positioned with other therapies. For induction of remission, most studies included patients with mild to moderate UC, and conventional FMT was offered as a concomitant therapy. There was significant heterogeneity in FMT administration with variable dose, frequency, route of administration, and duration of therapy, as well as how remission was defined. Some of the studies pooled stool from multiple donors to increase the diversity and richness of microbes in the stool specimen,[98] although high donor diversity may not necessarily be associated with a better outcome. There is emerging evidence that the right donor–recipient pairing may be a more important consideration.[103–106]

No guideline recommends use of FMT for treatment of UC. The British Society of Gastroenterology guideline authors note there is no place for FMT in the management of IBD unless complicated by CDI outside of the clinical trial setting.[107] Authors of an American College of Gastroenterology guideline wrote that FMT requires more study before use as a therapy for UC.[108] The authors of a prior AGA guideline recommended FMT for mild to moderate UC only in the context of a clinical trial.[102]

Future Directions

Future studies are needed to further define the characteristics of intervention in terms of route (upper vs lower gastrointestinal tract), frequency, type of donor (single vs pooled), timing (primary induction vs rescue/concomitant therapy), preparation of stool (aerobic vs anaerobic; frozen vs fresh), and duration of therapy. The panel also noted that sample size calculations in most of the studies considered a very large effect of FMT compared with control for induction of remission in UC and ranged from 25%[97] to 45%[98] more than control group; however, the effect of FMT might be more conservative, as shown in the pooled analysis, that is, approximately 15%. This means that a larger sample size might be required to detect this much difference. Future studies should also include larger and select populations, and rationale donor selection that targets UC-specific dysbiosis and uniform definitions of remission and optimal timing for assessing it.[70] Current data suggest microbial engraftment is correlated with a positive response. However, the degree of engraftment in UC is not at the same level as in recurrent CDI, where antibiotic-induced intestinal dysbiosis is the main driver of pathophysiology.[105] Furthermore, the dynamics and determinants of engraftment are not well understood, but are likely dependent on donor and recipient factors, including but not limited to genetics, comorbidities, medication use, diet, lifestyle, and baseline microbiome. Strain-level metagenomics analyses have also provided an ecological framework, and support the importance of deterministic, niche-based processes, such as the competition of, and exclusion of, closely related recipient and donor strains.[105,106] Further research should aim at identifying optimal donor–recipient pairing, the role of antibiotic preconditioning to improve engraftment, and biomarkers predictive of response, as well as potential adjunct therapies, such as precision diet, to enhance response.

In addition, the positioning of FMT with standard of care medications will need to be addressed. It is unclear whether FMT is better suited for induction of remission or maintenance of remission. Currently, the bulk of the evidence is with induction of remission. Numerous questions about FMT in maintenance of remission remain. The data on use of FMT for maintenance of remission in UC was available from 2 small studies and the evidence was not conclusive. Depending on the route of FMT administration, the response to FMT will need to be durable to be feasible and safe. Future studies, therefore, need to consider the dose, frequency, and route of administration and should plan for long-term follow-up of patients to assess for any adverse effects.

Question 5: In adults with Crohn's disease, should conventional fecal microbiota transplant be used?

Recommendation 5: In adults with Crohn's disease, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of a clinical trial. *(Conditional recommendation, very low certainty of evidence)*

Implementation Considerations

- The recommendation is specific to the use of conventional FMT for the treatment of CD. For patients with recurrent, severe, or fulminant CDI in the settings of CD, please refer to the recommendations of questions 1–3.

Summary of the Evidence

We did not find any RCTs that assessed the efficacy or safety of FMT for induction of remission in adult patients with active CD. We identified 1 RCT in 21 patients with CD in remission that compared conventional FMT with placebo.[109] The trial used corticosteroids to induce remission. Clinical outcomes were assessed at 24 weeks. A summary of the trial is included in Supplementary Table 15.

Benefits and Harms

Patients with CD randomized to receive conventional FMT were not more likely to have maintenance of clinical remission compared with controls (36% vs 30%: RR, 1.21; 95% CI, 0.36–4.14). There were no data on serious adverse events, quality of life, and maintenance of endoscopic remission.[5]

Certainty of Evidence

The CoE was very low for the outcomes of maintenance remission due to concerns related to risk of bias (lack of blinding and attrition bias; Supplementary Figure 27) and very serious imprecision (very small number of events and participants). We were unable to test for publication bias statistically, however, it was not suspected. The evidence profile is included in Supplementary Tables 16 and 17. Supplementary Table 18 summarizes the GRADE evidence-to-decision framework judgments.

Discussion

The panel made a conditional recommendation against the use of conventional FMT in adults with CD except in the context of clinical trials. The use of FMT for the treatment of CD is poorly studied. The panel did not find any RCTs that addressed the use of FMT for induction of clinical remission in CD. The study on use of conventional FMT for maintenance of remission in CD was small and the data were inconclusive. Guidelines do not recommend FMT for CD, given insufficient evidence.[107]

Future Directions

The panel suggested similar considerations for future research for use of FMT for CD as for UC noted above. Additional considerations for CD include the role of the microbiota on disease location, phenotype, and complications. Donor selection or rationale microbiota selection may be more important for certain phenotypes of CD. Many complications in CD, such as abscesses, fistulas, and peri-anal disease, are associated with bacterial overgrowth and are typically managed with antibiotics. Researchers will need to determine how FMT may ameliorate or exacerbate CD-related complications. The impact of FMT in the small bowel is likely an important differentiating factor from UC. Mechanistic studies are needed to understand how the immune response varies on the basis of location of FMT delivery. Although there is substantial hope for affecting the natural history of CD by means of manipulating the microbiota, substantial basic and translational research is required before larger clinical trials to test the efficacy of FMT in CD.

Question 6: In adults with pouchitis, should conventional fecal microbiota transplant be used?

Recommendation 6: In adults with pouchitis, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of clinical trials. *(Conditional recommendation, very low certainty of evidence)*

Implementation Considerations

- The recommendation is specific to the use of conventional FMT for the treatment of pouchitis. For patients with recurrent, severe, or fulminant CDI in the settings of pouchitis, please refer to the recommendations of questions 1–3.

Summary of the Evidence

We identified 2 RCTs in 32 patients with pouchitis that compared conventional FMT with placebo or autologous FMT.[110,111] The trials included patients with a history of ileal pouch–anal anastomosis after colectomy for UC. Patients had either frequent or continuous use of antibiotics for chronic pouchitis and/or active pouchitis defined as a modified pouch disease activity index score $\geq$5. The intervention in both trials was unrelated donor stool. In 1 trial, the FMT was delivered directly to the pouch via endoscopy, followed by oral capsules for 2 weeks.[110] This trial was stopped prematurely after 6 patients enrolled due to lower-than-expected clinical remission rate and low microbial engraftment. In the second trial, the FMT was delivered directly to the pouch with endoscopy, followed by a single FMT treatment given via transanal catheter.[111] A summary of the trials is included in Supplementary Table 19.

Benefits and Harms

Patients randomized to receive conventional FMT were not more likely to have maintenance of clinical remission compared with controls (24% vs 33%: RR, 0.80; 95% CI, 0.28–2.32). Quality of life was measured in 1 trial. Conventional FMT did not improve quality of life. No serious adverse events were reported in the 2 trials. A summary of the results is included in Supplementary Figures 28–31.

Certainty of Evidence

The CoE was rated down due to extremely serious imprecision (very small number of participants and events). The overall certainty in evidence of effects for conventional FMT in pouchitis was very low. The trials had low risk of bias overall (Supplementary Figure 32). We were unable to test for publication bias statistically, however, it was not suspected. The evidence profile is included in Supplementary Tables 20 and 21. Supplementary Table 22 summarizes the GRADE evidence-to-decision framework judgments.

Discussion

Restorative proctocolectomy with ileal pouch–anal anastomosis is a surgery for patients with UC and familial adenomatous polyposis. Pouchitis is a common long-term complication and is diagnosed on the basis of symptoms and endoscopic findings of inflammation.[112] The panel made a conditional recommendation against the use of conventional FMT in adults with pouchitis, except in the context of clinical trials. In the 2 small trials, patients randomized to receive conventional FMT were not more likely to have maintenance of clinical remission compared with controls. One trial was stopped prematurely due to poor rates of clinical remission.[110] The overall certainty in evidence was very low. Both studies were limited by the lack of a validated instrument for measuring pouchitis disease activity. A recent systematic review of single-arm observational studies found that the pooled rate of clinical remission in patients with chronic pouchitis that received conventional FMT was 20.1% (95% CI, 6.2–48.7), which is comparable with the rate of remission induced in the placebo arm of clinical trials.[113,114] Guidelines have not recommended FMT for pouchitis, given insufficient evidence.[107,112]

Future Directions

Primary or idiopathic pouchitis is believed to result from an abnormal immune response to luminal pouch dysbiosis in genetically susceptible hosts.[112] Pouchitis often responds to antibiotic therapy or select probiotic therapy; thus, microbiota as a therapeutic target may benefit select patients in this group. Future studies should include a well-defined population of patients with pouchitis. Response to FMT may differ depending on whether the patient has acute or chronic pouchitis and prior response to antibiotics. These factors will need to be considered in trial design. FMT engraftment in an ileal pouch is almost certainly different from a colon. It remains unclear whether donor-directed FMT, which is composed of predominantly colonic microbiota, is appropriate for engraftment into an ileal pouch. Engraftment may also depend on donor source (individuals with healthy colons, microbiota from small bowel, or individuals with ileal pouches without pouchitis) and recipient variables, including diet, comorbidities, medication use, diet, genetics, other environmental factors, such as pollution, beyond microbial characteristics and FMT delivery route and treatment intervals. Trials will need to include validated scores to measure disease activity and treatment response, a patient-reported outcome instrument, and pouch microbiome studies.[115,116] Mechanistic studies for a better understanding of the pouch microbiome and engraftment should also be explored.

Question 7: In adults with irritable bowel syndrome, should conventional fecal microbiota transplant be used?

Recommendation 7: In adults with irritable bowel syndrome, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of clinical trials. ***(Conditional recommendation, very low certainty of evidence)***

Implementation Considerations

- The recommendation is specific to the use of conventional FMT for the treatment of irritable bowel syndrome (IBS). For patients with recurrent, severe, or fulminant CDI in the settings of IBS, please refer to the recommendations of questions 1–3.

Summary of the Evidence

We identified 11 RCTs in 671 patients with IBS that compared conventional FMT with standard of care, placebo, or autologous FMT.[117–129] The trials included adults with Rome III or IV IBS. Most patients had moderate to severe disease. One trial was limited to post-infectious IBS only, 4 were diarrhea-predominant IBS and the other trials included a mix of subtypes. The studies included predominantly women with a mean age of 30–40 years. The intervention was unrelated (11 trials) donor stool delivered via oral capsules (4 trials) into the small bowel (3 trials) or via colonoscopy (4 trials). A single donor was used in 9 trials and multiple donors in 2 trials. A summary of the trials is included in Supplementary Table 23.

Benefits and Harms

One trial included the FDA responder end point for IBS. In that trial, a greater proportion of patients randomized to receive donor FMT had symptom relief (FDA responders) compared with control (61% vs 16%; RR, 3.70; 95% CI, 2.00–6.85). Most of the trials reported changes in IBS quality of life or IBS symptom severity scores at 12 weeks, which found no improvement except for the same trial that found symptom relief as defined by the FDA responder end point. Route of FMT and FMT donor type (single or multiple) did not change the results. Serious adverse events were rare. There were 2 events in patients randomized to receive FMT and none in the control arms (RR, 2.20; 95% CI, 0.24–20.55). The 2 events included a hospital admission for observation for nausea after FMT and acute cholecystitis. A summary of the results is included in Supplementary Figures 33–38.

Certainty of Evidence

The CoE was rated down due to serious inconsistency and very or extremely serious imprecision (wide CI and/or small number of events and participants). The trials were considered at low risk of bias overall (Supplementary Figure 39). We were unable to test for publication bias statistically, however, it was not suspected. The overall certainty in evidence of effects for FMT in IBS was very low. The evidence profile is included in Table 4. Supplementary Table 24 summarizes the GRADE evidence-to-decision framework judgments.

Discussion

IBS is a highly prevalent condition characterized by recurrent abdominal pain with associated changes in stool patterns, frequency, or form.[130] Increasingly recognized IBS pathophysiology extends beyond intestinal dysmotility to include intestinal dysbiosis and disordered gut–brain interactions. The panel made a conditional recommendation against the use of FMT in adults with IBS except in the context of clinical trials. Although safe, conventional FMT did not improve symptom severity or quality of life in patients with IBS. A single trial suggested that patients randomized to receive donor FMT had symptom relief compared with control, however, the findings were not replicated in other trials. The overall CoE was very low.

Few guidelines address FMT in patients with IBS. The American College of Gastroenterology and Italian guidelines recommend against the use of FMT for the treatment of IBS symptoms.[131,132] FMT in patients with IBS was mentioned in a guideline by the British Society of Gastroenterology and no recommendation was made due to insufficient evidence.[133]

Future Directions

IBS is a heterogenous condition with complex pathophysiology. It is plausible that certain subsets of patients with IBS, based on symptom phenotype or a particular

Table 4. Grading of Recommendations, Assessment, Development and Evaluation Evidence Profile: Fecal Microbiota Transplantation Compared With No Fecal Microbiota Transplantation for Treatment of Irritable Bowel Syndrome

Certainty assessment							No. of patients (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FMT	no FMT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
FDA response (follow-up: mean 12 wk) 1	Randomized trials	Not serious	Not serious	Not serious	Extremely serious[a]	None	66/109 (60.6)	9/55 (16.4)	RR, 3.70 (2.00–6.85)	442 more per 1000 (from 164 more to 957 more)	⨁◯◯◯ Very low	Critical
Improvement in IBS-QoL by at least 12 points (follow-up: mean 12 wk) 1	Randomized trials	Not serious	Not serious	Not serious	Extremely serious[b]	None	65/109 (59.6)	4/55 (7.3)	RR, 8.2 (3.2–21.3)	524 more per 1000 (from 160 more to 1000 more)	⨁◯◯◯ Very low	Critical
Serious adverse events (follow-up: range, 4–52 wk) 8	Randomized trials	Not serious	Not serious	Not serious	Very serious[c]	None	2/268 (0.7)	0/193 (0.0)	RR, 2.20 (0.24–20.55)	7 more per 1000 (from 3 fewer to 18 more)[d]	⨁⨁◯◯ Low	Critical
Improvement in IBSSS by at least 50 points (follow-up: mean 12 wk) 6	Randomized trials	Not serious	Serious[e]	Not serious	Very serious[f]	None	177/264 (67.0)	88/187 (47.1)	RR, 1.16 (0.67–2.51)	75 more per 1000 (from 155 fewer to 711 more)	⨁◯◯◯ Very low	Important
Change in IBSSS (follow-up: mean 12 wk) 8	Randomized trials	Not serious	Serious[g]	Not serious	Very serious[h]	None	284	211	—	MD 18.19 points lower (65.8 lower to 29.4 higher)	⨁◯◯◯ Very low	Important

Table 4. Continued

Certainty assessment							No. of patients (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FMT	no FMT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Change in IBS-QoL (follow-up: mean 12 wk) 6	Randomized trials	Not serious	Serious[i]	Not serious	Very serious[j]	None	237	161	—	MD 5.06 points higher (5.04 lower to 15.15 higher)	⨁◯◯◯ Very low	Important

IBS-QoL, Irritable Bowel Syndrome Quality of life; IBSSS, Irritable Bowel Severity Scoring System; MD, mean difference; RR, risk ratio.
[a]We rated down for extremely serious imprecision because the lower limit of absolute effect estimate indicates trivial effect and the upper limit indicates large effect. The ratio of the upper to the lower boundary of the RR CI is 3.4, indicating that the sample size is very far from meeting the optimal information size.
[b]We rated down for extremely serious imprecision because the lower limit of absolute effect estimate indicates trivial effect and the upper limit indicates large effect. The ratio of the upper to the lower boundary of the CI is 6.7, indicating that the sample size is very far from meeting the optimal information size.
[c]The point estimate shows harm but the CI includes possible harm and benefit. Also, the RR CI is very wide, indicating not meeting the optimal information size.
[d]As there were no events in the no FMT group, the absolute effect was calculated manually.
[e]The I^2 is 85% and the studies showed inconsistent findings.
[f]The point estimate shows trivial benefit but the CI includes possible harm and possible substantial benefit.
[g]The I^2 was 89% and some of the studies showed substantial improvement (El-Salhy et al[118] and Lin et al[11]), some of them showed no difference, and of few of them showed worsening (Mazzawi et al[127] and Halkjaer et al[121]).
[h]The point estimate shows trivial benefit but the CI includes the possibility of substantial important benefit. Also, the total number of participants is 495, which is smaller than the optimal information size required to observe small effect.
[i]The I^2 was 82% and the studies showed findings with 1 study showing important improvement (El Salhy et al), 1 study showed worsening (Lin et al), and most of the studies showing no difference.
[j]The point estimate shows trivial benefit but the CI includes possible harm and possible substantial benefit. The total number of patients is 398, which is 50% of the optimal information size required to observe a small effect.

bacterial or metabolic profile, may benefit from FMT. Future studies should include larger and select populations and consider factors outlined in the previous sections in CDI and UC in study designs and build in mechanistic studies to better understand how FMT mediates these effects. The variable dysbiosis in IBS will need to be better categorized and considered in FMT and eventually IBS-specific fecal microbiota–based therapy studies. The impact of colonic transit time on fecal microbiota samples should be considered and, when possible, colonic mucosal biopsies should be used to assess engraftment. Only 1 trial included the FDA responder end point. Trials should include the FDA composite end point for IBS, incorporate validated patient-reported outcome instrument, determine whether bacterial engraftment leads to a positive response, as well as determine an optimal FMT protocol for durable outcomes.

Plans for Updating This Guideline

This guideline will be updated in 3–5 years when new data become available.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2024.01.008.

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Conflicts of interest
Members of the guideline panel were selected after review of all conflicts of interest in a comprehensive and iterative vetting process performed before the guideline was initiated and throughout the guideline development process. The members of the guideline panel disclose no conflicts. The authors disclose no conflicts. We consider the authors all members of the guideline panel.

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