American Gastroenterological Association Clinical Practice Guideline on Intestinal Microbiota Transplantation for Gastrointestinal Diseases

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Short title
AGA Guideline IMT

Abbreviations
AGA (American Gastroenterological Association)
IMT (Intestinal microbiota transplant)
GRADE (Grading of Recommendations Assessment, Development and Evaluation)
CDI (Clostridioides difficile infections)
IBD (inflammatory bowel diseases)
IBS (irritable bowel syndrome)
RCTs (randomized controlled trials)
COI (conflict of interest)
UC Ulcerative colitis
CD Crohn’s disease

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ABSTRACT

Background & Aims: Intestinal microbiota transplant (IMT), historically termed fecal microbiota transplantation, is a treatment for gut dysbiosis. The American Gastroenterological Association (AGA) developed this guideline to provide recommendations on the use of IMT in adults with recurrent Clostridioides difficile (C. 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 IMT 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 use of IMT or fecal microbiota spores, live-brpk upon completion of standard of care antibiotics to prevent recurrence. Likewise, the AGA suggests use of IMT in mildly or moderately immunocompromised adults with recurrent C. difficile infection. The AGA suggests against the use of IMT to prevent C. difficile recurrence in severely immunocompromised adults. In adults with severe or fulminant C. difficile not responding to standard of care antibiotics, the AGA suggests use of IMT. The AGA suggests against the use of IMT as a treatment for inflammatory bowel diseases or irritable bowel syndrome except in the context of clinical trials.

Conclusions: IMT is an effective therapy to prevent recurrent C. difficile in select patients and as adjuvant treatment for patients with severe or fulminant C. difficile infection not responding to standard of care antibiotics. IMT cannot yet be recommended in other gastrointestinal conditions.

Keywords: intestinal microbiota transplant; fecal microbiota transplant; C. difficile infection, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, pouchitis, irritable bowel syndrome.
INTRODUCTION

Intestinal dysbiosis is characterized by decreased commensal microorganism diversity, loss of beneficial microbes, and pathogenic microbe overgrowth. Many digestive and systemic diseases are associated with dysbiosis. Intestinal dysbiosis can lead to loss of normal microbiota function (e.g., colonization resistance) and is associated with numerous immune-related diseases.\(^1,2\) Intestinal microbiota transplantation (IMT) can ameliorate dysbiosis, and potentially improve outcomes of dysbiosis associated diseases.

Many clinicians are aware that gut dysbiosis plays a central role in the pathogenesis of \textit{C. difficile} infections (CDI) and that IMT is used in the management of recurrent CDI. There is emerging awareness that dysbiosis may play a role in the inflammatory bowel diseases (IBD) including Crohn’s disease, ulcerative colitis and pouchitis, as well as irritable bowel syndrome (IBS).\(^3\) Trials have investigated IMT therapy in each of these conditions, but at the moment there is uncertainty regarding appropriate use of IMT.

There is a debate regarding the most accurate language to describe IMT therapy which was originally referred to as ‘fecal bacteriotherapy’ until the term fecal microbiota transplantation (FMT) emerged in 2010. Feces is a complex substance, derived from the Latin word for sediment, and can be used in a denigratory manner. While in many cases donor stool is collected, it is microbiota that is transplanted. Therapeutic effects are mediated by the engraftment of microbiota as well as other mechanisms, and the intestine is the source of the microbiota transplanted.\(^4\) Therefore, the terminology intestinal microbiota transplantation (IMT) is used throughout this guideline.

Objectives

The objective of this American Gastroenterological Association (AGA) guideline is to present clinical recommendations on the use of IMT therapy in adults with recurrent CDI, severe to fulminant
CDI, IBD (Crohn’s disease, ulcerative colitis 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 IMT for adults with recurrent CDI, severe to fulminant CDI, IBD, and IBS. The recommendations are summarized in Table 1.

METHODS

Overview

This document represents the official recommendations of the AGA for use of IMT for management of recurrent CDI, severe to fulminant CDI, IBD, pouchitis and IBS. 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 and provided implementation considerations for clinical practice.5, 6 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 based on clinical and methodological expertise and experience, and after review of all conflicts of interest in a comprehensive vetting process. The guideline panel included three members of the AGA guideline committee (AFP, Chair of the Guideline Panel; BL; SS), a senior methodologist (OA, Co-Chair of the guideline panel), junior methodologist (AI), and three experts in IMT (CK, DK, BV). 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 with the National Academy of Medicine recommendations for managing conflicts 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 prior to 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 accept new speaking engagements or consulting arrangements with an honorarium during the guideline development process, 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 IMT in adults for the management of recurrent CDI, severe to fulminant CDI, IBD, and IBS. The panel considered addressing use of IMT in multiple other conditions but decided to focus on the select 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 (C), 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 minimum clinically important difference (MCID) a priori to aid the certainty of evidence (CoE) assessment. The MCID was defined based on 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 resolution of recurrent CDI and serious adverse events as critical outcomes. We considered 15% increase in resolution of recurrent CDI and 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. The panel considered induction and maintenance 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 for individuals with IBD. As for individuals with IBS, the FDA responder endpoint (MCID 10%) and serious adverse events (MCID 10%) were determined as critical outcomes. If the FDA responder endpoint was not reported, we used global relief (MCID 10%) as measured by validated scoring systems (e.g. 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. For the IBD PICO questions, we used a recently published Cochrane systematic review. The panel conducted multiple systematic reviews to summarize and synthesize the evidence regarding the use of IMT 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 where 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 were adult patients aged 18 years or older. The intervention of interest was the administration of donor-based IMT. We considered studies with minimally-manipulated IMT using unrelated and unmanipulated donor stool, including fecal microbiota, live-jslm (a donor stool-derived microbiota suspension, formerly RBX2660), and CP101 (a lyophilized donor stool-derived product). The panel considered studies with IMT that varied by volume or dose, route of administration (e.g., via capsule, colonoscopy, enema, or nasogastric tube), and frequency of administration. Separately, we considered studies that used fecal microbiota spores, live-brpk (formerly SER-109), recently approved by the US Food and Drug Administration. Fecal microbiota spores, live-brpk is a product enriched with Firmicutes spores after treating donor stool with ethanol. The comparison arms included placebo, standard-of-care, autologous IMT, ulcerative colitis exclusion diet, or rectal bacteriotherapy (12 bacterial strains isolated from healthy donor stool). 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 (CENTRAL), 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 the 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, and the last date of search was on March 1st, 2023.

**Study selection, data collection, and analysis**

At least two members of the panel independently screened each relevant title and abstract retrieved from the search using Covidence software. Studies that met criteria for inclusion underwent full text review. At least two 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 discussion. Data from included studies was abstracted by at least two panel members independently. Conflicts were resolved by discussion. The panel extracted eligibility criteria for the study, details of study intervention (e.g., donor source, volume, frequency, and route of IMT 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 (ITT) basis, which accounts for the number of participants originally allocated to each group, and modified intention-to-treat (mITT), which may have some post-randomization exclusions. In cases where previously conducted reviews were considered for evidence synthesis, the data from all the included studies in those reviews was 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 IMT.

**Risk of bias assessment**

Risk of bias was assessed using the Cochrane Risk of Bias (RoB) tool for RCTs. The Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool was used for non-randomized
The risk of bias assessment for each study was assessed by both the senior and junior methodologists separately and in a blinded manner, and disagreements were resolved by discussion. The robvis visualization tool was used to produce the traffic light plots.

Data analysis

The quantitative data from RCTs and non-randomized 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% confidence intervals (95% CI). 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 between-study variance, in which case we used the fixed-effects model. For single arm studies, the proportion of individuals who had the outcome were pooled using the logit transformation and generalized linear mixed models. The statistical heterogeneity in the pooled estimates was assessed by visual inspection of the forest plots and the $I^2$ statistic. Statistical heterogeneity was deemed substantial if $I^2$ was greater than 60%. When a sufficient number of studies was presented with no substantial heterogeneity, we planned to assess for publication bias using funnel plot asymmetry tests. We used the package meta 6.1-0 in R, version 4.2.1 to conduct the analyses.

Assessments of the certainty of evidence

The panel assessed the overall certainty of the evidence (CoE) for use of IMT for each of the outcomes using the GRADE framework. The GRADE method rates the overall certainty of evidence 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 (Supplemental Document). The interpretation of the CoE of effects is summarized in Supplementary Table #.
Development of recommendations

The panel used the GRADE approach to make strong or conditional recommendations by using the evidence to decision framework. The evidence to decision framework considers criteria such as balance of benefits of harms of the intervention, certainty of evidence, resource use, cost, equity and health disparities, acceptability, and feasibility. 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 words “the guideline panel recommends” are used for strong recommendations, and “the guideline panel suggests” for conditional recommendations. The interpretation of the strength of recommendations are summarized in Table 2. GRADE evidence to decision tables are available for each PICO question (Supplemental Document).

The 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 2-week, open, public comment period. All comments were reviewed and carefully considered. 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 7,383 references after removal of duplicates. An additional 12 references were identified using a Cochrane systematic review. We included 66 studies in the technical review that informed this clinical guideline. Details of the screening process are presented in the PRISMA flow chart (supplemental Figure 1).

Question 1: In immunocompetent adults with recurrent C. difficile infection should IMT or fecal microbiota spores, live-brpk be used?

| In immunocompetent adults with recurrent C. difficile infection, the AGA suggests the use of IMT upon completion of standard-of-care antibiotics over no IMT (conditional recommendation, low certainty evidence). |
| In immunocompetent adults with recurrent C. difficile infection, the AGA suggests the use of fecal microbiota spores, live-brpk upon completion of standard-of-care antibiotics over no fecal microbiota spores, live-brpk (conditional recommendation, low certainty evidence). |

Implementation considerations
The following considerations are specific to immunocompetent adult patients with non-severe, non-fulminant recurrent CDI in the outpatient setting.

Diagnosis of recurrent CDI?
- A CDI diagnosis requires acute onset, clinically significant diarrhea (e.g., ≥ 3 unformed stools in 24 hours) and highly sensitive (nucleic acid amplification or glutamate dehydrogenase) alone or
in combination with highly specific (toxin enzyme immunoassay) testing plus resolution of diarrhea with *C. difficile* directed antibiotics.

- Recurrent CDI is defined as 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 diagnosis, 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 IMT (or fecal microbiota spores, live-brpk)?**

- Treatment with IMT or fecal microbiota spores, live-brpk can be considered in patients at high risk for recurrent CDI.

- Careful consideration prior to proceeding with IMT or fecal microbiota spores, live-brpk treatment is recommended in patients who require frequent antibiotics or long-term antibiotic prophylaxis, since ongoing antibiotics may diminish the efficacy of such treatment.

**How to administer IMT (or fecal microbiota spores, live-brpk)?**

- IMT or treatment with fecal microbiota spores, live-brpk should be performed upon completion of a course of standard-of-care antibiotics for recurrent CDI.

- Suppressive anti-CDI antibiotics (e.g., vancomycin) should be used to bridge standard-of-care antibiotics until IMT or fecal microbiota spores, live-brpk therapy.

- Antibiotics for CDI should be stopped 1-3 days prior to IMT to allow adequate time for antibiotics to wash-out of the system. If a bowel purge is given, IMT 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. When administering fecal microbiota spores, live-brpk, antibiotic
treatment for recurrent CDI should be stopped 2-4 days prior, followed by a split dose bowel purge.

- IMT should be performed with appropriately screened donor stool.\textsuperscript{19,20}
- IMT can be delivered by multiple routes. There is insufficient evidence to recommend a specific route.

**Alternatives to IMT (or fecal microbiota spores, live-brpk treatment)?**

- A vancomycin taper, tapered-pulsed fidaxomicin, or bezlotoxumab are reasonable alternative therapies in patients who do not have access to or who are not interested in IMT or treatment with fecal microbiota spores, live-brpk.

**Summary of the evidence**

**IMT.** We identified 10 RCTs including 990 patients with non-severe, non-fulminant recurrent CDI that compared IMT to standard of care, placebo, autologous IMT, or rectal bacteriotherapy (12 bacterial strains isolated from healthy donor stool then administered via enema).\textsuperscript{21-35} The panel agreed that 12-strain bacterial strains administered via enema is similar to placebo. Most trials included adults with a history of multiply recurrent, non-severe, non-fulminant CDI. One trial included patients with one episode of CDI. Trial participants were predominantly older, immunocompetent women. The trial interventions included unrelated and minimally manipulated donor stool, including fecal microbiota, live-jslm (a donor stool-derived microbiota suspension, formerly RBX2660), or CP101 (donor stool-derived complete microbiome in lyophilized form). IMT was delivered by oral capsules, nasoenteric tube infusion, colonoscopy with lavage, or enema. A summary of the trial characteristics is included in supplemental Table 2.
**Fecal microbiota spores, live-brpk.** We identified 2 RCTs including 271 patients with non-severe, non-fulminant recurrent CDI that compared fecal microbiota spores, live-brpk to placebo.\textsuperscript{36, 37} The trials included immunocompetent adults with a history of multiply recurrent, non-severe, non-fulminant CDI. The trial intervention was fecal microbiota spores, live-brpk (prepared from donor stool, treated with ethanol, enriched with Firmicutes spores). Fecal microbiota spores, live-brpk was delivered by oral capsules. A summary of the trial characteristics is included in **supplemental Table 5.**

**Benefits and harms**

**IMT.** Patients randomized to IMT were more likely to have resolution of recurrent CDI compared to controls (71.9% v 49.9%; RR, 1.63; 95% CI 1.25-2.14). The absolute effect estimates showed that 314 more per 1000 patients with recurrent CDI treated with IMT had resolution compared to control (95% CI from 125 to 569 more per 1000). There were no differences between groups in serious adverse events (11.2% v 11.8%; RR, 1.08; 95% CI 0.74-1.59). Quality of life was studied in one trial, which failed to show improvement following IMT. A summary of the results including outcomes of all-cause mortality, hospitalization, and colectomy is included in **supplemental Figures 2-7.**

**Fecal microbiota spores, live-brpk.** Patients randomized to fecal microbiota spores, live-brpk were more likely to have resolution of recurrent CDI compared to control (75.0% v 56.9%; RR, 1.42; 95% CI 1.20-1.68). The absolute effect estimates showed that 239 more per 1000 patients with recurrent CDI treated with fecal microbiota spores, live-brpk had resolution compared to control (95% CI from 114 to 387 more per 1000). There were no differences between groups in serious adverse events (10.7% v 14.9%; RR, 0.76; 95% CI 0.26-2.22). Patients randomized to the fecal microbiota spores, live-brpk were more likely to have an improvement in quality of life (66.3% v 48.4%; RR, 1.37; 95% CI 1.06-1.77). A summary of the results including all-cause mortality is included in **supplemental Figures 9-12.**

**Certainty of evidence**
**IMT.** The CoE was rated down due to serious risk of bias (lack of or poorly described blinding for subjective outcomes, multiple truncated trials, and the use of post-protocol therapies) and serious to very serious imprecision (wide confidence intervals 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 IMT in recurrent CDI was low. The evidence profile is included in **supplemental Table 3**.

**Fecal microbiota spores, live-brpk.** The CoE was rated down due to serious to very serious imprecision (wide confidence intervals spanning multiple effect sizes or small number of events) and inconsistency (trials showed increased and decreased risk of serious adverse events). We were unable to test for publication bias statistically, however, it was not suspected. The trials were considered to have a low risk of bias. The overall certainty in evidence of effects for fecal microbiota spores, live-brpk in recurrent CDI was low. The evidence profile is included in **supplemental Table 6**.

**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 US annually. Recurrence is common, difficult to treat, and a detriment to patients’ quality of life. The panel made a conditional recommendation for the use of IMT or fecal microbiota spores, live-brpk in immunocompetent adults with recurrent CDI. The effect of IMT or fecal microbiota spores, live-brpk on reducing the risk of recurrence was moderate compared to controls. The 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 or no effect. In contrast, completed trials had mild to moderate effects. The panel suspects that the terminated trials, if completed, could have shown different results. The benefit of IMT may decrease with the use of novel or extended antibiotic courses. The current recommendation
applies to using IMT following standard of care (10-days of vancomycin or fidaxomicin) antibiotic treatment. It is essential to incorporate the underlying risk of CDI recurrence following antibiotic usage with the benefit of IMT. There was limited evidence for improvement in quality of life as few trials included these metrics. The therapies were well tolerated with no differences in the risk of serious adverse events. There was insufficient data to analyze effectiveness based on route of administration. Route of administration may impact patient tolerability, safety, and efficacy.

The panel decided that use of IMT or fecal microbiota spores, live-brpk 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. While cost of therapy was not considered in recommendations, cost and coverage of commercial microbiota products may impact access. At the time of this writing, IMT material for CDI is available commercially, via non-profit stool banks, and within select academic centers. Healthcare systems and policy makers should consider how IMT material acquisition will affect cost and access.

Multiple guidelines recommend IMT to reduce the risk of recurrence in patients with a history of two or more recurrences of CDI. This includes guidelines from the American College of Gastroenterology, the European Society of Clinical Microbiology and Infectious Disease, the Infectious Diseases Society of American and Society for Healthcare Epidemiology of America, and the British Society of Gastroenterology and Healthcare Infection Society. Fecal microbiota spores, live-brpk is a new product not yet included in guidelines. The panel intentionally refrains from recommending IMT after the second recurrence to accommodate a subset of patients at increased risk of recurrence associated with high morbidity and mortality who could benefit from IMT after the first recurrence.

**Future directions**
Given many unique characteristics of IMT, it poses a challenge for regulatory bodies on how to regulate it. For example, in the US and Canada, it is considered a biologic drug, while in the UK, it is regulated as a medicinal product, yet in the EU counties it is classified as a tissue.\textsuperscript{44} On the other hand, it remains unregulated in other counties, such as Finland, China, and India. IMT use in clinical care and in research in the US is challenging due to regulatory hurdles including, requiring an investigational new drug (IND) application for clinical trials. Though stool banks have supplied donor material for IMT for over a decade, updates to FDA guidance now limit the policy of enforcement discretion to establishments under which IMT products are collected or prepared for local treatment of patients. This policy was enacted to “control risks presented by centralized manufacturing,” and stool banks will now have to maintain an IND in order to continue to supply IMT material for clinical use.\textsuperscript{45} The real-world effectiveness of recently approved live biotherapeutic products such as fecal microbiota, live-jslm and fecal microbiota spores, live-brpk is uncertain, as clinical trials of these products excluded patients with common comorbidities such as IBS and IBD.\textsuperscript{46} Furthermore, these were not approved for use in pediatric populations and costs may limit access in resource poor settings. IMT regulations should be revised to make clinical applications and research in this space feasible. The mechanisms by which IMT is effective in recurrent CDI are complex, poorly understood and need to be defined. There is a clear need for research on host microbial interactions following IMT and mechanistic studies using multi-omics technology and multidisciplinary expertise. Trials are needed to assess IMT as primary prevention in patients at high risk of CDI, IMT as first line treatment after short course of anti CDI therapy, IMT as treatment for CDI (not prevention), and combination of IMT and bezlotoxumab treatment. Comparative effectiveness studies are needed to address the impact of IMT route on CDI outcomes and to compare conventional donor IMT to approved live biotherapeutic products. It is unclear if manipulation of donor microbiota effects the efficacy for preventing recurrent CDI. The potential trade-offs between safety and
efficacy between microbiota therapeutics is 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 (e.g. bezlotoxumab, fidaxomicin) vs earlier use of IMT. Live biotherapeutic products are being developed and will reduce the unwanted infectious risk of donor stool.

**Question 2: In immunocompromised adults with recurrent *C. difficile* infection should IMT be used?**

<table>
<thead>
<tr>
<th>In mildly or moderately immunocompromised adults with recurrent <em>C. difficile</em> infection, the AGA suggests the use of IMT upon completion of standard-of-care antibiotics over no IMT (conditional recommendation, very low certainty evidence).</th>
</tr>
</thead>
<tbody>
<tr>
<td>In severely immunocompromised adults with recurrent <em>C. difficile</em> infection, the AGA suggests against the use of IMT upon completion of standard-of-care antibiotics over no IMT (conditional recommendation, very low certainty evidence).</td>
</tr>
</tbody>
</table>

**Implementation considerations**

The following considerations are specific to immunocompromised adult patients with non-severe, non-fulminant recurrent CDI in the outpatient setting. Severely immunocompromised includes patients receiving active cytotoxic therapy for solid tumors and hematologic malignancies, patients who have received CAR-T-cell therapy or hematopoietic cell transplant (only while neutropenic), any neutropenia, patients with severe primary immunodeficiency, patients with advanced or untreated HIV infection (CD4 counts < 200/mm³, 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 IMT implementation considerations for immunocompetent adults with recurrent CDI (pages XXX-XXX) can be used in the mildly or moderately immunocompetent population, with the exception of using fecal microbiota spores, live-brpk. There is insufficient evidence to recommend fecal microbiota spores, live-brpk in immunocompromised adult patients with recurrent CDI.

• IMT should be performed with appropriately screened donor stool and special testing may be necessary. For example, if an immunocompromised individual is CMV negative, the donor should be specifically tested for CMV.

Summary of the evidence

We did not identify any RCTs or comparative observational study that directly compared IMT to placebo or standard of care in immunocompromised adults with non-severe, non-fulminant 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 in immunocompromised patients with non-severe recurrent or severe CDI.47-71 The type of immunocompromise included patients with malignancy (n=84 patients), IBD (n=461 patients), solid organ transplant (n=115 patients), 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 unrelated and minimally manipulated donor stool. While IMT was delivered via colonoscopy in most of the studies all the administration routes were observed. A summary of the observational study characteristics is included in supplemental Table 8.

Benefits and harms
Data from the observational studies suggest that the rates of resolution of recurrent CDI in immunocompromised individuals that received IMT (85% malignancy, 84% IBD, 67% solid organ transplant, and 79% immunocompromised) were comparable to the pooled estimate of the rate of resolution of recurrent CDI in the IMT arms (77.6%) of the RCTs that evaluated IMT in immunocompetent individuals.\(^{21-35}\) There was little to no difference in rates of resolution of recurrent CDI in immunocompromised patients compared to immunocompetent patients (RR 0.96, with 95% CI 0.90 to 1.02). Data from observational studies also showed that the rates of serious adverse events in immunocompromised individuals who received IMT (3% malignancy, 11% IBD, 4% in solid organ transplant, and 14% in immunocompromised) was comparable to events in the intervention arm of trials in immunocompetent patients with recurrent CDI (11%).\(^{21-35}\) There was no quality-of-life or all-cause mortality data available in the immunocompromised population. A summary of the results is included in supplemental Figures 14-18.

**Certainty of evidence**

The CoE was downgraded due to serious risk of bias (observational single arm studies with concern for selection bias), inconsistency (the 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 confidence interval) for all critical outcomes. Publication bias was also strongly suspected (the studies were case series).\(^{72}\) The overall certainty in evidence of effects for IMT in immunocompromised adults with recurrent CDI was very low. The evidence profile is included in supplemental Table 9.

**Discussion**

The panel made a conditional recommendation for the use of IMT in mildly or moderately immunocompromised adults with recurrent CDI. The effect of IMT on reducing the risk of recurrence
was similar to the immunocompetent adults with recurrent CDI. There was no quality-of-life data available. IMT appears to be well tolerated with no differences in the risk of serious adverse events. Use of IMT in immunocompromised adults with recurrent CDI requires shared decision making, acknowledgement 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.

In severely immunocompromised adults, the panel made a conditional recommendation against the use of IMT to prevent recurrent CDI. Severely immunocompromised adults are at increased risk for serious or life-threatening infections with the use of IMT. 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 IMT may vary by type of immunocompromising condition. Extended or suppressive antibiotic therapy until immune recovery is likely a safer option.

IMT 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, or the Infectious Diseases Society of American and Society for Healthcare Epidemiology of America guideline. The American College of Gastroenterology guideline noted that IMT is considered the best treatment option for multiply recurrent CDI and that rigorous donor screening is critical in immunocompromised populations. The authors of the British Society of Gastroenterology and Healthcare Infection Society guideline recommend that IMT be offered with caution to immunosuppressed CDI patients, in whom IMT appears efficacious without significant additional adverse effects.

**Future directions**

The panel suggested similar considerations for future research for use of IMT 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 for CDI which increases risks for mortality and colectomy in hospitalized patients with both IBD and CDI compared to those with IBD alone. A prospective study demonstrated that IMT is effective for treatment of CDI in patients with IBD with favorable IBD-related outcomes. However, it remains uncertain whether escalation of IBD therapy should proceed before or after IMT 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 is lacking on effectiveness and safety of recently approved live biotherapeutic products in immunocompromised patients.

**Question 3: In adults with severe or fulminant *C. difficile* infection should IMT be used?**

| In adults with severe or fulminant *C. difficile* infection not responding to antimicrobial therapy, the AGA suggests the use of IMT over no IMT (conditional recommendation, very low certainty evidence). |

**Implementation considerations**

The following considerations are specific to adult patients 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 IMT?**
• Patients with severe or fulminant CDI require multidisciplinary care including critical care, surgery, gastroenterology, and infectious disease.

• IMT should be considered in patients not responding to standard of care antibiotics, generally within 2 to 5 days after initiating CDI treatment.

• IMT is not advised in patients with a bowel perforation, obstruction, or those who are severely immunocompromised.

**How to administer IMT?**

• IMT should be performed with appropriately screened donor stool.

• A bowel purge prior to IMT may not be feasible or safe. In these cases, IMT should be performed without a bowel preparation.

• First dose of IMT should be delivered by colonoscopy. Colonoscopy allows the provider to confirm the diagnosis and determine CDI severity. There is insufficient evidence in severe or fulminant CDI for IMT by enema or capsules. Administration of IMT via nasoenteric tube is discouraged given the increased risk of fecal aspiration.

**Follow up after IMT?**

• 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 IMT. The exact timing should be based on the patient’s response to treatment, local protocols, and multidisciplinary care. The route of repeated IMT dosing will depend on local expertise and treatment response.77, 78

• Anti-CDI antibiotics may need to be continued after IMT.77-79 Most published reports resume anti-CDI antibiotics or continue anti-CDI antibiotics while administering IMT.
• After resolution of colitis, suppressive vancomycin should be continued at discharge and a **final** IMT performed as an outpatient to prevent CDI recurrence. This IMT can be administered by colonoscopy or capsule.

**Alternatives to IMT?**

• 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 596 patients with severe or fulminant CDI that compared donor IMT to standard of care including colectomy.\(^{80-84}\) Most trials included adults with severe or fulminant CDI. One trial included only patients with fulminant CDI.\(^ {83}\) Trial participants were predominantly older adults with a high Charlson comorbidity index. Immune status was not reported in most studies. The intervention in all the studies was unrelated and unmanipulated donor stool. IMT was delivered by nasogastric tube, small bowel enteroscopy, flexible sigmoidoscopy, or colonoscopy. A small number of patients in 1 study had IMT by enema. Some of the trials repeated IMT every 3-5 days until resolution of pseudomembranes. A summary of the study characteristics is included in **supplemental Table 11.**

**Benefits and harms**

Patients with severe or fulminant CDI treated with IMT had a reduced risk of mortality compared to standard of care (RR, 0.37; 95% CI 0.23-0.59). Treatment with IMT 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 two studies (OR, 0.29; 95% CI 0.07-1.11). A summary of the results is included in **supplemental Figures 19-24.**
Certainty of evidence

The CoE was rated down due to very serious risk of bias (due to confounding and selection in majority of the studies), 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 certainty in evidence of effects for IMT in severe or fulminant CDI was very low. The evidence profile is included in supplemental Table 12.

Discussion

Severe or fulminant CDI can be fatal. The panel made a conditional recommendation for the use of IMT in adults with severe or fulminant CDI not responding to antimicrobial therapy. Treatment with IMT was associated with a reduced risk of mortality compared to standard of care. IMT was not associated with an increased risk of serious adverse events. Use of IMT in adults with severe or fulminant CDI not responding to antimicrobial therapy requires shared decision making with a multidisciplinary team, acknowledgement of the very low certainty evidence, 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 following colectomy near 50%, thus limiting surgical options. It is notable that IMT has a benefit when patients are not a candidate for surgery. It is critical for a care team to include surgical colleagues to accurately portray the surgical risk on an individual basis.

While controlled studies of IMT protocols are lacking, some general themes for use of IMT in severe/fulminant CDI exist. Cessation of other non-essential antibiotics is essential when possible and highlights the importance of multidisciplinary care with infectious disease consultants. IMT earlier into 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 IMT is likely to be insufficient and multiple IMTs are generally needed. Most published reports also resume anti-CDI antibiotics or continue anti-CDI antibiotics while administering IMT. The evidence to date includes observational studies with heterogeneous populations.

IMT treatment in patients with severe or fulminant CDI is inconsistently addressed in guidelines. IMT was recommended for patients with severe and fulminant CDI refractory to antibiotics by the authors of the American College of Gastroenterology guideline. A guideline by the European Society of Clinical Microbiology and Infectious Diseases noted that IMT may be a rescue therapy for patients with fulminant CDI that have deteriorated despite CDI antibiotic treatment and for whom surgery is not feasible. IMT 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.

**Future directions** Severe/fulminant CDI is relatively uncommon but associated with significant risk of morbidity and mortality. Research in this space is limited and needs urgent attention. Future multi-center studies should better define which patients with severe or fulminant CDI benefit from IMT, timing of IMT treatment, management of concomitant anti-CDI antibiotics, ideal number and route of IMT treatments, and whether such an approach reduces colectomy and/or mortality or whether aforementioned IMT derivatives have a similar impact. The AGA National FMT Patient Registry is initiating a sub study to focus on detailed clinical outcomes after FMT in acute/severe and fulminant infections which will include fecal sample collections to analyze changes in the microbiota including non-bacterial microbes and the resistome.
Question 4: In adults with ulcerative colitis should IMT be used?

In adults with ulcerative colitis, the AGA suggests against the use of IMT except in the context of clinical trials (conditional recommendation, very low certainty of evidence).

Implementation considerations

- IMT 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.

Summary of the evidence

Induction of remission. We identified 9 RCTs in 447 patients with active UC that compared IMT to standard of care (2 trials), placebo (4 trials), autologous IMT (2 trials), or UC exclusion diet (1 trial). The trials included adults with active (median Mayo scores 5-10 or Simple Clinical Colitis Activity Index 7-10) ulcerative colitis and either left-sided disease or pancolitis. Some of the studies excluded patients with a history of biologic treatment exposure, while others included patients on stable biologic therapy. Some of the trials pre-treated both arms with a course of antibiotics. Some of the trials use single donor while others used pooled donors. Trials required that patients be on stable doses of concomitant ulcerative colitis therapies. The route (enema, capsules, colonoscopy, nasoduodenal tube), number of treatments (1 to 82), and duration (one time treatment to multiple treatments over 8 weeks) of IMT varied markedly between RCTs. The 9 RCTs had 6 to 12 weeks of follow up. There was variation in the definition of remission among the studies. A summary of the trials is included in supplemental Table 14.

Maintenance of remission. We identified 2 RCTs in 71 patients with UC in remission. The first RCT contributed data for induction of remission in active UC. At baseline, most (70-73%) patients had left-sided disease and a total Mayo score of 5-7 before induction. In this RCT, patients who received
IMT during the induction phase and went into clinical remission were re-randomized to IMT versus IMT withdrawal. Patients randomized to IMT in this RCT (n=10) received IMT 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 IMT 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 IMT versus placebo. Patients randomized to IMT, received IMT from a single donor via colonoscopy at week 0, 8, 16, 24, 32, 40 and 48 (total 7 doses). Both the intervention and comparison group also received standard of care therapy (mesalamine +/- azathioprine or mercaptopurine). None of the patients in this RCT were on biologic therapy during the study. Almost a quarter of patients (22-23%) in this RCT had previous exposure to biologics. The 2 RCTs had 48 to 56 weeks of follow up. A summary of the trials is included in supplemental Table 14.

Benefits and harms

Induction of remission. Patients randomized to IMT were more likely to achieve induction of clinical remission compared to control (32.8% vs 16.3%; RR 1.95, 95 % CI 1.17 to 3.26). The data was very uncertain for the outcomes of serious adverse events (7.3% vs 5.1%; RR 1.55, 95 % CI 0.74 to 3.27), quality of life scores (mean difference 7.57 higher on the IBD questionnaire in the IMT group vs control, 95 % CI 3.9 to 19.1 higher) and induction of endoscopic remission (15.6% vs 9.6%; RR 1.46, 95 % CI 0.65 to 3.28). A summary of the results is included in supplemental Figures 26-29.

Maintenance of remission. The data from the two RCTs showed a very uncertain effect of IMT on maintenance of clinical remission (88.6% vs. 55.6%; RR 2.97, 95% CI 0.26 to 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 IMT group vs control) and maintenance of endoscopic remission (62.9% vs. 22.2%; RR 3.28, 95% CI 0.73 to 14.7).8

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), and imprecision (wide confidence interval and/or small number of events). We were unable to test for publication bias statistically, however, it was not suspected. The overall certainty in evidence was very low. The evidence profile is included in supplemental Table 15.

Maintenance of remission. The CoE was very low for all the outcomes due to serious risk of bias (lack of blinding), 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 supplemental Table 16.

Discussion

The panel made a conditional recommendation against the use of IMT in adults with UC except in the context of clinical trials. This recommendation supersedes a prior recommendation around IMT in UC.97 While there is promising evidence in this area, at this time it is unclear which patients with UC may benefit from IMT and how IMT should be positioned with other therapies. For induction of remission, most studies included patients with mild to moderate UC and IMT was offered as a concomitant therapy. There was significant heterogeneity in IMT 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,93 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.98-101
No guideline recommends use of IMT for treatment of UC. The British Society of Gastroenterology guideline authors note there is no place for IMT in the management of IBD unless complicated by CDI outside of the clinical trial setting. Authors of an American College of Gastroenterology guideline wrote that IMT requires more study before use as a therapy for UC. The authors of a prior AGA guideline recommend IMT for mild to moderate UC only in the context of a clinical trial.

**Future directions**

Future studies are needed to further define the characteristics of intervention in terms of route (upper versus lower gastrointestinal tract), frequency, type of donor (single versus pooled), timing (primary induction versus rescue/concomitant therapy), preparation of stool (aerobic versus anaerobic; frozen versus fresh), and duration of therapy. The panel also noted that sample size calculation in most of the studies considered a very large effect of IMT compared to control for induction of remission in UC and ranged from 25% to 45% more than control group; however, the effect of IMT might be more conservative as shown in the pooled analysis i.e., around 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. Current data suggests 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. 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.\textsuperscript{100, 101} Further research should aim at identifying optimal donor-recipient pairing, the role of antibody preconditioning to improve engraftment, biomarkers predictive of response, as well as potential adjunct therapies, such as precision diet, to enhance response.

Additionally, the positioning of IMT with standard of care medications will need to be addressed. It is unclear if IMT 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 IMT in maintenance of remission remain. The data on use of IMT for maintenance of remission in UC was available from two small studies and the evidence was not conclusive. Depending on the route of IMT administration, the response to IMT 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 IMT be used?**

| In adults with Crohn's disease, the AGA suggests against the use of IMT except in the context of a clinical trial (conditional recommendation, very low certainty of evidence). |

**Summary of the evidence**

We did not find any RCTs that assessed the efficacy or safety of IMT for induction of remission in adult patients with active Crohn's disease. We identified one RCT in 21 patients with Crohn’s disease in remission that compared donor IMT to placebo.\textsuperscript{105} The trial used corticosteroids to induce remission. Clinical outcomes were assessed at 24 weeks. A summary of the trial is included in supplemental Table 18.

**Benefits and harms**
Patients with Crohn’s disease randomized to IMT were not more likely to have maintenance of clinical remission compared to controls (36% vs 30%; RR, 1.21; 95% CI 0.36-4.14). There was no data on serious adverse events, quality of life and maintenance of endoscopic remission.\textsuperscript{8}

**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) 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 supplemental Tables 19-20.

**Discussion**

The panel made a conditional recommendation against the use of IMT in adults with Crohn’s disease except in the context of clinical trials. The use of IMT for the treatment of Crohn’s disease is poorly studied. The panel did not find any RCTs that addressed the use of IMT for induction of clinical remission in Crohn’s disease. The study on use of IMT for maintenance of remission in Crohn’s disease was small and the data were inconclusive. Guidelines do not recommend IMT for Crohn’s disease given insufficient evidence.\textsuperscript{102}

**Future directions.**

The panel suggested similar considerations for future research for use of IMT for Crohn’s disease as for UC noted above. Disease location and phenotype will also need to be considered.

**Question 6: In adults with pouchitis should IMT be used?**

| In adults with pouchitis, the AGA suggests against the use of IMT except in the context of clinical trials (conditional recommendation, very low certainty of evidence). |

**Summary of the evidence**
We identified 2 RCTs in 32 pouchitis patients that compared donor IMT to placebo or autologous IMT.\textsuperscript{106,107} The trials included patients with a history of ileal pouch-anal anastomosis after colectomy for ulcerative colitis. 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 ≥ 5. The intervention in both trials was unrelated donor stool. In one trial, the IMT was delivered directly to the pouch with endoscopy followed by oral capsules for 2 weeks.\textsuperscript{106} 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 IMT was delivered directly to the pouch with endoscopy followed by a single IMT treatment given by transanal catheter.\textsuperscript{107} A summary of the trials is included in \textit{supplemental Table 22}.  

**Benefits and harms**

Patients randomized to IMT were not more likely to have maintenance of clinical remission compared to controls (24% vs 33%: RR, 0.80; 95% CI 0.28-2.32). Quality of life was measured in one trial. IMT did not improve quality of life. No serious adverse events were reported in the two trials. A summary of the results is included in \textit{supplemental Figures 32-35}.  

**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 IMT in pouchitis was very low. We were unable to test for publication bias statistically, however, it was not suspected. The evidence profile is included in \textit{supplemental Tables 23-24}.  

**Discussion**

Restorative proctocolectomy with ileal pouch-anal anastomosis is a surgery for patients with ulcerative colitis and familial adenomatous polyposis. Pouchitis is a common long-term complication and is diagnosed based on symptoms and endoscopic findings of inflammation.\textsuperscript{108} The panel made a
conditional recommendation against the use of IMT in adults with pouchitis except in the context of clinical trials. In the two small trials, patients randomized to IMT were not more likely to have maintenance of clinical remission compared to controls. One trial was stopped prematurely due to poor rates of clinical remission. 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 showed that the pooled rate of clinical remission in patients with chronic pouchitis that received IMT was 20.1% (95% CI 6.2–48.7), which is comparable to the rate of remission induced in the placebo arm of clinical trials. [cite Barnes and Kahan] Guidelines have not recommended IMT for pouchitis given insufficient evidence.102, 108

Future directions

Primary or idiopathic pouchitis is believed to result from an abnormal immune response to luminal pouch dysbiosis in genetically susceptible hosts. 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 pouchitis patients. Response to IMT 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. IMT engraftment in an ileal pouch is almost certainly different from a colon. It remains unclear if donor directed IMT, which is comprised 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 IMT 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
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 IMT be used?**

| In adults with irritable bowel syndrome, the AGA suggests against the use of IMT except in the context of clinical trials (conditional recommendation, very low certainty of evidence). |

**Summary of the evidence**

We identified 11 RCTs in 671 IBS patients that compared donor IMT to either standard of care, placebo, or autologous IMT. 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, four were diarrhea predominant IBS, and the other trials included a mix of subtypes. The studies predominantly included women with a mean age 30-40 years old. The intervention was unrelated (11 trials) donor stool delivered by oral capsules (4 trials), into the small bowel (3 trials), or by 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 supplemental Table 26.

**Benefits and harms**

One trial included the FDA responder end point for IBS. In that trial, a greater proportion of patients randomized to donor FMT had symptom relief (FDA responders) compared to control (61% vs 16%; RR, 3.70; 95% CI, 2.00-6.85). The majority of the trial reported changes in IBS-quality of life or IBS-symptom severity scores at 12 weeks, which showed no improvement except for the same trial that showed symptom relief as defined by the FDA responder end point. Route of IMT and IMT donor type (single or multiple) did not change the results. Serious adverse events were rare. There were 2 events in patients randomized to IMT and none in the control arms (RR, 2.20; 95% CI, 0.24-20.55). The two
events include a hospital admission for observation for nausea after IMT and acute cholecystitis. A summary of the results is included in supplemental Figures 37-42.

Certainty of evidence

The CoE was rated down due to serious inconsistency and very or extremely serious imprecision (wide confidence interval and/or small number of events and participants). The trials were considered at low risk of bias overall. We were unable to test for publication bias statistically, however, it was not suspected. The overall certainty in evidence of effects for IMT in IBS was very low. The evidence profile is included in supplemental Table 27.

Discussion

IBS is a highly prevalent condition characterized by recurrent abdominal pain with associated changes in stool patterns, frequency, or form.\textsuperscript{124} 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 IMT in adults with IBS except in the context of clinical trials. Although safe, IMT did not improve symptom severity or quality of life in patients with IBS. A single trial suggested that patients randomized to donor IMT had symptom relief compared to control. The overall certainty in evidence was very low.

Few guidelines address IMT in patients with IBS. The American College of Gastroenterology and Italian guidelines recommend against the use of IMT for the treatment of IBS symptoms.\textsuperscript{125, 126} IMT in patients with IBS was mentioned in a guideline by the British Society of Gastroenterology and no recommendation was made due to insufficient evidence.\textsuperscript{127}

Future directions

IBS is a heterogenous condition with complex pathophysiology. It is plausible that certain subsets of IBS patients based on symptom phenotype, or a particular bacterial or metabolic profile, may
benefit from IMT therapy. 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 IMT mediates these effects. Only one trial included the FDA responder end point. Trials should include the FDA composite endpoint for IBS, incorporate validated patient-reported outcome instrument, determine whether bacterial engraftment leads to a positive response as well as determine an optimal IMT protocol for durable outcomes.

**Plans for updating this guideline**

This guideline will be updated in 3-5 years when new data becomes available.
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33. Feuerstadt P, Dubberke ER, Guo A, et al. 522. Significant Improvement in Health-Related Quality of Life (HRQL) with RBX2660: Results from a Phase 3 Randomized, Placebo-Controlled Trial in Recurrent Clostridiodes Difficile Infection (PUNCH CD3). Open Forum Infectious Diseases 2022;9.
difficile Infection: Results From a Randomized, Placebo-Controlled Trial. Official journal of the American College of Gastroenterology | ACG 2021;116:S57.


Table 1. Executive summary of recommendations and implementation considerations

1. In immunocompetent adults with recurrent *C. difficile* infection, the AGA suggests the use of IMT upon completion of standard-of-care antibiotics over no IMT (conditional recommendation, low certainty of evidence).

In immunocompetent adults with recurrent *C. difficile* infection, the AGA suggests the use of fecal microbiota spores, live-brpk upon completion of standard-of-care antibiotics over no fecal microbiota spores, live-brpk (conditional recommendation, low certainty of evidence)

### Implementation considerations

#### Diagnosis of recurrent CDI?
- A CDI diagnosis requires acute onset, clinically significant diarrhea (e.g., ≥ 3 unformed stools in 24 hours) and highly sensitive (nucleic acid amplification or glutamate dehydrogenase) alone or in combination with highly specific (toxin enzyme immunoassay) testing plus resolution of diarrhea with *C. difficile* directed antibiotics.
- Recurrent CDI is defined as 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 diagnosis, 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 IMT (or fecal microbiota spores, live-brpk)?
- Treatment with IMT or fecal microbiota spores, live-brpk can be considered in patients at high risk for recurrent CDI.
- Careful consideration prior to proceeding with IMT or fecal microbiota spores, live-brpk treatment is recommended in patients who require frequent antibiotics or long-term antibiotic prophylaxis, since ongoing antibiotics may diminish the efficacy of such treatment.

#### How to administer IMT (or fecal microbiota spores, live-brpk)?
- IMT or treatment with fecal microbiota spores, live-brpk should be performed upon completion of a course of standard-of-care antibiotics for recurrent CDI.
- Suppressive anti-CDI antibiotics (e.g., vancomycin) should be used to bridge standard-of-care antibiotics until IMT or fecal microbiota spores, live-brpk therapy.
- Antibiotics for CDI should be stopped 1-3 days prior to IMT to allow adequate time for antibiotics to wash-out of the system. If a bowel purge is given, IMT 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. When administering fecal microbiota spores, live-brpk, antibiotic treatment for recurrent CDI should be stopped 2-4 days prior, followed by a split dose bowel purge.
- IMT should be performed with appropriately screened donor stool.
- IMT can be delivered by multiple routes. There is insufficient evidence to recommend a specific route.

#### Alternatives to IMT (or fecal microbiota spores, live-brpk treatment)?
- A vancomycin taper, tapered-pulsed fidaxomicin, or bezlotoxumab are reasonable alternative therapies in patients who do not have access to or who are not interested in IMT or treatment with fecal microbiota spores, live-brpk.
2. In mildly or moderately immunocompromised adults with recurrent *C. difficile* infection, the AGA suggests the use of IMT upon completion of standard-of-care antibiotics over no IMT (conditional recommendation, very low certainty of evidence).

In severely immunocompromised adults with recurrent *C. difficile* infection, the AGA suggests against the use of IMT upon completion of standard-of-care antibiotics over no IMT (conditional recommendation, very low certainty of evidence).

**Implementation considerations**
- The IMT implementation considerations for 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. There is insufficient evidence to recommend fecal microbiota spores, live-brpk in immunocompromised adult patients with recurrent CDI.
- IMT should be performed with appropriately screened donor stool and special testing may be necessary. For example, if an immunocompromised individual is CMV negative, the donor should be specifically tested for CMV.

3. In adults with severe or fulminant *C. difficile* infection not responding to antimicrobial therapy, the AGA suggests the use of IMT over no IMT (conditional recommendation, very low certainty of evidence).

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

- **How to administer IMT?**
  - IMT should be performed with appropriately screened donor stool.
  - A bowel purge prior to IMT may not be feasible or safe. In these cases, IMT should be performed without a bowel preparation.
  - First dose of IMT should be delivered by colonoscopy. Colonoscopy allows the provider to confirm the diagnosis and determine CDI severity. There is insufficient evidence in severe or fulminant CDI for IMT by enema or capsules. Administration of IMT via nasoenteric tube is discouraged given the increased risk of fecal aspiration.

- **Follow up after IMT?**
  - 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 IMT. The exact timing should be based on the patient’s response to treatment, local protocols, and multidisciplinary care. The route of repeated IMT dosing will depend on local expertise and treatment response.
Anti-CDI antibiotics may need to be continued after IMT. Most published reports resume anti-CDI antibiotics or continue anti-CDI antibiotics while administering IMT.

After resolution of colitis, suppressive vancomycin should be continued at discharge and a final IMT performed as an outpatient to prevent CDI recurrence. This IMT can be administered by colonoscopy or capsule.

Alternatives to IMT?
- 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 IMT except in the context of clinical trials (conditional recommendation, very low certainty of evidence).

Implementation considerations
- IMT 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.

5. In adults with **Crohn's disease**, the AGA suggests against the use of IMT except in the context of a clinical trial (conditional recommendation, very low certainty of evidence).

6. In adults with **pouchitis**, the AGA suggests against the use of IMT except in the context of clinical trial (conditional recommendation, very low certainty of evidence).

7. In adults with **irritable bowel syndrome**, the AGA suggests against the use of IMT except in the context of clinical trials (conditional recommendation, very low certainty of evidence).
Table 2. Interpretation of strong and conditional recommendations using the Grading of Recommendations Assessments, Development and Evaluation Framework

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

NOTE. Strong recommendations are indicated by statements that lead with “we recommend” and conditional recommendations are indicated by statements that lead with “we suggest.”