Washington State Health Care Authority
Health Technology Assessment

FINAL Key Questions and Background

Fecal Microbiota Transplantation (FMT)

Background

Fecal microbiota transplantation (FMT) is a procedure whereby donor fecal matter is placed into a patient's gastrointestinal system in order to recolonize it with normal gut bacteria that have been killed or suppressed. The most common use for FMT is treatment of *Clostridium difficile* infections.

Clostridium difficile infections have become increasingly common in the US in recent years. The number of diagnoses doubled between the years 2001 and 2005,[3] and it is currently estimated that *C. difficile* infects nearly 500,000 people and causes 15,000 deaths every year in the US, 80% of which occur in persons aged 65 years and older.[6,7] At the same time, infections have become more severe and difficult to treat, and the FDA currently recognizes *C. difficile* infections as one of the highest drug-resistant threats in the US.[6] The condition typically impacts older persons, particularly those who are hospitalized or in nursing home facilities, although younger persons are also at risk. The bacteria spread via fecal-to-mouth transmission, and infections most commonly impact patients who have received recent treatment with antibiotics (which disrupts the normal gut flora) and were exposed to the bacteria.[3] Other risk factors include hospitalization, older age, proton pump inhibitor use, immunosuppression, and chronic kidney disease.[3,5] Upon colonization of *C. difficile* in the colon, toxin is produced and leads to inflammation.[3] Symptoms include severe diarrhea, fever, and abdominal pain; if inadequately treated, dehydration, kidney failure, and death may result.[3,7] The infection is typically treated with the antibiotics metronidazole, vancomycin, or fidamoxin, with metronidazole and vancomycin being first-line antibiotics, vancomycin used for more severe illness, and fidamoxin typically reserved for recurrent infection.[3] However, approximately 20% to 60% of patients have recurrence after antibiotic treatment,[5,7,8] and those who develop multiple recurrences become increasingly resistant to antibiotic treatment.[3]

Fecal microbiota transplantation (FMT) is a treatment alternative for *C. difficile infections*, particularly those that are recurrent or resistant to standard antibiotic therapy.[3,5] Although this treatment has been used for centuries, it has only recently to gained traction in the medical community.[5] Infusion of feces from a healthy donor into the gastrointestinal tract of the infected person is thought to restore normal gut flora, which will aid in elimination of *C. difficile*.[3,5] Prior to infusion, the donor feces is screened for transmissible diseases (e.g., HIV, hepatitis, etc.).[2] Transplantation can be performed via nasogastric tube, colonoscopy, or enema; and fecal material may be either fresh or frozen.[2,4,9,11] It has been suggested that FMT is an effective treatment for *C. difficile* infections, and that the majority of patients recover after only one procedure.[2,4,5] Other conditions for which FMT use is being explored are varied, and include inflammatory bowel disease, ulcerative colitis, and Crohn's disease.[4] However, while current FDA

regulations permit use of FMT for treating *C. difficile* infections that have not responded to standard antibiotic therapy, use of FMT for any other indication requires submittal and approval of an IND (investigational new drug) application to the FDA.[1,10]

The primary aim of this assessment is to systematically review and synthesize evidence on the efficacy, safety, and cost-effectiveness of FMT for *C. difficile* infections and inflammatory bowel disease.

Policy Context

Primary use is to treat individuals with difficult to treat infections caused by Clostridium difficile (C. difficile). Frozen stool from healthy donors is transplanted to the infected individual's bowel to restore the normal balance of bacteria in the gut. Concerns are considered medium for safety, high for efficacy, and low for cost-effectiveness.

Scope

Population: Patients undergoing therapeutic treatment for *Clostridium difficile* (*C. difficile* or CDI) infection or inflammatory bowel disease (including ulcerative colitis and Crohn's disease)

Intervention: Fecal microbiota transplantation (FMT)

Comparators: Alternative treatment(s) (e.g., antibiotics, disease-specific medication, bowel lavage), different types of fecal preparations (e.g., fresh versus frozen), different routes of administration (e.g., nasoduodenal vs. colonoscopic)

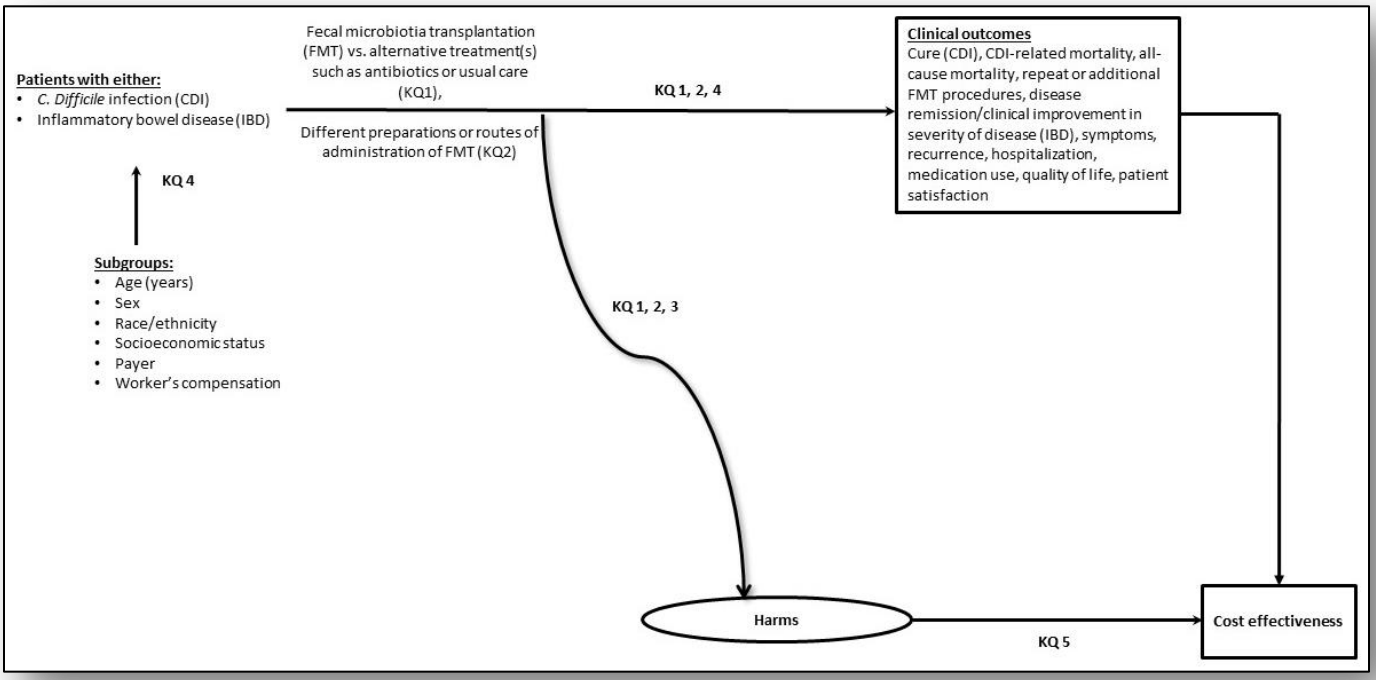
Outcomes: Cure (CDI) (primary), death from CDI (primary), repeat or additional FMT procedures (primary), all-cause mortality (primary), disease remission/clinical improvement in disease severity (IBD) (primary), symptoms, recurrence, hospitalization, medication use, quality of life, patient satisfaction, adverse events (primary). Excluded from the scope: non-clinical and intermediate outcomes (e.g., gut microflora characteristics, biomarkers of disease).

Key Questions

With included conditions (*C. difficile*, irritable bowel disease) evaluated separately:

1. What is the evidence of the efficacy and effectiveness of fecal microbiota transplant (FMT)?
2. Does the efficacy and effectiveness of FMT vary by route of administration, timing of administration, or type of preparation (i.e., fresh versus frozen)?
3. What is the evidence of the safety of FMT?
4. Is there evidence of differential efficacy or safety of FMT compared with alternative treatment options in subpopulations? Include consideration of age, sex, race, ethnicity, payer, and worker's compensation.
5. What is the evidence of the cost-effectiveness of FMT compared with alternative treatment options?

Figure 1. Analytic Framework



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Public Comment & Response

None received.