QUERI

Fecal Microbiota Transplantation for *Clostridium Difficile* Infection: A Systematic Review of the Evidence

July 2014

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research and Development Service
Washington, DC 20420

Prepared by:
Evidence-based Synthesis Program (ESP) Center
Minneapolis VA Medical Center
Minneapolis, MN
Timothy J. Wilt, M.D., M.P.H., Director

Investigators:
Principal Investigator:
Dimitri Drekonja, M.D., M.S.

Co-Investigators:
Jon Reich, M.D.
Selome Gezahegn, M.D.
Nancy Greer, Ph.D.
Aasma Shaukat, M.D., M.P.H.
Timothy Wilt, M.D., M.P.H.

Research Associates:
Roderick MacDonald, M.S.
Indy Rutks, B.S.

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) clinicians, managers and policymakers as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout the VA, and some evidence syntheses inform the clinical guidelines of large professional organizations.

QUERI provides funding for four ESP Centers and each Center has an active university affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence;
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of HSR&D Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at Nicole.Floyd@va.gov.

Recommended citation: Drekonja D, Reich J, Gezahegn S, Greer N, Shaukat A, MacDonald R, Rutks I, and Wilt TJ. Fecal Microbiota Transplantation for Clostridium Difficile Infection: A Systematic Review of the Evidence. VA ESP Project #09-009; 2014.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at Minneapolis VA Medical Center, Minneapolis, MN, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. Drs. Drekonja and Shaukat are principal proponents of the following randomized controlled trial currently under review for planning and conduct through the VA Cooperative Studies Program: "The Veterans Affairs Fecal Microbiota Therapy Trial for Recurrent Clostridium difficile Infection: A Planning Request for a VA Cooperative Study". No other investigators have any affiliations or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

EXECUTIVE SUMMARY

INTRODUCTION

Since its discovery as the cause of pseudomembranous colitis in 1978, *Clostridium difficile (C. difficile)* has become an increasingly important pathogen. Initially, *C. difficile* infection (CDI) was largely confined to patients with healthcare exposure; however, it is now also affecting those with no or limited contact with the healthcare system. In 2013, the U.S. Centers for Disease Control and Prevention placed *C. difficile* into its top threat category of "urgent" in its first threat report on antimicrobial resistance.

A major challenge in treating CDI is the high rate of recurrent disease. Recurrence occurs in 15-30% of patients, and among those with a single episode of recurrence, the risk of further recurrence increases after each episode. Multiple treatment/recurrence episodes can result in repeated hospitalizations, clinic visits, deconditioning, malnourishment, and fecal continence issues. These effects are debilitating, contribute to decreased quality of life and prolonged courses of antimicrobial treatment and rarely can be fatal. Antimicrobial treatment for these episodes of recurrent disease yields reported success rates between 30% and 80%, depending on the number of recurrences, and on the agent and duration of treatment selected. These sub-optimal response rates have helped spur the investigation of additional therapeutic options including fecal microbiota transplantation (FMT) for the treatment of CDI.

CDI is characterized by severe alterations in the colonic microbiome (normal colonic bacteria). Restoring the normal microbiome has been proposed as a method for preventing recurrence. The most widely utilized intervention has been probiotics yet these products provide only a limited number and diversity of microorganisms. Fecal microbiota transplantation is increasingly utilized as a treatment for patients with recurrent CDI; based on the idea that to restore all the organisms that comprise the normal colonic flora, simply import the colonic microbiome of a healthy person. FMT has been performed in hundreds of patients, with outcomes from more than 500 cases reported in the medical literature - most in non-controlled case series. Reported success rates of up to 100% and the recent publication of a randomized controlled trial (RCT) comparing FMT to antimicrobial treatment have increased interest in the procedure.

Purpose of Review

The Minneapolis VA Evidence-based Synthesis Program was asked to conduct a systematic evidence review regarding the effectiveness of FMT for treatment of CDI, in part to help guide policy makers within the Veterans Health Administration determine if the evidence supporting FMT was sufficient to implement FMT programs in their facilities. The topic was nominated by Jason Dominitz, MD, MHS on behalf of the VA Gastroenterology Field Advisory Committee.

The key questions for the review were:

KQ1. What is the effectiveness of fecal microbiota transplantation for recurrent CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

KQ2. What is the effectiveness of fecal microbiota transplantation for refractory CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

KQ3. What is the effectiveness of fecal microbiota transplantation as initial therapy for CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

KQ4. What are the harms of fecal microbiota transplantation therapy compared to standard therapy for initial, recurrent, or refractory CDI? Do the harms vary by method of transplantation?

KQ5. Is the procedure acceptable to patients? Does patient acceptability vary by method of transplantation?

METHODS

Data Sources and Searches

We searched MEDLINE (OVID) for articles published from 1980 through May 2014 (Appendix A). Our search was designed to identify studies of any design although we excluded case reports except for those that reported harms. We limited the search to studies involving human subjects published in the English language. Additional articles were identified from hand-searching reference lists of existing systematic reviews and included studies.

Study Selection

Two investigators independently reviewed full text of articles identified as potentially eligible.

Data Abstraction and Quality Assessment

Study characteristics, patient characteristics, and outcomes data were abstracted from articles eligible for inclusion. Since all but 2 of the included studies were case series or case reports, we did not formally assess study quality, but rather note that conventional methods for rating strength of evidence would classify even well-conducted and reported case series as high risk of bias. Therefore, strength of evidence would typically be considered insufficient or low. Our key outcomes included: resolution of symptoms (primary outcome), time to resolution of symptoms, recurrence, all-cause mortality, and adverse events. In many cases, it was difficult to ascertain whether the resolution of symptoms was due to the pre-FMT antimicrobials for CDI, the FMT procedure, or a combination of the two. Similarly, the outcomes of resolution and recurrence were often combined as "resolution of diarrhea without relapse," or "durable resolution."

Data Synthesis and Analysis

Most findings are summarized narratively. We calculated weighted resolution rates and 95% confidence intervals for the studies of FMT for recurrent CDI stratified by FMT method. There were insufficient studies of refractory CDI or FMT as initial therapy for CDI for numerical synthesis.

RESULTS

Results of Literature Search

Our literature search yielded 161 abstracts or titles. We excluded 100 after abstract review and performed full text review of 61 articles. We excluded 51 leaving 10 included articles. From

hand-searching of reference lists of systematic reviews and included studies and suggestions from reviewers, we identified another 21 articles for a total of 31 included studies – 2 RCTs, 25 case series, and 4 case reports.

Summary of Results for Key Questions

KQ1. FMT for Recurrent CDI

Two small moderate risk of bias RCTs and 19 case series (range 2 to 74 participants; total n=480 receiving FMT) reported use of FMT for patients with *recurrent CDI* (Executive Summary Figure). Patients were older age, the majority female, and all had multiple (3 to 12) CDI recurrences prior to undergoing FMT. FMT was performed 3 to 27 months from the time of the patients' initial episode of CDI. Mean follow-up after FMT ranged from 1 to 30 months. We identified few qualitative differences in baseline characteristics according to treatment approach. Donor screening and selection criteria as well as patient selection, pre-transplant preparation and FMT preparation and delivery varied. A high proportion of patients treated with FMT had resolution of symptoms. However, authors commonly reported that antimicrobials for CDI were given prior to FMT to ensure that patients were asymptomatic or had a "reduction in symptoms" at the time of FMT. Thus, in most cases FMT was administered when patients were asymptomatic or symptoms were resolving, with the FMT possibly contributing to further symptom resolution, prevention, or both. In the RCT comparing FMT via nasoduodenal tube to 2 control groups (n=43), 81% of patients in the FMT group achieved resolution of symptoms within the first 3 months and the results were significantly different from the vancomycin (31%) or vancomycin plus bowel lavage (23%) control groups. In the RCT comparing 2 FMT treatment approaches (n=20), a high proportion of patients in each group had resolution of symptoms; the difference between treatment approaches was not significant (60% in the nasogastric tube group and 80% in the colonoscopy group, P=.63). Across all studies of patients with recurrent CDI, including FMT via an upper gastrointestinal (GI) (k=6), colonoscopy (k=10, including the RCT with both upper GI and colonoscopy groups), enema (k=5), or combination approach (k=1), resolution of symptoms was observed in 83% (95%CI 77%, 87%). Although comparisons across studies should be interpreted with considerable caution, FMT involving colonoscopy resulted in the highest overall symptom resolution rates, followed by upper GI tract and enema. Eleven case series assessed time to resolution of symptoms; 3 reported resolution within 24 hours and the others reported means or medians of one to 7 days. Two reports of FMT focused on immunocompromised patients; one included patients already reported in other case series. Resolution after an initial FMT (methods varied) was reported in 50% of a small series (n=2) and 78% of a larger series (n=80).

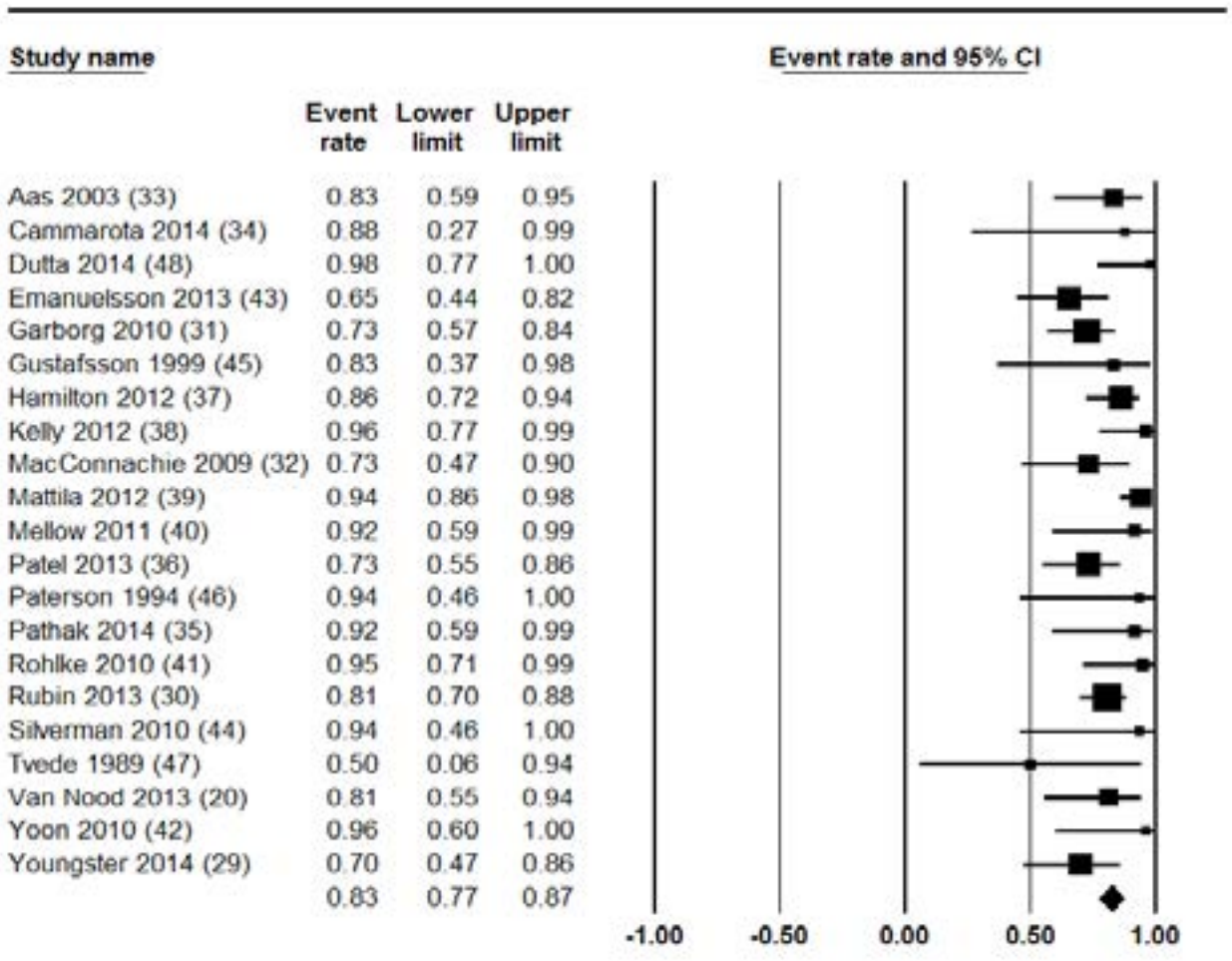
KQ2. FMT for Refractory CDI

We identified 5 case series among patients with refractory CD (117 participants; 112 treated via enema and 5 via colonoscopy). Mean age ranged from 52 to 73 years and between 25% and 67% were male. Reported resolution of symptoms ranged widely (0% to 100%, mean=53%).

KQ3. FMT for Initial CDI

We identified only one patient treated with FMT for *initial CDI*. The patient's symptoms resolved following FMT via enema.

Executive Summary Figure. Reported Resolution of Symptoms after Initial FMT for Recurrent CDI, All Routes for Infusion of Donor Feces*



*Due to small sample sizes in 5 studies that reported 100% success (Cammarota 2014,[34] Yoon 2010,[42]Silverman 2010,[44] Paterson 1994,[46] and Dutta 2014[48]) the software used to generate this figure lowered the estimates for these studies from 100% to 88%, 96%, 94%, 94%, and 98%, respectively, to allow the upper limit of the 95%CI to be 1.0. Actual reported resolution of symptoms is 84%.

KQ4. FMT Adverse Events

Few serious *adverse events* were reported and no clear link between FMT and serious adverse events could be established. In one series of immunocompromised patients, serious adverse events and adverse events were each observed in 15% of patients with approximately one-third considered related to FMT. Long-term safety data regarding FMT are lacking.

KQ5. FMT Acceptability

No study systematically assessed *acceptability* to patients with prior or current episodes of CDI. Anecdotal findings suggest that the procedure was an acceptable alternative for patients with recurrent CDI.

DISCUSSION

Key Findings and Strength of Evidence

Based on results from 2 moderate-quality (moderate risk of bias) RCTs and 23 case series enrolling patients with recurrent, refractory, or an initial episode of CDI, we found low strength evidence (recurrent CDI) or insufficient evidence (refractory CDI or initial episode of CDI) that treatment with FMT led to a large proportion of patients experiencing short-term resolution of symptoms. The pooled reported success rates (*ie*, resolution of symptoms or resolution of symptoms without recurrence at 3 months or less) were 83% for patients with recurrent CDI and 53% for patients with refractory CDI which are substantially better than success rates reported for various medical therapies for recurrent or refractory CDI. Furthermore, in the RCT that directly compared FMT with vancomycin, FMT resulted in a higher percentage of resolution (13 of 16 patients, 81%) compared to either vancomycin (4/13, 31%) or vancomycin plus bowel lavage (3/13, 23%). One death was reported in the vancomycin group. A second small (n=20) RCT found no statistically significant difference in resolution between groups treated via nasogastric tube (6/10, 60%) or colonoscopy (8/10, 80%).

Applicability

Several limitations in the evidence threaten broader applicability. Treatment protocols varied widely with few reports following identical protocol. Patient demographic and disease characteristics as well as donor selection and FMT preparation and delivery methods varied. Only one small non-US RCT directly compared FMT to antibiotic therapy. Most enrollees had 4 or more episodes of CDI prior to enrollment. In contrast, trials of antimicrobial therapy for CDI enrolled those with at most a single recurrence, and had higher antimicrobial success rates. Thus the effectiveness and comparative effectiveness in individuals with fewer recurrences is not known. The high response rates in case series likely represent optimal outcomes. Publication bias may exist whereby lower response rates are not reported. Additionally, several studies reported "symptom resolution" following FMT infusion among patients who were without symptoms at time of infusion-presumably believing that without FMT symptoms would have reoccurred. None of the reported studies were conducted at VA medical centers; many were conducted outside the US, derived from selected samples of subjects with CDI, and did not account for all treated patients. Most study participants were older adults and FMT was initiated after a wide range of CDI recurrences. Most studies used fresh fecal material however, donor screening and selection, fecal material preparation, and FMT dose and delivery varied widely. Nonetheless, CDI in Veterans is common and results in considerable morbidity and health care utilization and costs. Additional, safe, acceptable and effective treatment options are needed especially for individuals with recurrent CDI. The incidence of CDI in VA is approximately 1% of all hospitalized patients; recurrence rates are 22% to 30%. In 2012, 6,046 cases of CDI and 1,517 cases of recurrent CDI were identified using VA inpatient data sources and 8,878 cases when outpatient CDI diagnoses were included.

Research Gaps/Future Research

While a large percentage of patients had resolution after FMT, the current evidence is of low methodological quality and limited applicability. Our findings are based on small case series and 2

very small RCTs of selected individuals. Thus we have low certainty about the efficacy, widespread effectiveness and comparative effectiveness (especially related to alternative antimicrobial-based regimens) of FMT for patients with recurrent or refractory CDI. Almost no data exist on FMT for initial treatment of CDI. Furthermore, many studies attributed "resolution of symptoms" to FMT even among patients who were without symptoms at the time of FMT. Whether resolution was due to the pre-FMT antimicrobials, the FMT procedure, or a combination of the two, was difficult to ascertain. Therefore, any reported effect estimate is likely greater than would be observed in broader clinical settings especially among individuals with ongoing symptoms. Additional data from RCTs, nonrandomized controlled studies or higher quality cohort studies would be of value, in particular to more adequately address the comparative effectiveness of FMT vs. optimal medical management. Because recurrent CDI is defined by stool frequency plus a confirmatory microbiological test (which frequently can remain positive in the absence of symptoms), using standardized stool frequency assessment is of key importance. This is because exceeding a specific threshold typically initiates the evaluation for recurrent disease and can alter definitions of "disease recurrence" and estimates of treatment effectiveness. Additionally, multiple factors can influence stool frequency including knowledge of treatment received. Therefore, future trials should be evaluated with blinding of both patients and providers. Numerous examples exist from uncontrolled studies or small controlled studies showing large symptomatic improvements in conditions that are attributed to interventions which are later not confirmed or markedly attenuated when randomly compared to placebo, sham or blinded interventions (*eg,* knee arthroplasty for knee pain, acupuncture for numerous conditions, medications for restless legs syndrome or chronic insomnia). Future research is also needed to clarify important elements of FMT including: the number of CDI episodes after which FMT provides the greatest benefit (should it exist), optimal medical management (antibiotic type, dose, delivery and duration), and the preferred methods for fecal material and patient preparation, preferred donor selection, and optimal delivery and timing of FMT.

Conclusions

We found low strength evidence from small RCTs and case series that FMT may have a substantial effect and few short-term adverse events for adults with recurrent CDI. One small moderate quality RCT study found that FMT reduced symptom recurrence compared to standard CDI therapy that included vancomycin and one very small moderate quality RCT found FMT resulted in high symptom resolution rate that did not differ by delivery routes (nasogastric tube vs. colonoscopy). There is insufficient evidence on FMT for patients with refractory CDI and only a single case report for initial treatment of CDI. Evidence is insufficient whether treatment effects vary by FMT donor, preparation or delivery method.

ABBREVIATIONS TABLE

CDI	*Clostridium difficile* infection
C. difficile	*Clostridium difficile*
FMT	Fecal microbiota transplantation
FY	Fiscal year
GI	Gastrointestinal
RCT	Randomized, controlled trial
VA	Department of Veterans Affairs