

Fecal microbiota transplantation

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**Washington State
Health Care Authority**

FECAL MICROBIOTA TRANSPLANT

November 18, 2016

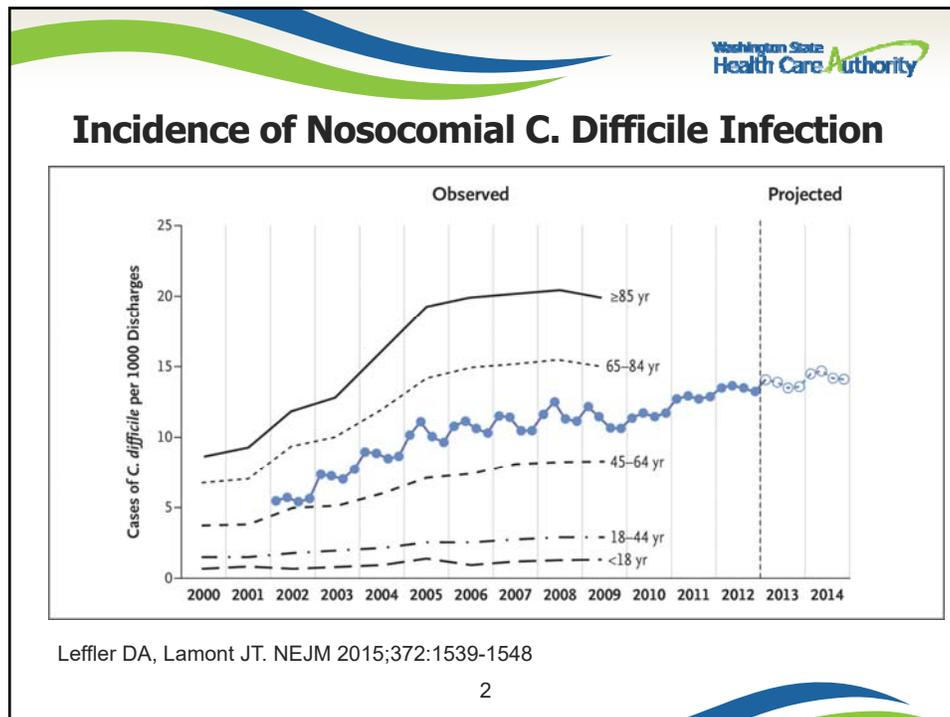
Daniel Lessler, MD
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WA - Health Care Authority



Background

- Clostridium difficile is a gram positive, spore forming anaerobe
- Toxigenic and non-toxigenic strains exist
- Most toxigenic strains produce toxins A and B; some produce only B
- C. Difficile diarrhea is mediated by toxin A and B; leading cause of nosocomial gastroenteritis and associated with considerable morbidity and mortality
- The most important risk factor is antibiotic use. 2011 surveillance study identified:
 - 453,000 cases of C. difficile infection
 - 29,000 deaths associated with C. difficile infection
 - Approximately 25% of these infections were community acquired

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C. Difficile: Diagnosis and Treatment

- C. difficile infection is diagnosed either by enzyme immunoassay for toxins in stool, or DNA-based tests that identify toxigenic C. difficile toxin genes
- Treatment:
 - First episode = antibiotics (vancomycin or metronidazole most commonly; fidaxomicin also effective, but expensive)
 - First recurrence = typically also treated with antibiotics
 - Second and subsequent recurrences difficult to cure, b/c of persistence of spores in the bowel and difficulty in mounting immune response

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Treatment of Recurrent C. Difficile Infection

Fecal Microbial Transplantation (FMT)

- Stool obtained from a healthy donor is instilled into the GI tract of a patient
- Human colonic microbiota provides resistance against bacterial pathogens
- FMT restores microbial diversity
- The components of the fecal microbiome that provide protection against C. difficile are not known

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Inflammatory Bowel Disease

- Most common forms of Inflammatory Bowel Disease (IBD) are Ulcerative Colitis (UC) and Crohn's Disease
- UC: chronic inflammatory disease that involves mucosa of rectum and proximal extension into colon toward cecum
- Crohn's Disease: patchy, trans-mural inflammation that can affect any part of the GI tract
- Symptoms of IBD include blood in stool; abdominal pain; fatigue; bloating and weight loss
- Aberrancies in host microbiota may play a role in the pathogenesis of IBD

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Agency Medical Director Concerns

- SAFETY = MEDIUM
- EFFICACY = HIGH
- COST = LOW

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Current State Agency Policy

PEBB –Covered for the treatment of patients with recurrent (second or subsequent episodes) *Clostridium difficile* infections (also known as *clostridium difficile* colitis, or pseudomembranous colitis). Fecal microbiota transplantation is considered **investigational** for all other indications.

Medicaid FFS and Managed Care – Requires PA

Labor and Industries – Not Covered

Dept. of Corrections –Requires PA

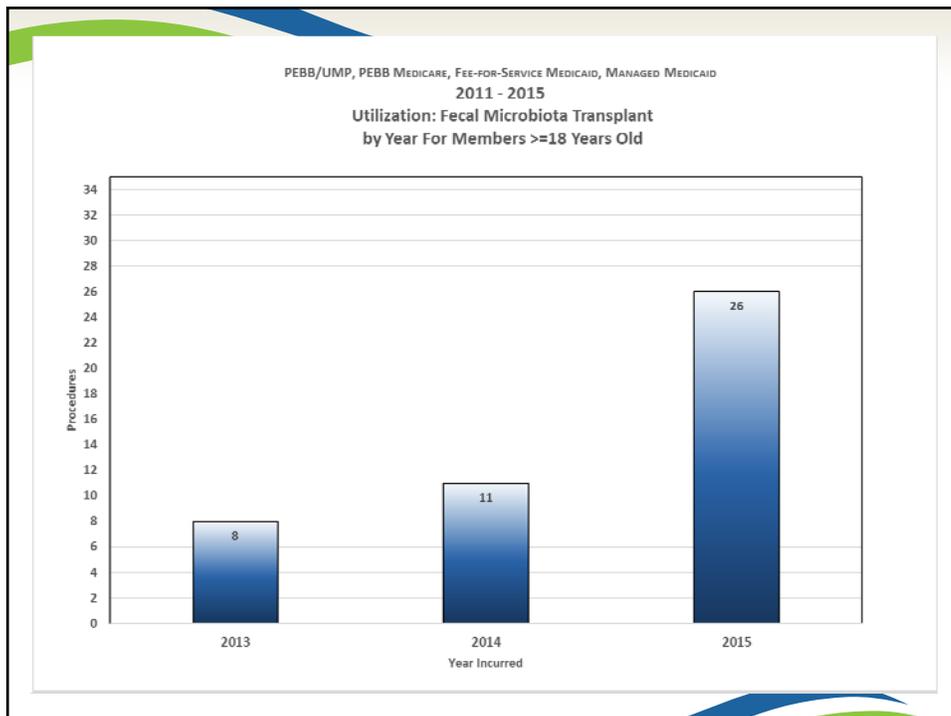
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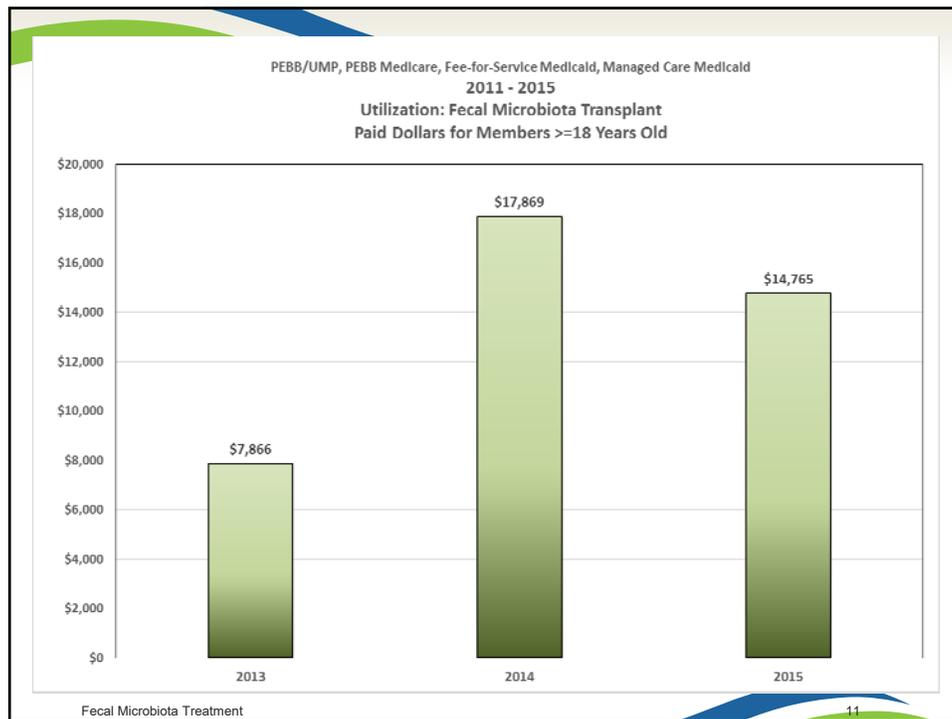


Agency Utilization of FMT

- FMT is viewed as an “emerging technology”
- Overall utilization is low; agency data are aggregated for presentation
- Average FMT patient age = 49 yrs.
- Relevant diagnostic codes:
 - 8.45 = Intestinal infection due to C. difficile
 - A04.7 = Enterocolitis due to C. difficile

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Key Questions

1. What is the evidence of efficacy and effectiveness of FMT?
2. Does the efficacy and effectiveness of FMT vary by route of administration, timing of administration, or type of preparation?
3. What is the safety of FMT?
4. Is there evidence of differential efficacy or safety of FMT compared with alternative treatments in subpopulations?
5. What is the evidence of cost-effectiveness of FMT compared with alternative treatment options?

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Effectiveness of FMT

Treatment of *C. difficile*

- Available evidence supports the effectiveness of FMT in the treatment of recurrent *C. difficile* infection
- The role of FMT in the treatment of primary *C. difficile* infection is unclear

Treatment of inflammatory bowel disease (IBD)

- Insufficient evidence to determine the effectiveness of FMT in the treatment of IBD

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Fecal Microbiota Transplantation for *C. difficile*

Safety

- FMT is typically associated with relatively minor, self-limiting adverse events (e.g. bloating; cramping; diarrhea)
- More serious adverse events (bacteremia; sepsis; death) appear to be infrequent, and it is unclear the extent to which these complications are caused by FMT vs. other underlying patient characteristics b/c of lack of comparative data
- Limited long term data on safety

Administration

- No difference between frozen vs. fresh feces (low quality evidence)
- Insufficient evidence regarding route and timing of administration

Cost-effectiveness

- Available economic models suggest that FMT is cost-effective relative to antibiotics

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Coverage Policies for FMT

- No CMS National Coverage Determination
- Many plans cover FMT for C. difficile for recurrent infection that has failed vancomycin treatment
 - Exact criteria differ somewhat, especially with respect to the number of recurrences patient must experience prior to use of FMT

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Clinical Guidelines

American College of Gastroenterology, 2013

- FMT should be considered in patients with a 3rd recurrence of C. difficile after a pulsed vancomycin regimen

European Society of Clinical Microbiology and Infectious Diseases, 2014

- FMT in combination with oral antibiotic treatment is strongly recommended for multiple, recurrent C. difficile infections unresponsive to antibiotic treatment

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Agency Recommendation

- Cover with conditions
- Fecal Microbiota Transplantation (fresh or frozen feces, administered either by NG tube or via the colon) is covered for a third recurrence of C. difficile infection after a pulsed vancomycin regimen.
- Fecal Microbiota Transplantation is not covered for treatment of Inflammatory Bowel Disease

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Questions?

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Order of scheduled presentations:

Fecal microbiota transplantation

Name	
1	
2	
3	
4	
5	
6	

No requests to provide public comment on this technology review were received.

Fecal Microbiota Transplantation

October 18, 2016

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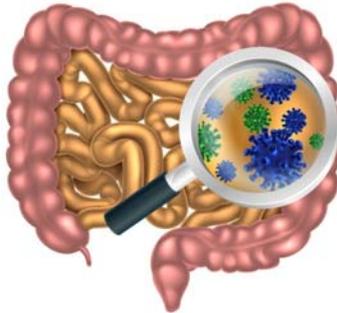
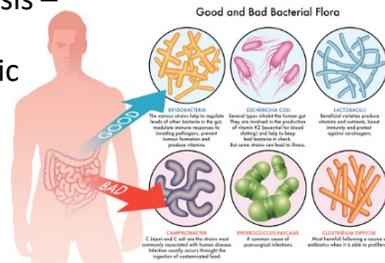


Image from <https://med.stanford.edu/news/all-news/2015/12/new-technique-reveals-gut-bacteria-diversity.html>

Background

Fecal Microbiota Transplantation (FMT)

- Healthy donor stool is introduced into the recipient's bowel to restore the normal balance of bacteria in the gut
- Considered after antibiotic treatment has failed.
- The normal gut is home to trillions of bacterial cells, many of which are benign or even beneficial
- A disruption in bacterial homeostasis – such as is caused by antibiotic treatment – can allow opportunistic pathogens (such as *C. difficile*) to proliferate.



<https://www.dreamstime.com/stock-illustration-intestinal-bacterial-flora-medical-illustration-good-bad-image41327669>

Indications for FMT

(in included studies)

Recurrent or relapsing *Clostridium difficile* infection (CDI)

- *C. difficile* produces toxins which cause diarrhea and gastrointestinal inflammation
- Inadequate treatment can lead to dehydration, kidney failure, and death
- Risk factors include broad-spectrum antibiotic use, hospitalization, and older age
- Conventionally treated with antibiotics (metronidazole, vancomycin, fidaxomicin).
- Approximately 20% to 60% of patients have CDI recurrence after antibiotic treatment; multiple recurrences are associated with increased resistance to antibiotic treatment and may develop into chronic CDI.



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Indications for FMT

(in included studies)

Inflammatory bowel disease (IBD) (Off-label use)

- Chronic inflammation of the digestive tract.
- Ulcerative colitis and Crohn's disease are the most common forms.
 - Ulcerative colitis (UC): disease of the mucosa, affects only the colon and rectum
 - Crohn's disease (CD): transmural, may affect any part of the digestive system
- Symptoms: diarrhea, blood in the stool, abdominal pain, fatigue, vomiting, bloating, weight loss.
- Gradual onset, with periods of active disease and disease remission.
- Treatment focuses on symptom management.



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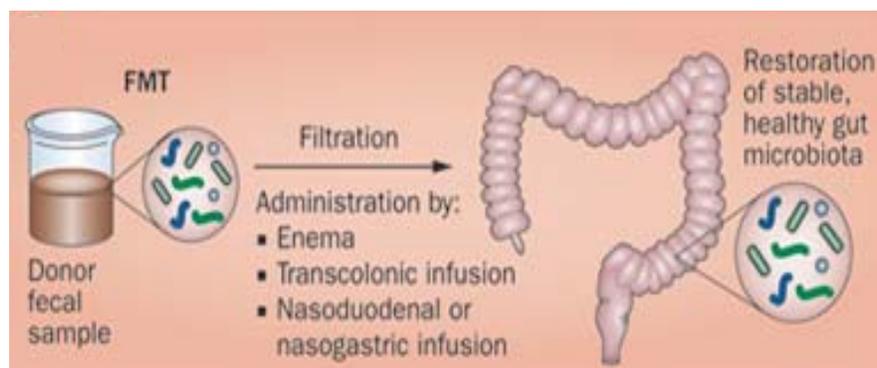
Donor Selection and Screening

- Donors can be relatives or close friends, or universal donors
- Screening focuses on risk reduction and is completed within ~4 weeks of donation:
 - Blood: HIV, Hepatitis (A, B and C), Syphilis, others
 - Stool: ova and parasites (Giardia, cryptosporidium and others), Helicobacter pylori, *C. difficile* toxin, and routine bacterial culture for enteric pathogens
- Donor screening questionnaire – similar to current protocol for screening blood donors



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FMT procedure



http://www.nature.com/nrgastro/journal/v9/n2/fig_tab/nrgastro.2011.244_F1.html 6

Key Questions

With included conditions (recurrent *C. difficile*, IBD) evaluated separately:

1. What is the evidence of the **efficacy and effectiveness** of 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?



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Inclusion Criteria

• **Population:**

- Patients undergoing therapeutic treatment for recurrent *C. difficile* infection (CDI) or IBD (including ulcerative colitis and Crohn's disease)
- (conditions for which FMT use is investigational such as obesity, metabolic syndrome, slow transit constipation were excluded)

• **Intervention:**

- Fecal Microbiota Transplantation (FMT)

• **Comparators:**

- Alternative treatment(s) (e.g., antibiotics, bowel lavage)
- Different types of fecal preparations (i.e., fresh vs. frozen)
- Different routes of administration (i.e., nasoduodenal vs. colonoscopic vs. enema)



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Inclusion Criteria

- **Outcomes:**

- Primary outcomes:

- Cure (CDI)
 - Disease remission/clinical improvement in disease severity (IBD)
 - Death attributed to CDI
 - Repeat or additional FMT procedures
 - All-cause mortality
 - Adverse events

- Secondary outcomes:

- Symptoms, recurrence, hospitalization, medication use, quality of life, patient satisfaction
 - (Nonclinical or intermediate outcomes were excluded)



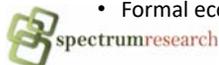
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Inclusion Criteria

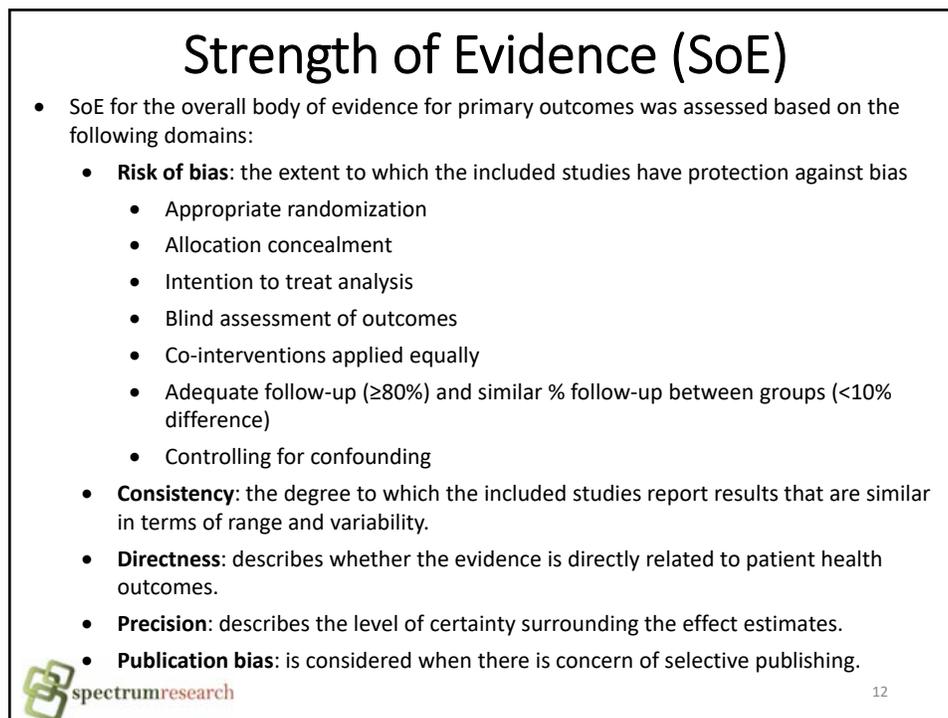
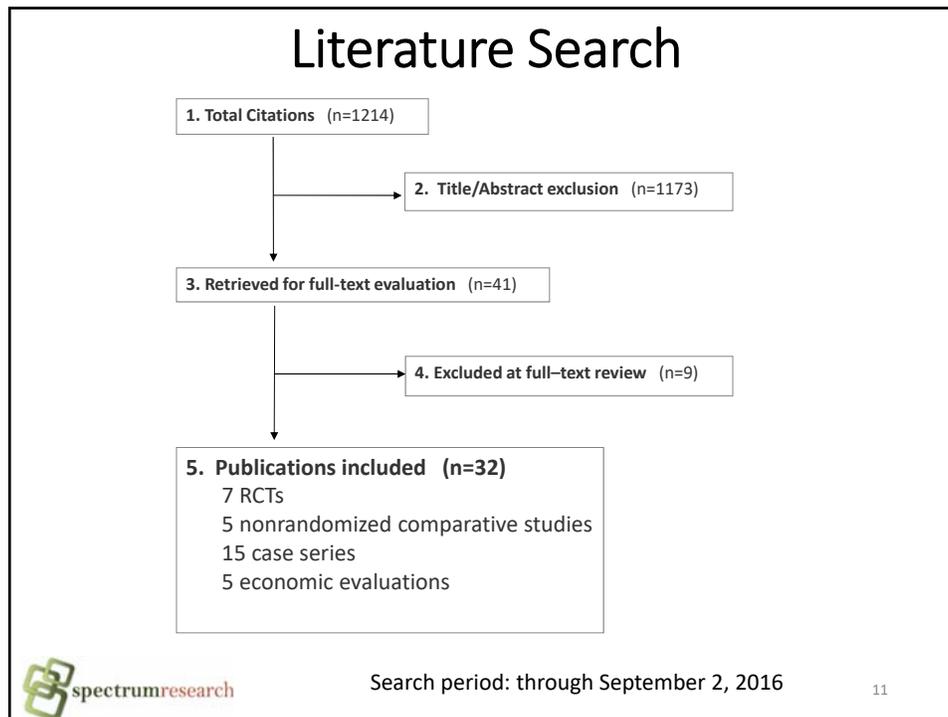
- **Study design:**

Focus was on studies with the least potential for bias.

- KQs 1 and 2 (efficacy, effectiveness; route, timing of administration, type of preparation):
 - RCTs
 - Nonrandomized comparative (cohort) studies
 - Noncomparative studies (case series) considered in the absence of sufficient comparative evidence
- KQ3 (safety)
 - RCTs
 - Nonrandomized comparative (cohort) studies
 - Noncomparative studies (case series) specifically designed to evaluate harms/adverse events
- KQ4 (differential efficacy and safety)
 - RCTs that stratified results for both treatment groups by patient characteristics of interest, e.g.:
- KQ5 (cost-effectiveness)
 - Formal economic analyses



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Overall Strength of Evidence (GRADE)

Quality rating	Interpretation
High	High confidence that the evidence reflects the true effect.
Moderate	Moderate confidence in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Insufficient	Very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

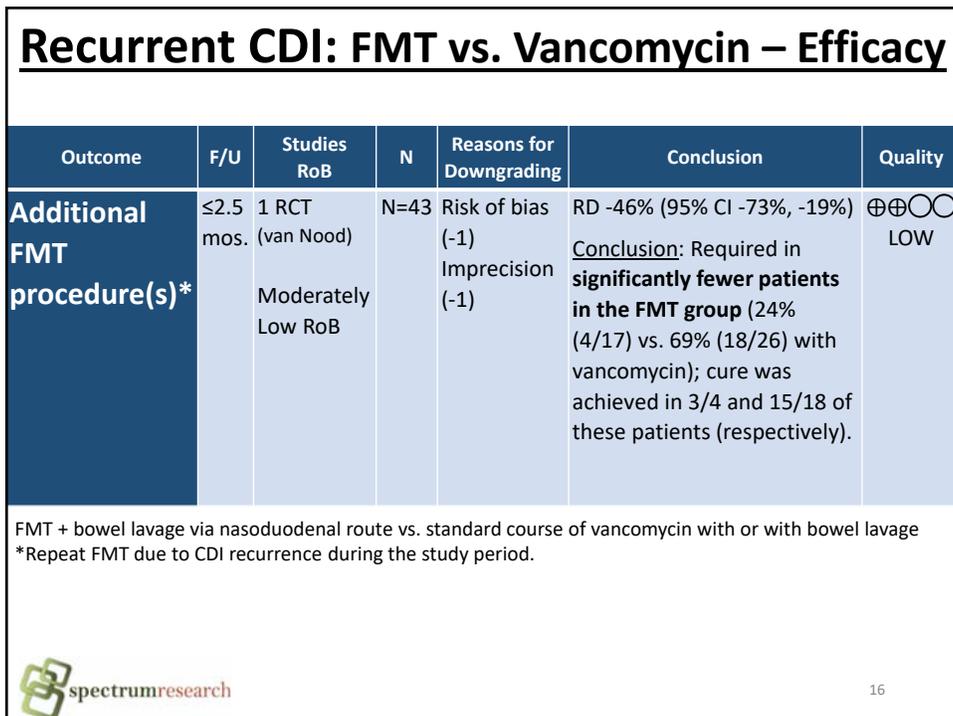
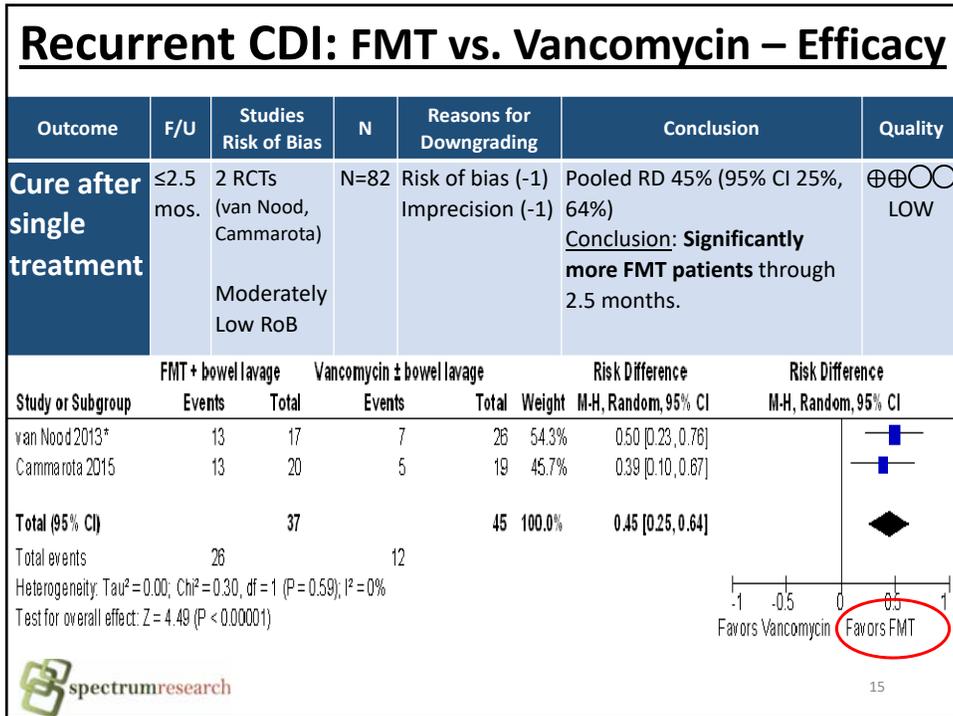
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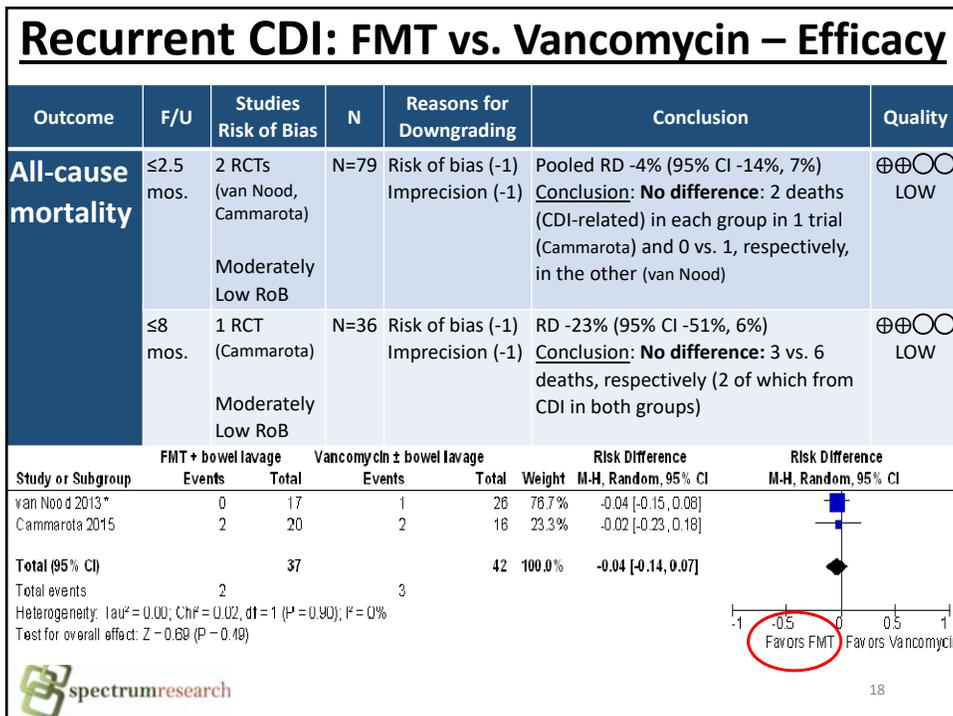
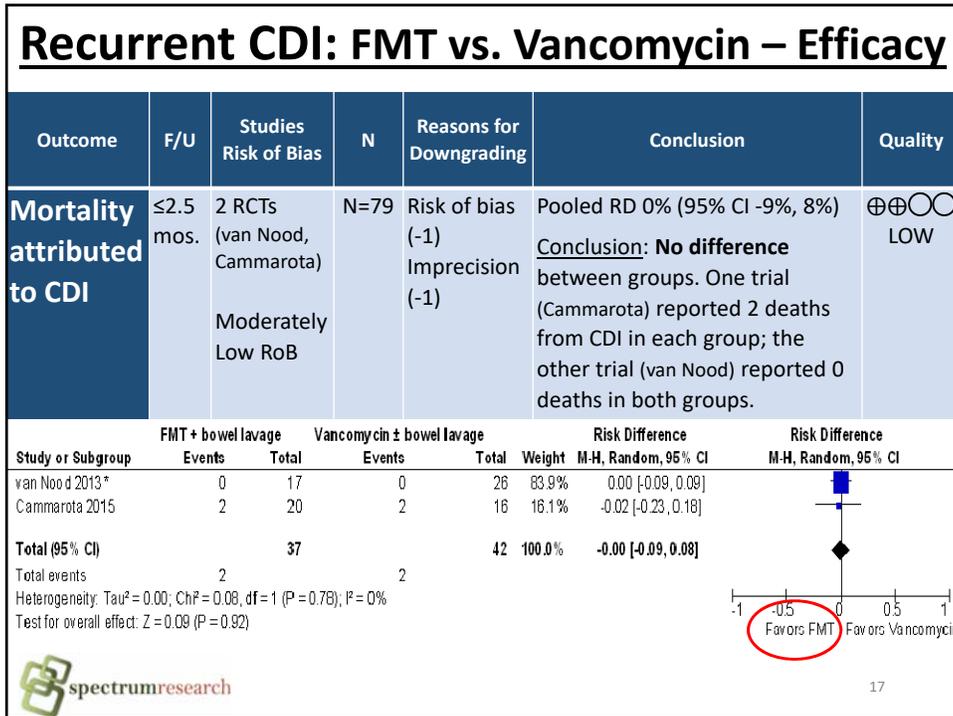
KQ1: Efficacy and Effectiveness

Recurrent or relapsing *Clostridium difficile* infection (CDI)

Comparisons	Studies	Risk of Bias
FMT vs. antibiotics	2 RCTs (N=39, 43) 1 prospective cohort (n=61)	Moderately Low Moderately High
FMT vs. placebo infusion	1 RCT (N=46)	Low
FMT (noncomparative)	13 case series (N=32-229, N=20 [2 pediatric case series])	High

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Recurrent CDI: FMT vs. Placebo – Efficacy

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
Cure* after single treatment	2 mos.	1 RCT (Kelly) Low RoB	N=46	Imprecision (-1)	RD 28% (95% CI 6%, 51%) Conclusion: Significantly more FMT patients (91%, 20/22) achieved cure through 2 months compared with placebo (63%, 15/24).	⊕⊕⊕○ MODERATE

FMT + bowel lavage with infusion of donor (FMT) or autologous (placebo) feces via colonoscopy.
 *Cure was defined as the resolution of diarrhea (i.e., <3 unformed stools/day) in the absence of antibiotic treatment with no recurrence. No stool testing was performed.



Recurrent CDI: FMT vs. Placebo – Efficacy

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
Additional FMT procedure(s)*	2 mos.	1 RCT (Kelly) Low RoB	N=46	Imprecision (-1)	RD -33% (95% CI -54%, -12%) Conclusion: Significantly fewer patients in the FMT group (5% (1/22) vs. 38% (9/24) with placebo) required repeat FMT (all using donor feces). Cure was achieved in all patients who underwent an additional FMT procedure.	⊕⊕⊕○ MODERATE

FMT + bowel lavage with infusion of donor (FMT) or autologous (placebo) feces via colonoscopy.
 *Repeat FMT using donor feces was offered to all patients who had CDI recurrence during the eight-week study period.



Recurrent CDI: FMT vs. Placebo – Efficacy

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
CDI-related or all-cause mortality	6 mos.	1 RCT (Kelly) Low RoB	N=46	Imprecision (-1)	<u>Conclusion:</u> For those patients with complete follow-up, no deaths were reported to occur in either group (0% (0/21) donor vs. 0% (0/22) autologous feces).	⊕⊕⊕○ MODERATE

FMT + bowel lavage with infusion of donor (FMT) or autologous (placebo) feces via colonoscopy.



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Summary: Recurrent CDI Efficacy

In general, compared with Vancomycin (Low SoE; 2 RCTs, N=82) and with Placebo (Moderate SoE; 1 RCT, N=46), outcomes following FMT were:

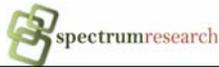
- **Superior** with regards to cure (after single treatment) and less need for additional FMT procedures through 2-2.5 months
- **Similar** when considering mortality (CDI-related or all-cause) over 2-2.5 months and 6-8 months.



KQ1: Efficacy and Effectiveness (cont.)

Inflammatory Bowel Disease (IBD) Ulcerative Colitis (UC)

Comparisons	Studies	Risk of Bias
FMT vs. placebo infusion	2 RCTs (N=75, 48)	Low, Moderately High
FMT (noncomparative)	2 case series (N=41 [Crohn's disease], 10 [pediatric])	High



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Ulcerative Colitis: FMT vs. Placebo – Efficacy

Outcome Definition	F/U	Studies Risk of Bias	N	Reasons for Downgrading	Conclusion	Quality
Clinical remission + endoscopic response (composite)						
Full Mayo score <3; endoscopic Mayo score = 0	1.75 mos.	1 RCT (Moayyedi) Low RoB	N=75	Imprecision (-1)	RD 18% (95% CI 3%, 34%) Conclusion: Slightly more FMT vs. placebo patients achieved this outcome (24% [9/38] vs. 5% [2/37]), however, the trial was ended early due to futility.	⊕⊕⊕○ MODERATE
SCCAI score ≤2; ≥1 point ↑ on combined endoscopic Mayo score	3 mos.	1 RCT (Rossen) Moderately High RoB	N=48	Risk of Bias (-1) Imprecision (-1)	RD 10% (95% CI -14%, 35%) Conclusion: Slightly more FMT patients achieved the outcome (30% [7/23] vs. 20% [5/25], p=NS); this trial also ended early because of futility.	



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Ulcerative Colitis: FMT vs. Placebo – Efficacy

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
Clinical remission (SCCAI score ≤2)	3 mos.	1 RCT (Rossen) Moderately High RoB	N=48	Risk of bias (-1) Imprecision (-1)	RD -2% (95% CI -28%, 25%) <u>Conclusion: No difference</u> between FMT and placebo groups (30% vs. 32%).	⊕⊕○○ LOW

FMT + bowel lavage with infusion of donor (FMT) or autologous (placebo) feces via nasoduodenal route



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Ulcerative Colitis: FMT vs. Placebo – Efficacy

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
Clinical response						
↓ full Mayo clinic score ≥3 points	1.75 mos.	1 RCT (Moayyedi) Low RoB	N=75	Imprecision (-1)	RD 15% (95% CI -6%, 36%) <u>Conclusion: No difference</u> between FMT and placebo* groups (39% vs. 24%).	⊕⊕⊕○ MODERATE
↓ SCCAI score ≥1.5 points	3 mos.	1 RCT (Rossen) Moderately High RoB	N=48	Risk of bias (-1) Imprecision (-1)	RD -4% (95% CI -32%, 24%). <u>Conclusion: No difference</u> between FMT and placebo* groups (48% vs. 52%).	

-Moayyedi: FMT or water (placebo) via retention enema
-Rossen: FMT + bowel lavage with donor (FMT) or autologous (placebo) feces via nasoduodenal route



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Ulcerative Colitis: FMT vs. Placebo – Efficacy

Outcome	F/U	Studies Risk of Bias	N	Reasons for Downgrading	Conclusion	Quality
Additional procedures*	3 mos.	1 RCT (Rossen) Moderately High RoB	N=48	Risk of bias (-1) Imprecision (-1)	RD 10% (95% CI -11%, 31%) <u>Conclusion:</u> No difference between FMT and placebo groups (22% vs. 12%).	⊕⊕○○ LOW

FMT + bowel lavage with infusion of donor (FMT) or autologous (placebo) feces via nasoduodenal route
 *Rescue therapy (not defined) for ongoing disease flare.



Ulcerative Colitis: FMT vs. Placebo Efficacy

- Insufficient evidence:
 - Clinical remission + endoscopic response over the longer-term (12 months) – no comparative data (1 RCT, n=75; Low RoB)
- No evidence:
 - Mortality
- Secondary outcomes:
 - No difference between groups at 1.75 months
 - Improvement in symptoms (Mayo Score, IBDQ score) (1 RCT, n=75; Low RoB)
 - Quality of Life (EQ-5D) (1 RCT, n=75; Low RoB)



Summary: Ulcerative Colitis Efficacy

In general, when compared with placebo:

- FMT **may provide a benefit** when considering the composite outcome (clinical remission + endoscopic response) over 1.75 to 3 months (Moderate SoE; 2 RCTs, N=123); however, statistical significance was not uniformly reached across trials and outcomes definitions differed.
- FMT provided **similar results** over 1.75 to 3 months for:
 - Clinical remission (Low SoE; 1 RCT, N=48)
 - Clinical response (Moderate SoE; 2 RCT, N=123)
 - Additional procedures (Low SoE; 1 RCT, N=48)
 - QoL and symptom improvement (1 RCT, N=75)
- **No evidence** for mortality



KQ2: Route, Timing and Preparation

Recurrent *Clostridium difficile* infection (CDI)

Comparisons	Studies	Risk of Bias	Strength of Evidence
Colonoscopic vs. Nasogastric FMT	1 RCT (N=20)	Moderately Low	INSUFFICIENT for all outcomes (cure, additional procedures, CDI-related and all-cause mortality)
“Timely” vs. “Delayed” FMT*	1 retrospective cohort (N=75)	Moderately High	INSUFFICIENT for all outcomes (cure; <i>no evidence</i> for additional procedures, mortality)
Frozen vs. Fresh feces for FMT	1 RCT (N=219) 1 retrospective cohort (N=49)	Moderately Low Moderately High	(See following slides)

*Following 2 vs. ≥3 recurrences of CDI

➤ Inflammatory Bowel Disease (IBD): *No evidence*



Recurrent CDI: FMT using Frozen vs. Fresh Feces

Cure

Outcome	F/U	Studies Risk of Bias	N	Reasons for Downgrading	Conclusion	Quality
Cure* after single treatment	≤3.25 mos.	1 RCT (Lee) Moderately Low RoB	N=219	Risk of bias (-1) Imprecision (-1)	RD 2.3% (95% CI -10.9%, 15.6%) <u>Conclusion: No difference</u> between frozen vs. fresh feces (52.8% (57/108) vs. 50.5% (56/111)).	⊕⊕○○ LOW

FMT via retention enema.
*Resolution of diarrhea in the absence of antibiotic treatment with no recurrence

➤ Additional procedures outcome: *No evidence*



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Recurrent CDI: FMT using Frozen vs. Fresh Feces

CDI-related Mortality

Outcome	F/U	Studies Risk of Bias	N	Reasons for Downgrading	Conclusion	Quality
Mortality Attributed to CDI	≤3.25 mos.	1 RCT (Lee) Moderately Low RoB	N=219	Risk of bias (-1) Imprecision (-1)	RD 0.1% (95% CI -3.5%, 3.6%) <u>Conclusion: No difference</u> between frozen vs. fresh feces (1.9% (2/108) vs. 1.8% (2/111)).	⊕⊕○○ LOW

FMT via retention enema.



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Recurrent CDI: FMT using Frozen vs. Fresh Feces

All-cause Mortality

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
All-cause mortality	≤3.25 mos.	1 RCT (Lee)	N=219	Risk of bias (-1) Imprecision (-1)	RD -6.2% (95% CI -13.5%, 1.2%)	⊕⊕○○ LOW
		Moderately Low RoB			Conclusion: No statistical difference between frozen vs. fresh feces, although the incidence of death from any cause was slightly lower in the frozen feces group (5.6% (6/108) vs. 11.7% (13/111)).	

FMT via retention enema.



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KQ3: Safety

Recurrent *Clostridium difficile* infection (CDI)

- FMT vs. Vancomycin
- FMT vs. Placebo (autologous feces)
- Fresh vs. Frozen Feces for FMT

INSUFFICIENT evidence for the following: Colonoscopic vs. Nasogastric FMT and “Timely vs. “Delayed FMT

Inflammatory Bowel Disease (IBD)

- FMT vs. Placebo (water, autologous FMT)

INSUFFICIENT evidence for the following: non-comparative data (any route, preparation)



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Recurrent CDI: FMT vs. Vancomycin – Safety

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
Serious adverse events	≤2.5 mos.	2 RCTs (van Nood, Cammarota) Moderately Low RoB	N=82	Risk of bias (-1) Imprecision (-1)	RD 0% <u>Conclusion:</u> No serious adverse events (including death) occurred in either treatment group.	⊕⊕○○ ○ LOW
Non-serious adverse events	≤2.5 mos.	1 RCT (van Nood) Moderately Low RoB	N=43	Risk of bias (-1) Imprecision (-1)	<u>Conclusion:</u> Occurred with statistically similar frequency between groups as measured between the first day after treatment and 2.5 months follow-up: <i>constipation, infection, GI complaints, indigestion, nausea, belching, vomiting, abdominal cramps, diarrhea</i>	⊕⊕○○ ○ LOW

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Recurrent CDI: FMT vs. Placebo – Safety

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
Serious adverse events	≤6 mos.	1 RCT (Kelly) Low RoB	N=43	Imprecision (-2)	<u>Conclusion:</u> For those patients with complete follow-up, no serious adverse events were attributed to the procedure in either group.	⊕⊕○○ ○ LOW
Non-serious adverse events	≤6 mos.	1 RCT (Kelly) Low RoB	N=43	Imprecision (-2)	<u>Conclusion:</u> Aside from chills, which was slightly (but not significantly) more common with autologous FMT, the following non-serious procedure-related events occurred with statistically similar frequency between FMT and placebo groups (all reported within 1 week): <i>fever, abdominal pain, bloating, nausea, vomiting, diarrhea, flatulence, anorexia, and constipation; however, no data were reported.</i>	⊕⊕○○ ○ LOW

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Recurrent CDI: Fresh vs. Frozen Feces – Safety

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
Serious adverse events	≤3.25 to 12 mos.	1 RCT (Lee) Moderately Low RoB 1 cohort (Satokari) Moderately High RoB	N=261	Risk of bias (-1) Imprecision (-1)	RD: 0% Conclusion: No serious adverse events (including death) were attributed to FMT using feces prepared by either method as reported by the RCT (N=219) and cohort study (N=42).	⊕⊕○○ LOW
Non-serious adverse events	≤24 hrs.	1 RCT (Lee) Moderately Low RoB	N=232	Risk of bias ¹ (-1) Imprecision (-1)	Conclusion: The following mild to moderate symptoms occurred similarly between groups , however data were not stratified by groups and patient numbers were not reported: <i>Transient diarrhea (70%), abdominal cramps (10%), nausea (<5%)</i>	⊕⊕○○ LOW


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Recurrent CDI: Noncomparative – Safety

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
Non-serious adverse events	≤48 hrs.	3 RCTs (van Nood, Cammarota, Youngster) 1 cohort study (Lagier) 2 case series (Kelly, Kronman)	N=146 (+ 33 FMTs)	Risk of bias (-1) Imprecision (-1)	Conclusion: Numerous non-serious FMT-related adverse events were reported across 3 RCTs (N=56), 1 cohort (33 FMTs), and 3 case series (N=90); range: 0% to 94%. The most common events were: <ul style="list-style-type: none"> • <i>Diarrhea:</i> 73%–94% (2 RCTs, 1 cohort) • <i>Abdominal cramps:</i> 47% (2 RCTs) • <i>Abdominal discomfort/pain:</i> 4%–39% (2 RCTs, 1 case series) • <i>Belching:</i> 19% (1 RCT) • <i>Muroid stools:</i> 10% (1 case series of pediatric patients) • <i>Vomiting:</i> 0%–10% (1 RCT, 1 case series of pediatric patients) 	⊕⊕○○ LOW


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Ulcerative Colitis: FMT vs. Placebo – Safety

Outcome	F/U	Studies RoB	N	Reasons for Downgrading	Conclusion	Quality
Serious adverse events	1.75-3 mos.	2 RCTs (Moayyedi, Rossen) Low, Moderately High RoB	N=123	Risk of bias (-1) Imprecision (-1)	Pooled RD 2% (95% CI -7%, 11%) Conclusion: Both RCTs reported no difference between groups in the overall incidence of “serious” adverse events (pooled, 8% (5/61) vs. 6% (4/62)), including: <ul style="list-style-type: none"> Worsening colitis (w/ colectomy): 0% (0/38) vs. 3% (1/37) (1 RCT) New diagnosis of CD: 5% (2/38) vs. 3% (1/37) (1 RCT) <i>C. difficile</i> infection: 3% (1/38) vs. 0% (0/37) (1 RCT) Severe illness from CMV infection: 0% (0/23) vs. 4% (1/25) (1 RCT) Severe small bowel CD, late abdominal pain, and operation for cervical carcinoma: not stratified by treatment group in one RCT 	⊕⊕○○ LOW

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Ulcerative Colitis: FMT vs. Placebo – Safety

Outcome	F/U	Studies Risk of Bias	N	Reasons for Downgrading	Conclusion	Quality
Non-serious adverse events	Peri-op	1 RCT (Rossen) Moderately High RoB	N=23	Risk of bias (-1) Imprecision (-1)	78% (18/23) vs. 64% (16/25) RD 14% (-11%, 40%) Conclusion: There was no difference between groups in the overall incidence of FMT-related non-serious adverse events. <ul style="list-style-type: none"> Increased stool frequency/diarrhea was more common with FMT: 30% vs. 4%, RD 26% (95% CI 6%, 47%) Abdominal cramps were less common with FMT: 0% vs. 24%, RD -24% (95% CI -41%, -7%) All other peri-procedural events occurred with similar frequency between groups.†	⊕⊕○○ LOW

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Summary: Safety

In general, **no difference** between groups for safety outcomes for the treatment of both **recurrent CDI** [FMT vs. vancomycin (2 RCTs, N=82) and vs. placebo (1 RCT, N=43); and fresh vs. frozen FMT (1 RCT and 1 cohort, N=261)] and **ulcerative colitis** [FMT vs. placebo (2 RCTs, N=123)]:

Recurrent CDI (all Low SoE)

- No serious adverse events occurred; similar frequency of non-serious adverse events between groups over various time points

Ulcerative Colitis (all Low SoE)

- No difference between groups in overall incidence of serious and non serious adverse events between groups over various time points



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KQ4: Differential Efficacy and Safety

Recurrent *Clostridium difficile* infection (CDI)

- Frozen vs. Fresh Feces for FMT (1 RCT, N=219, Moderately Low RoB)
 - Age, hospitalization status at time of FMT, strain of CDI, and CDI severity did not modify cure rates (**INSUFFICIENT** strength of evidence).
- All other comparisons for CDI: *no evidence*

Inflammatory Bowel Disease (IBD)

- No evidence



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KQ5: Cost effectiveness

***Clostridium Difficile* Infection (CDI): FMT vs. Antibiotics**

- 5 cost utility studies (overall, relatively well conducted)
 - Hypothetical adults populations with recurrent CDI (4 studies) and initial CDI occurrence (1 study)
 - Primarily payer perspective; costs from various sources including CMS
 - Time horizon varied: 90 days to 1 year
 - Cost components = treatment (typically to include donor testing for FMT), hospitalization for recurrent CDI, adverse events, and outpatient visits
 - Components used for QALY = cure, recurrence following initial cure, mortality, adverse events, colectomy, fulminant colitis, hospitalization, and ileostomy (from published literature)



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KQ5: Cost effectiveness (cont.)

***Clostridium Difficile* Infection (CDI): FMT vs. Antibiotics**

- Conclusions: In general, FMT was more cost-effective than antibiotic treatment for first or recurrent CDI.
- Limitations: lack of long-term follow-up, use of hypothetical populations, use of nonrandomized studies for assumptions regarding clinical outcomes, assumed high cure rates (81%–95% vs. 52%–80% in included RCTs) and relatively low recurrence rates following FMT, and no analysis of severe and/or complicated CDI.

Inflammatory Bowel Disease (IBD)

- No evidence



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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 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)

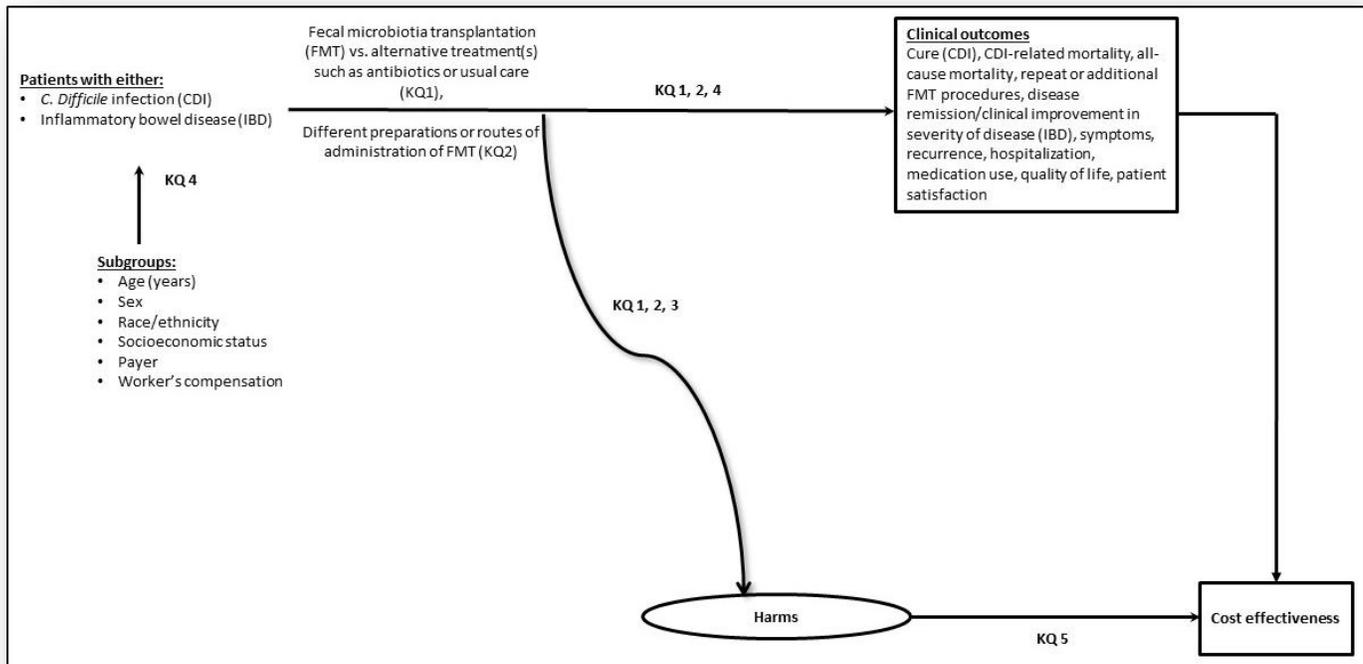
Outcomes: Cure (CDI) (primary), death from CDI (primary), repeat or additional FMT procedures (primary), all-cause mortality (primary), disease remission/clinical improvement in disease severity (IBD) (primary), symptoms, recurrence, hospitalization, medication use, quality of life, patient satisfaction, 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



References

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Public Comment & Response

None received.

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective¹ as expressed by the following standards²:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms³:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

¹ Based on Legislative mandate: See RCW 70.14.100(2).

² The principles and standards are based on USPSTF Principles at: <http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm>

³ The principles and standards are based on USPSTF Principles at: <http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm>

- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of Evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the Evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence⁴ using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- The amount of evidence (sparse to many number of evidence or events or individuals studied);
- Consistency of evidence (results vary or largely similar);
- Recency (timeliness of information);
- Directness of evidence (link between technology and outcome);
- Relevance of evidence (applicability to agency program and clients);
- Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. Factors for Consideration - Importance

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology’s safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

⁴ Based on GRADE recommendation: <http://www.gradeworkinggroup.org/FAQ/index.htm>

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

Clinical Committee Findings and Decisions

Efficacy Considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
 - Direct outcome or surrogate measure
 - Short term or long term effect
 - Magnitude of effect
 - Impact on pain, functional restoration, quality of life
 - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy?
 - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
 - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
 - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?

Next Step: Cover or No Cover

If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions

If covered with conditions, the Committee will continue discussion.

- 1) Does the committee have enough information to identify conditions or criteria?
 - Refer to evidence identification document and discussion.
 - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
 - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.
- 2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
 - What are the known conditions/criteria and evidence state
 - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical Committee Evidence Votes

First Voting Question

The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety Outcomes	Importance of Outcome	Safety Evidence / Confidence in Evidence
Serious adverse events (e.g. death)		
Non-serious adverse events (e.g. chills, fever, abdominal pain, cramping)		

Efficacy – Effectiveness Outcomes	Importance of Outcome	Efficacy / Effectiveness Evidence
Cure after single treatment		
Additional FMT treatments		
Mortality attributed to Clostridium Difficile infection		
All-cause mortality		
Mayo score for Ulcerative Colitis		
Endoscopic Mayo score		
SCCAI score		
Clinical remission (ulcerative colitis) SCCAI <=2		

Cost Outcomes	Importance of Outcome	Cost Evidence
Cost-utility		
Cost-effectiveness		
Direct cost		

Special Population / Considerations Outcomes	Importance of Outcome	Special Populations/ Considerations Evidence
Age		
Hospitalization status		
CDI severity		

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

For Safety: Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

For Efficacy/Effectiveness: Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

For Cost Outcomes/Cost-Effectiveness: Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all

Discussion

Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote

Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

Not Covered Covered Unconditionally Covered Under Certain Conditions

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next Step: Proposed Findings and Decision and Public Comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

- 1) Based on public comment was evidence overlooked in the process that should be considered?
- 2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next Step: Final Determination

Following review of the proposed findings and decision document and public comments:

Final Vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome Chair will lead discussion to determine next steps.

Medicare Coverage and Guidelines

[From page 61 of the Final Evidence Report]

Centers for Medicare Service (CMS): National Coverage Determination for Blood-Derived Products for Chronic Non-Healing Wounds

There are currently no National Coverage Decisions published from the Centers for Medicare and Medicaid services.

Guidelines

[From page 40 of the Final Evidence Report]

Table 2. Summary of Clinical Guidelines

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
<p>American College of Gastroenterology (ACG)¹²³</p> <p>2013</p> <p><i>Guidelines for Diagnosis, Treatment, and Prevention of Clostridium difficile Infections</i></p>	<p>5 case series, 2 case reports, 1 RCT, 1 SR, 4 study type NR</p>	<p>In patients with recurrent <i>C. difficile</i>, if there is a third recurrence after a pulsed vancomycin regimen, FMT should be considered.</p>	<p>Conditional recommendation, Moderate-quality evidence*</p>
<p>European Society of Clinical Microbiology and Infectious Diseases (ESCMID)³⁹</p> <p>2014</p> <p><i>European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection</i></p>	<p>1 RCT, 22 study type NR</p>	<p>For multiple, recurrent <i>C. difficile</i> infections unresponsive to antibiotic treatment, fecal transplantation in combination with oral antibiotic treatment is strongly recommended.</p>	<p>A-I†</p>
<p>The Ohio State University Wexner Medical Center¹⁰⁵</p> <p>2014</p> <p><i>Fecal Microbiota Transplant (FMT) for the Treatment of Clostridium difficile Infection</i></p>	<p>NR</p>	<p>FMT can be considered for patients with recurring <i>C. difficile</i> after ≥2 episodes of mild-to-moderate <i>C. difficile</i> and failure to respond to appropriate antimicrobial treatment regimens‡, OR patients with ≥2 episodes of severe <i>C. difficile</i> resulting in hospitalization and significant morbidity within 1 year, OR patients with a severe first episode of active <i>C. difficile</i> requiring hospitalization and non-responsive to maximal medical therapy.‡</p>	<p>NR</p>

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
		A second FMT may be considered in patients who failed the first FMT treatment.	
Public Health England ¹³⁶ 2013 <i>Updated guidance on the management and treatment of Clostridium difficile infection</i>	1 SR, 1 RCT	In patients with multiple recurrent <i>C. difficile</i> infections with evidence of malnutrition, wasting, etc., donor stool transplant can be considered as one of several treatment alternatives (including reviewing all antibiotics and drug therapies, a supervised trial of anti-motility agents alone, fidaxomicin (10-14 days) if not previously received, vancomycin tapering/pulse therapy (4-6 weeks), or IV immunoglobulin).	C§
National Institute for Health and Care Excellence (NICE) ⁴³ 2013 <i>Faecal Microbiota transplant for recurrent Clostridium difficile infection: interventional procedure guidance</i>	1 RCT, 1 SR, 1 comparative cohort	FMT should only be considered for patients with recurrent <i>C. difficile</i> infections that have failed to respond to antibiotics and other treatments.	NR
Fecal Microbiota Transplantation Workgroup (Bakken, Borody, Surawicz et al.) ¹¹ 2011 <i>Treating Clostridium difficile Infection with Fecal Microbiota Transplantation</i>	NR	FMT may be given to patients who have: <ul style="list-style-type: none"> • Recurrent or relapsing <i>C. difficile</i>. <ul style="list-style-type: none"> ○ ≥ 3 episodes of mild to moderate <i>C. difficile</i> and failure of a 6- to 8-week taper with vancomycin with or without an alternative antibiotic (e.g., rifaximin, nitazoxanide). ○ ≥ 2 episodes of severe <i>C. difficile</i> resulting in hospitalization and associated with significant morbidity. • Moderate <i>C. difficile</i> not responding to standard therapy (vancomycin) for at least a week. • Severe (and perhaps even fulminant <i>C. difficile</i> colitis) with no response to standard therapy after 48 hours. 	NR

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Guideline	Evidence Base	Recommendation	Rating/ Strength of Recommendation
<p>New Zealand Society of Gastroenterology⁴²</p> <p>2015</p> <p><i>New Zealand Society of Gastroenterology Guidelines for the Management of Refractory Ulcerative Colitis</i></p>	<p>1 meta-analysis of 17 case series/reports, 2 RCTs</p>	<p>There is some evidence that FMT might be a potential effective and safe treatment in ulcerative colitis, but issues such as the most advantageous microflora in the donor stool need to be carefully considered before FMT can be recommended in routine practice.</p>	<p>NR</p>
<p>Canadian Association of Gastroenterology⁸⁹</p> <p>2014</p> <p><i>Canadian Association of Gastroenterology position statement: Fecal microbiota transplant therapy</i></p>	<p>3 case reports, 5 case series, 1 review</p>	<p>Currently, there is sufficient evidence to recommend FMT in patients with CDI that have failed or had recurrent infection after two rounds of different antibiotics (usually metronidazole and vancomycin). This intervention should only be performed by health care practitioners experienced in giving FMT using donors that are healthy and are extensively screened for communicable disease.</p> <p>There is currently insufficient evidence to recommend FMT for patients with IBD and this should only be given in the context of a clinical study. Although not considered here, other potential indications for FMT are not supported by evidence and should only be explored as a part of a research protocol.</p> <p>There is an urgent need to standardize how FMT donors are screened and we recommend that all groups undertaking therapeutic FMT should set up prospective adverse events registries to follow patients in the short and long term.</p>	<p>NR</p>