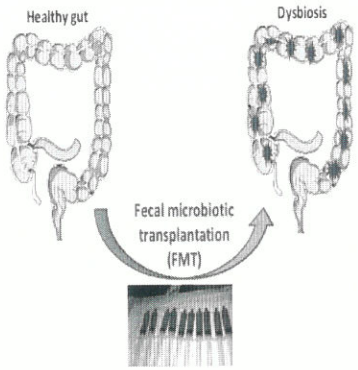
Contents

- **Fecal microbiota transplantation (FMT) - Overview**

FMT

- Fecal microbiota transplant (FMT), also known as a stool transplant, is the process of transplantation of fecal bacteria from a healthy individual into a recipient.



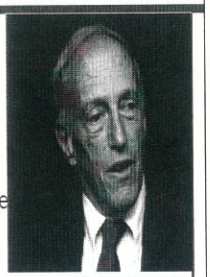
History of FMT

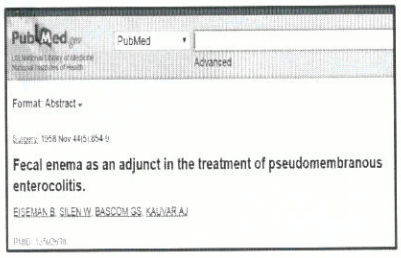
- **4th century:**
  - ✓ Chinese medical literature mentions its use for treating food poisoning and severe diarrhea
  - ✓ **Ge Hong :** firstly used what he called 'yellow soup' to treat his patients with severe diarrhea. The' soup' was administered orally.

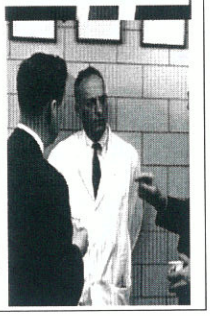
- **16th century:**
  - ✓ **Li Shizhen:** Chinese physician, herbalist, and acupuncturist, used 'yellow soup,' 'golden syrup,'and other remedies containing fresh, dried, or fermented stool to treat abdominal diseases

History of FMT

- The **first description of FMT**
  - Published in 1958 by Ben Eiseman, MD
  - Surgeon of Colorado university hospital
  - He treated four critically ill patients with fulminant pseudomembranous colitis (before C. difficile was the known cause) using fecal enemas, which resulted in a rapid return to health

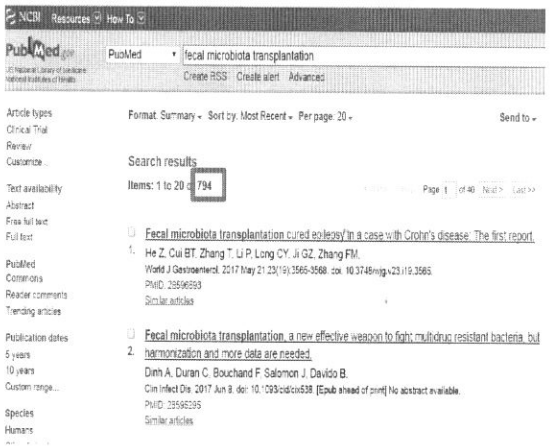

November 2, 1917 - November 19, 2012


PubMed
Format: Abstract
Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis.
EISEMAN B, SILEN W, BASCOM GS, KAUVAR AJ



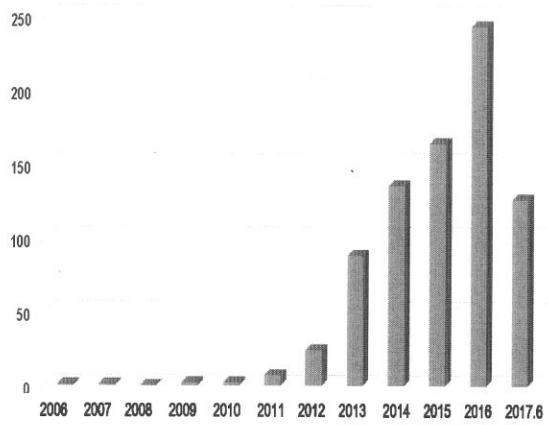
공학이 대변 분야에서 앞서 있다.11

FMT related publication

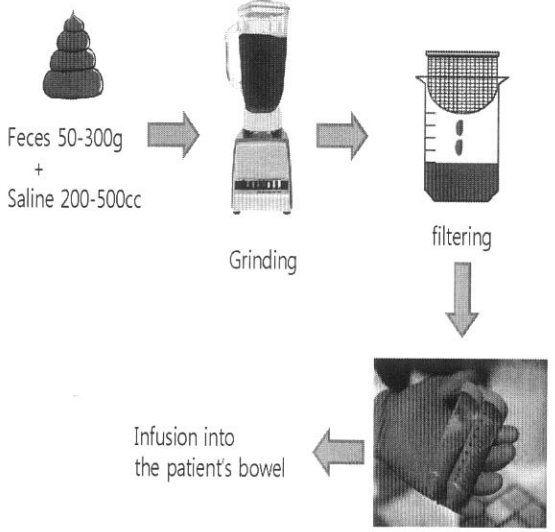


FMT related publication

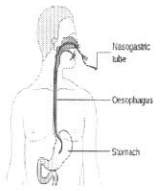
Number of publications



FMT procedure

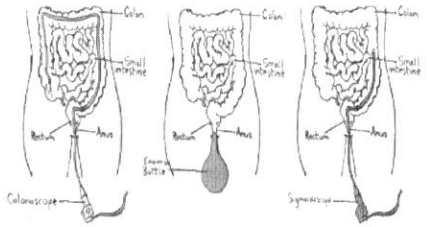


Route of administration



Nasogastric tube

EGD



Colonoscopy Enema Sigmoidoscopoy

Application of FMT

◆ Gastrointestinal (GI) disease
- ✓ Clostridium infection
- ✓ Inflammatory bowel disease
- ✓ Irritable bowel syndrome & chronic constipation

◆ Non-GI disease
- ✓ Autoimmune disease
- ✓ Neurologic disorder
- ✓ Obesity
- ✓ Chronic fatigue syndrome
- ✓ Autism

상당한 폭의 적응증이 있다.

Olga C. Aroniadis et al, Curr Opin Gastroenterol 2013, 29:79–84

FMT for Recurrent Clostridium difficile Infection (CDI)

- The greatest evidence for FMT is for treatment of recurrent CDI.
- The effectiveness of FMT for this indication has been impressive, with numerous studies demonstrating cure rates greater than 85%~90%.
- Guidelines recommend FMT for recurrent CDI
  - ✓ American College of Gastroenterology
  - ✓ European Society of Clinical Microbiology and Infectious Diseases

Stephen M et al, Gastroenterol Clin N Am 46 (2017) 171–185

605. 대변 세균총 이식

2016년 제4차 신의료기술평가
- 안전성.유효성이 있는 의료기술로 인정

가. 기술명

○ 한글명 : 대변 세균총 이식

○ 영문명 : Fecal Microbiota Transplantation

나. 사용목적

○ 클로스트리디움 디피실 감염 치료

다. 사용대상

○ 재발성 또는 기존 항생제 치료에 반응하지 않는 클로스트리디움 디피실 감염 환자

라. 시술방법

○ 공여자 선별을 통한 건강한 자의 대변 채취 후 희석 및 처리과정을 거쳐 상부 또는 하부 위장관을 통해 주입

마. 안전성.유효성 평가결과

○ 대변 세균총 이식은 주합병증 발생 사례고 적고 대부분 경미한 수준으로 안전성은 수용 가능한 수준임

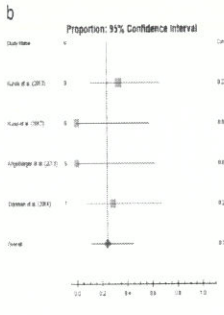
○ 대변 세균총 이식은 기존 반코마이신 치료와 비교시 설사 증상이 유의하게 개선되었고, 재발률이 수용 가능한 수준이므로 유효한 기술임

○ 따라서, 대변 세균총 이식은 재발성 또는 기존 항생제 치료에 반응하지 않는 클로스트리디움 디피실 감염 환자를 대상으로 감염을 치료하는 데 있어 안전하고 유효한 기술임

FMT for IBD

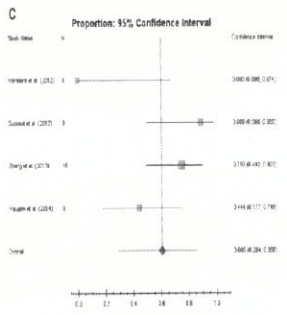
- 122 patients in 18 (9 cohort studies, 8 case studies and 1 randomized controlled trial) studies

Ulcerative colitis



Clinical remission
24.1% (95% CI 11.1%–44.9%).

Crohn's disease



Clinical remission
60.5% (95% CI 28.4%–85.6%).

Colman RJ et al, J Crohns Colitis. 2014 Dec;8(12):1569-81

3

Adverse events reported during FMT & follow-up (n = 7 in 9 cohort studies).

	FMT administration	Adverse events per patient	Time span & action
Vermeire et al. (2012)[27]	Single NJ tube	• 3/4 patients high fever and abdominal tenderness (n = 3)	• Start at day of FMT and disappeared after 2 days
Kunde et al. (2013)[23]	Daily enemas ×5 consec days	• Moderate fever & chills 3 h after FMT (n = 1) • Single episode low grade fever no Rx necessary (n = 1) • Other GI symptoms (n = 9) • Fatigue (n = 3)	• All self-limiting except 1 fever. • (n = 1) Required acetaminophen and diphenhydramine.
Kump et al. (2013)[22]	Single colonoscopy	Self-limiting fever + incr stool frequency (+CRP, and IL-6 elevation) (n = 1)	Day 1 post-FMT–day 3 (self-limiting).
Angelberger et al. (2013)[20]	NJ + enema (both on 3 consec days)	• Fever + CRP elevation (n = 5) • NJ tube irritation (n = 5) • Flatulence (n = 2) • Vomiting (n = 1)	After fever in subject 1, all patients received metronidazole pre-FMT and some received probiotics.
Suskind et al. (2014)[25]	Single NG	Mild gassiness and bloating (n = 3)	Day after FMT no intervention.
Zhang et al. (2013)[28]	Single gastroscopic	Increased diarrhea (n = 5)	Onset within 3 h (self-limiting)
Vaughn et al. (2014)[26]	Single colonoscopic	No immediate complications or adverse events in the first 4 weeks post-FMT.	

NJ = Nasojejunal tube. NG = nasogastric tube.

⇒ FMT is a safe, but variably efficacious treatment for IBD

Colman RJ et al, J Crohns Colitis. 2014 Dec;8(12):1569-81

Contents

- **FMT Data for FGID**

FMT for FGID

- Limited data are available for FGID
- Moreover, full publication data are also lacking

Summary of studies examining FMT for the treatment of FGID

Study	Year	FGID subcategory	Number of patients	Route	Follow-up period	Response
Borody	1989	IBS (also included IB D and CDI)	55	Enema	1-12 months	Cure: 20 (36%) Symptom relief: 9 (16%) No relief: 26 (47%)
Andrews	1995	Chronic constipation	45	Colonoscopy, followed by enema	9-19 months	Immediate: 40/45 (89%) At follow-up: 18/30 (60%)
Pinn	2013	IBS-D IBS-C IBS-M	9 3 1	EGD	6-18 months	Symptom relief: 9 No relief: 4

IBS, Irritable bowel syndrome; IBD, Inflammatory bowel disease; CDI, Clostridium difficile infection; EGD, Esophagogastroduodenoscopy; FMT, Fecal microbiota transplantation; FGID, Function gastrointestinal disorders.

Borody TJ et al. Med J Aust 1989; 150: 604.
Andrews P et al. Gastroenterology 1995; 108: A563.
Pinn D et al, Am J Gastroenterol 2013; 108(Suppl 1s): S1862.

Is Fecal Microbiota Transplantation the Answer for Irritable Bowel Syndrome? A Single-Center Experience

David M. Pinn, MD[1], Olga C. Aroniadis, MD[2] and Lawrence J. Brandt, MD, MACG[2]

LETTERS TO THE EDITOR

Pinn DM et al, Am J Gastroenterol 2014;109(11):1831-2.

- IBS patients who were not responsive to traditional treatment and who underwent FMT between October 2011 and October 2012

- Nonresponsive IBS:
  Failure to achieve symptomatic relief with dietary changes, antidepressants, probiotics, antibiotics, or other therapeutic modalities

- Donors : chosen by the FMT recipient and were screened in accordance with current recommendations

- A fecal suspension of 50–100 ml was infused into the distal duodenum or proximal jejunum by esophagogastroduodenoscopy in all patients

- 13 patients (mean age of 45 years; 54% female)
- IBS-D : 9, IBS-C : 3, IBS-M : 1
- Mean time from IBS diagnosis until FMT : 73 months

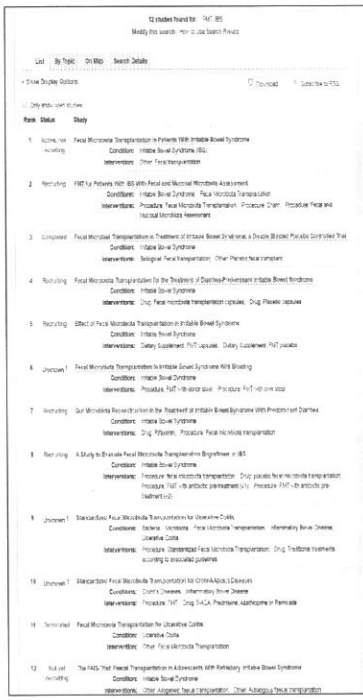
- **Results**

  ✓ Resolution or improvement of symptoms : 70%
  ✓ Specifically those with Abdominal pain (72%)
  Dyspepsia (67%)
  Bloating (50%)
  Flatus (45%).

  ✓ Improvement of overall well-being: 46%

  ✓ One adverse event : transient increase in flatus
  ✓ There were no long-term side effects
  ✓ None of the participants developed any new diseases

Pinn DM et al, Am J Gastroenterol 2014;109(11):1831-2.



12 studies found for: "FMT IBS"

List | By Topic | On Map | Search Details

♦ clinicaltrial.gov

Multiple studies underway, including randomized controlled trials, evaluating the efficacy of FMT for treatment of IBS

Contents

- **Considerations in administering FMT for IBS**

5

Donor selection and screening

- Criteria for donor exclusion and donor and recipient screening have been previously outlined in the literature
- These guidelines, however, are based on expert opinion and are not evidence-based.

Table 2 Donor exclusion criteria based on history

Antibiotic use within preceding 3 months
Immunosuppressive agents (including chemotherapy) within preceding 3 months
Known or recent exposure to HIV, hepatitis B or C
A current communicable disease
Participation in high-risk social or sexual behaviors
Use of illicit drugs
History of recent incarceration
Travel within 6 months to areas with endemic diarrheal illnesses
History of inflammatory bowel disease, IBS, diarrhea, constipation, GI malignancy or polyposis
Atopy, obesity, metabolic syndrome, diabetes mellitus

Table 3 Donor Screening Tests

Serology testing
HIV types 1 and 2 antibody
Hepatitis A IgM, IgG
Hepatitis B surface antigen
Hepatitis B core IgM, IgG
Hepatitis B antibody
Hepatitis C antibody
Syphilis
Stool testing:
Stool culture
Clostridium difficile toxin
Stool ova and parasites
Giardia stool antigen
Cryptosporidium antigen
Helicobacter pylori stool antigen
Isospora (acid fast stain)
Rotavirus

Donor selection and screening

- In a small, retrospective study of 13 patients who underwent FMT for the treatment of refractory IBS, 38% of donors were spouses, 31% were first-degree relatives, and 31% were unrelated; improvement of IBS symptoms was not influenced by the relationship between FMT recipient and donor

Pinn DM et al, Am J Gastroenterol 2013;108(Suppl 1s):S1862

- Conversely, a systematic analysis of FMT for the treatment of recurrent CDI reported slightly higher CDI resolution rates in FMT recipients who were closely related to their donors, either intimately (e.g., spouses and partners), or genetically (e.g., firstdegree or other close relatives) compared with recipients who had no relationship with their donors

Gough E et al, Clin Infect Dis 2011; 53: 994–1002

Route of administration

- Systematic review of 12 studies (182 patients with recurrent CDI treated by FMT)
- Colonoscopic route resulted in higher cure rates compared with NG or nasoenteric infusion (93.2% vs 85.3% respectively) with trend (p = 0.162).

Postigo R et al, Infection 2012; 40: 643–8.

- While CDI is usually an isolated colonic infection, IBS, and many other FGIDs are theorized to involve both the upper and lower GI tracts.
- No studies exist that directly compare FMT delivery routes in IBS

◆ Considerations in choosing the route of administration of FMT for FGID

Capsule (manufactured)
Pros: Non-invasive route of administration; obviates risk and cost of endoscopy and donor screening
Cons: Efficacy in CDI and FGID is unknown; unknown safety profile
Nasogastric Tube
Pros: minimally invasive; can be performed at home or by a non-gastroenterologist; low cost
Cons: uncomfortable; potential side effects, e.g., vomiting and aspiration
EGD
Pros: ability to evaluate the small bowel and exclude other pathology at the time of FMT; may be more efficacious in FGID which involves the small bowel
Cons: invasive; requires sedation; expensive
Colonoscopy
Pros: ability to evaluate the colonic mucosa at the time of FMT; more appealing to patients than FMT via upper tract route
Cons: invasive; requires sedation; expensive; may have decreased efficacy in FGID which not only affects the colon but also the small bowel
Flexible Sigmoidoscopy
Pros: ability to evaluate the colonic mucosa at the time of FMT; no sedation; can be performed by a non-gastroenterologist
Cons: invasive; examination limited to maximum 60 cm of distal colon
Enema
Pros: minimally invasive; can be self-administered; low cost
Cons: may have decreased efficacy in FGID which not only affects the colon but also the small bowel

PINN et al, Neurogastroenterol Motil (2015) 27, 19–29

Patient acceptance of FMT

- Patient acceptance does not appear to be a factor precluding FMT
- A questionnaire study of 77 patients who had been treated with FMT for recurrent CDI
  - ✓ 97% of participants were willing to undergo FMT again if needed, and, if C. difficile infection were to recur after FMT
  - ✓ 53% expressed a desire to have FMT as first-line of treatment.

Zipursky JS et al, Clin Infect Dis. 2012; 55:1652–8.

Safety of FMT

- Because stool is a biologically active substance replete with thousands of strains of bacteria, and in view of the growing appreciation that certain bacteria may be associated with specific diseases, there is concern that FMT could lead to the development of new diseases.
- FMT is an overall safe therapy with minimal adverse effects.
  → Any adverse events are mild and transient, such as abdominal discomfort, nausea, vomiting, bloating, or flatulence
- It is often difficult to know if these symptoms are related to the underlying disease that triggered the need for FMT (such as postinfectious IBS).

Stephen M et al, Gastroenterol Clin N Am 46 (2017) 171–185

Safety of FMT

- There has been ongoing concern that immunocompromised patients may be at greater risk for infection and sepsis following FMT
- A multicenter, retrospective study examining post-FMT adverse events in 80 immunocompromised patients
  - ✓ High CDI cure rates (78%)
  - ✓ Two patients died (one from unrelated pneumonia and the other following an aspiration event during sedation for colonoscopy)
  - ✓ There were no infections linked to FMT
  - ✓ Among mild adverse events, 3 patients reported abdominal discomfort post-FMT

Kelly CR et al, Am J Gastroenterol 2014;109(7):1065–71.

♦ Potential adverse events of FMT

Minor (and common):
- Nausea/vomiting (particularly with oral FMT route)
- Abdominal discomfort or pain
- Bloating
- Flatulence
- Diarrhea/constipation
- Low-grade fever

Severe:
- Sedation related (eg, aspiration)
- Endoscopy related (eg, bleeding, perforation)
- Infection ± sepsis (infection may be a long-term sequelae)
- Inflammatory bowel disease flare
- Postinfectious irritable bowel syndrome

Potential:
- Risk of chronic disease development related to changes in gut microbiome
- Other unknown?

Stephen M et al, Gastroenterol Clin N Am 46 (2017) 171–185

7

Summary & Conclusion

- Intestinal dysbiosis is involved in the pathogenesis of FGID, and affects peripheral and central pathways involved in motility, immunity and brain-gut communication
- Restoration of intestinal homeostasis via FMT holds promise for FGID treatment
- FMT appears to be a safe, accepted, and well-tolerated therapy, although continued monitoring for long-term adverse events is imperative
- Large randomized, double-blinded placebo controlled studies are needed to verify the efficacy of FMT for the management of FGID (IBS)
- Furthermore, clarification regarding the optimal administration methods and dosing is needed

18