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What the Surgeon Should Know about Medical Therapy and Fecal Microbiota Transplantation for *C. difficile* infection

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Conflict of Interest

OpenBiome: Research Support

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Outline

Overview of *C. difficile* infection (CDI)

- Pathogenesis
- Epidemiology
- Risk Factors
- Clinical Manifestations

Medical therapy for CDI

- Antibiotic Therapy
- Fecal Microbiota Transplantation (FMT)
  - History
  - Methodology
  - Efficacy
  - Safety

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Clostridium difficile Infection

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Clostridium difficile

Pathogenesis

- Colonic, enteric infection
- Gram-positive, anaerobic, spore-forming organism
- Fecal-oral route of transmission
- Ubiquitous, environmental
- Dysbiosis → disease
- Spores germinate and produce toxins A and B
  - Disorganization of actin cytoskeleton > apoptosis
  - Impairment of tight junctions > increased intestinal permeability

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Johanesen, et al. Genes, 2015

Clostridium difficile

Epidemiology

- Most frequently reported healthcare-associated pathogen (>500,000 cases in 2011)
- Community-acquired CDI is on the rise
- Reported 30-day crude case-fatality rate is 9.3%
- 32% increase in rate of colectomies from 2006-2010
- Annual economic burden from $436 mil to $3 bil

Lessa FC, et al. NEJM 2015
Halabi WJ, et al. J Am Coll Surg 2013
Nguyen, et al. Am J Gastroenterol 2008
Kelly CP. JAMA 2009
Anathakrishnan, et al. Gut 2008

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Clostridium difficile

Host Risk Factors

- Older age (>65 years)
- Comorbid disease (e.g. renal, IBD, cirrhosis)
- Immunosuppression
- Altered microbiome
  - Antibiotics (increased risk with longer duration)
  - Acid-suppression (PPI)
  - Non-surgical GI procedures (e.g. NGT passage)

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Clostridium difficile

Environmental Risk Factors

- Hospitalization (increased risk with longer duration)
- ICU admission
- Nursing home residence

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Johanesen, et al. Genes, 2015

Clostridium difficile

Risk Among Surgical Patients

Surgical Procedure	CDI Incidence
Gastrointestinal Surgeries *Highest risk: CRC surgery, emergency surgery, bowel resection* *Hypothesis: Increased risk due to a change in bowel flora*	**0.3-6.8%**
Solid Organ Transplantation	**0.7-7.4%**
Liver	3.0-19%
Kidney	3.5-16%
Pancreas/Kidney	1.5-7.8%
Intestinal	9%
Heart	8-15%
Lung	7-31%
Orthopaedic Surgery *Highest risk: hip fractures; lowest risk: spine surgery*	**0.1-7.1%**
Cardiac Surgery	**0.8-1.1%**
Aortic Surgery	**Up to 8.4%**
36.4 fold increase in mortality in patients acquiring postoperative CDI vs no CDI	

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Masgala, et al. J Infect Dis Ther, 2014

Clostridium difficile

Manifestations

- Carrier state (asymptomatic)
- *C. difficile*-associated diarrhea (CDAD)
- *C. difficile* colitis
- Pseudomembranous colitis
- Fulminant colitis and toxic megacolon

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Napolitano LM, Edmiston CE, Surgery 2017

Antibiotic-Associated Diarrhea

- Occurs with any antibiotics
- Non-infectious
  - No fever or leukocytosis
- Likely related to a change in normal bowel flora
  - Unabsorbed CHOs reach colon intact
    - Bacterial fermentation → SCFAs → secretion of Na^+ and H_2O
    - Osmotic diarrhea
- D/C antibiotics → diarrhea resolves

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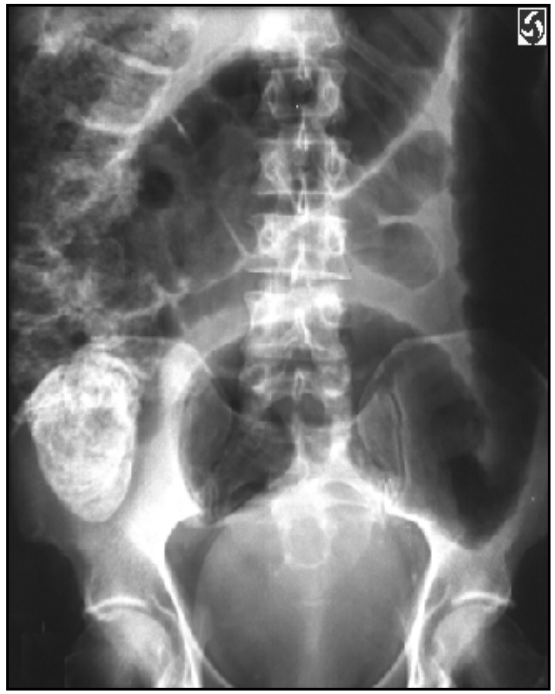
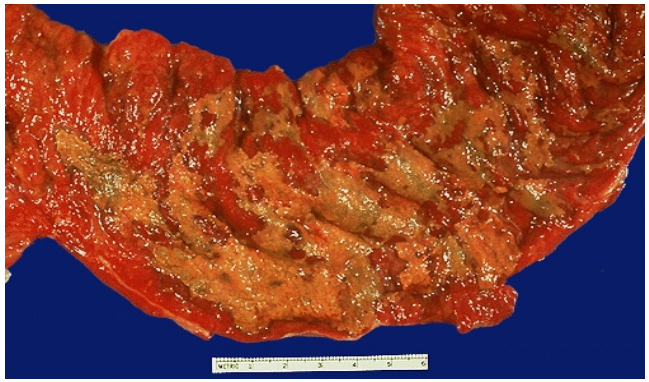
Clostridium difficile

Fulminant colitis

- Rare (2-3%) but increasing
- Clinical manifestations
  - Fever, hypotension
  - Abdominal distention
  - Oliguria
  - Azotemia, acidosis, low albumin
  - Ileus
  - Rapid deterioration
  - Megacolon
  - Perforation
  - Death





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Clostridium difficile

Recurrence

- First: 10-25%
- Second: 30-45%
- Third: 45-60%
- Treatment with antibiotics is often unsuccessful
- Prompted the need for alternative therapies

Aroniadis OC, Brandt LJ. Gastroenterol Hepatol 2014
Lessa FC, et al. NEJM 2015

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Medical Treatment of CDI

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Medical Therapy

Approach

- Confirm diagnosis
- Fluid and electrolyte resuscitation
- Infection control measures
- Discontinue inciting antimicrobials - if possible
- Initiate antibiotic therapy

Aroniadis OC, Brandt LJ. Gastroenterol Hepatol 2014
Lessa FC, et al. NEJM 2015

Classification of Disease

Definitions

- **Mild-moderate CDI:** Diarrhea, plus any additional sign or symptom not meeting criteria for severe or complicated disease

- **Severe CDI:** serum albumin <3g/dl, WBC≥15,000 cells/mm or significant abdominal tenderness

  (IDSA/SHEA - WBC≥15,000 and Cr >1.5x the premorbid level)

- **Severe-complicated CDI:** ICU admission for CDI, hypotension, T ≥38.5^{0}C; ileus; abdominal distention, altered mental status; multi-organ failure; WBC≥35,000 cells/mm or <2,000 cells/mm; serum lactate >2.2 mmol/l

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CDI Treatment Guidelines

Disease State	ACG American College of Gastroenterology	IDSA/SHEA Infectious Diseases Society of America/Society Healthcare Epidemiology of America	ESCMID European Society of Clinical Microbiology and Infectious Diseases	WSES World Society of Emergency Surgery	ASID Australasian Society for Infectious Diseases
Mild-moderate*	Metronidazole 500mg PO q8h x 10-14 days *ACG - if unable to tolerate or no response in 5-7d, then PO vanco 125mg q6h* *ESCMID - stop inciting abx and observe 48h in non-epidemic situations + clearly demonstrated that abx induced CDI*				
Severe	Vanco 125mg PO q6h x 10-14 days				
Severe-Complicated	Vanco 500mg PO q6h + Vanco 500mg PR q6h + Metronidazole IV 500mg q8h + surgical consult	Vanco 500mg PO q6h + Metronidazole IV 500mg q8h (if ileus, consider PR vanco) + surgical consult	If fail to respond to antibiotics or progress, then surgical intervention	Vanco 500mg PO or PR q6h + Metronidazole IV 500mg q8h + surgical consult	N/A

*Paradigm shift – less use of metronidazole for initial event, PO vanco for initial event will likely be recommended in future guidelines

Fidaxomicin

Recommendations

- **Initial CDI:** No recommendations for use
- **Recurrent CDI or high risk of recurrence:** Recommended
- **Severe CDI:** No available data

- *Dosing: 200mg q12h for 10 days ($3360!)*

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Management of Recurrent CDI

First Recurrence

- Same regimen used for initial episode if non-severe CDI
- If severe or severe-complicated CDI, then PO vanco

Second Recurrence

- Pulsed PO vanco regimen
  - Vanco 125mg q6h x 14 days
  - Vanco 125mg q12h x 7 days
  - Vanco 125mg daily x 7 days
  - Vanco 125mg every other day x 14 days

≥ Three Recurrences

- Pulsed PO vanco regimen
- Consider fecal microbiota transplantation

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History of Fecal Microbiota Transplantation

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History

Fecal Microbiota Transplantation

- Infusion of fecal material (and its microbial community) from a healthy donor into an individual with a specific disease for the purpose of providing relief of symptoms or cure of that disease
- 4th century China

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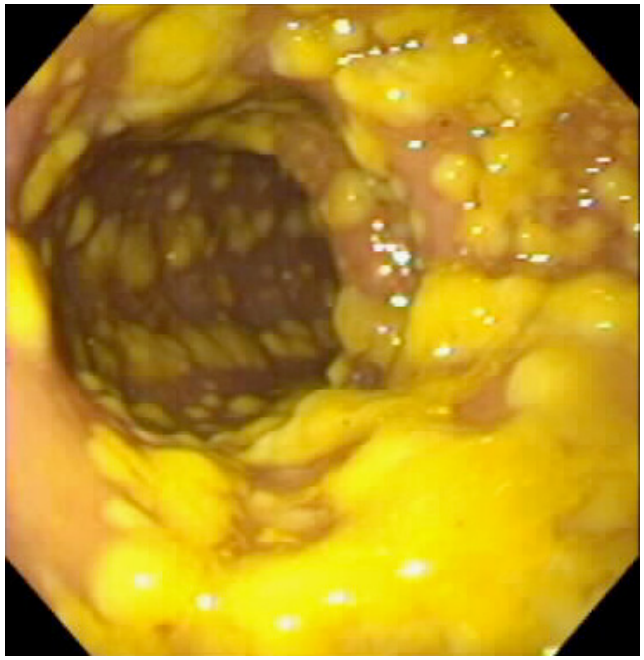
Zhang, et al. Am J Gastroenterol, 2012

History

Fecal Microbiota Transplantation

- 17th century veterinary medicine – “transfaunation”
- 1958: Eiseman for pseudomembranous colitis from *Micrococcus pyogenes*



Borody, et al. J Clin Gastroenterol, 2004
Eiseman. Surgery, 1958

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Performing a Fecal Microbiota Transplantation

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FMT: The Basics

- Donor identified
- Donor and recipient screened for pathogens
- Stool prepared
- Fecal material infused from donor into the patient
- Patient monitored for symptomatic improvement and adverse events

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FMT Routes

Upper or lower routes

- 4th Century China, per os[1]
- 1989, retention enema[2]
- 1991, nasogastric tube/EGD[3]
- 2000, colonoscopy/flex sig[4]
- 2015…

[1]Zhang, et al. Am J Gastroenterol, 2012
[2]Bakken, et al. Clin Gastroenterol Hepatol, 2011
[3]Flotterod, et al. Tidsskr Nor Laegeforen, 1991
[4]Persky and Brandt. Am J Gastroenterol, 2000

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FMT Capsules

The New York Times

Fecal Transplants Made (Somewhat) More Palatable

By Andre Smith, November 9, 2015

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Past

Present

Patient-identified donor → Standard donor stool biobank

Fresh Stool → Frozen Stool

Whole Stool → Specific Bacteria

Convenient
Reduced cost
Greater precision
Standard/rigorous screening protocols
Safer

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FMT Methodology

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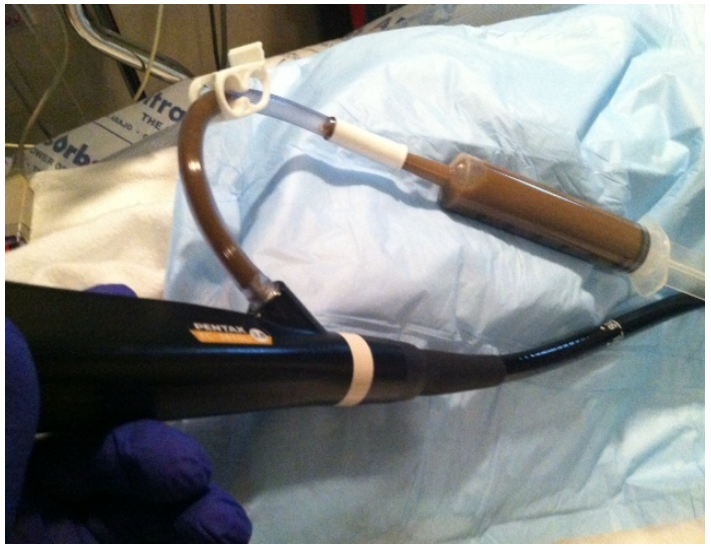
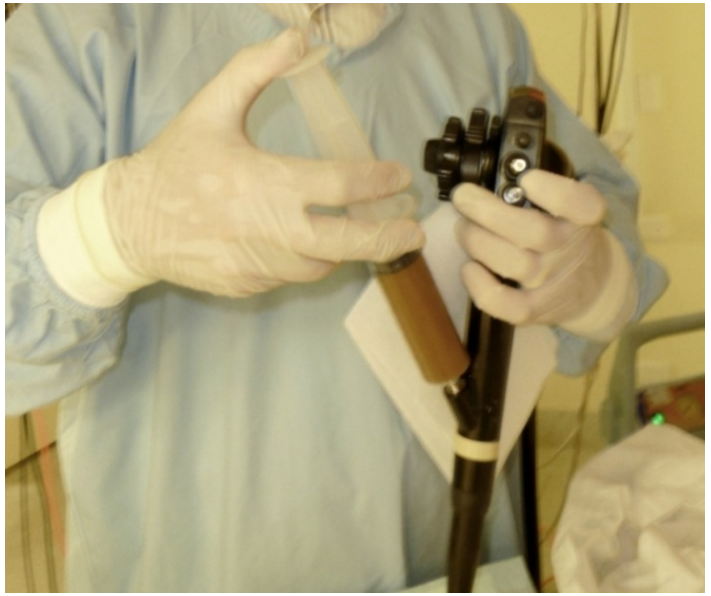
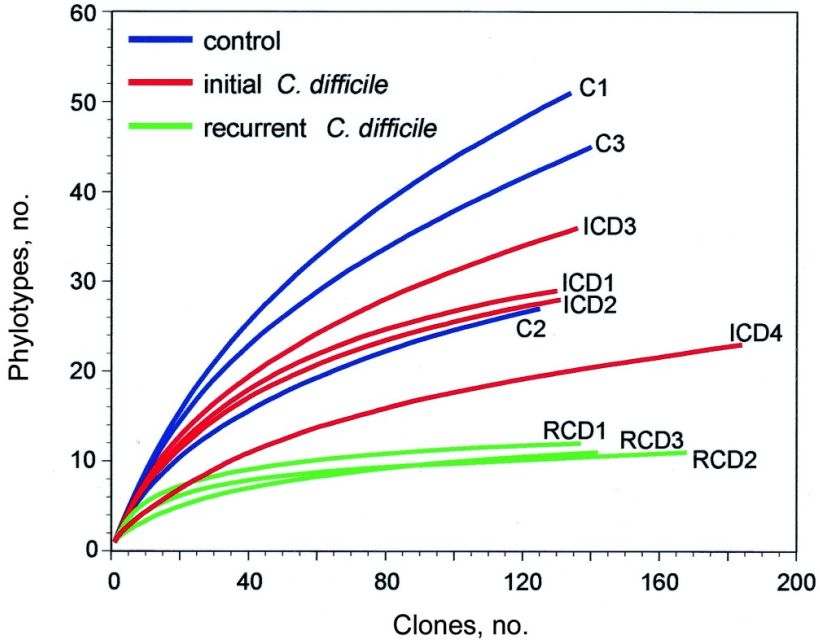
FMT Methodology



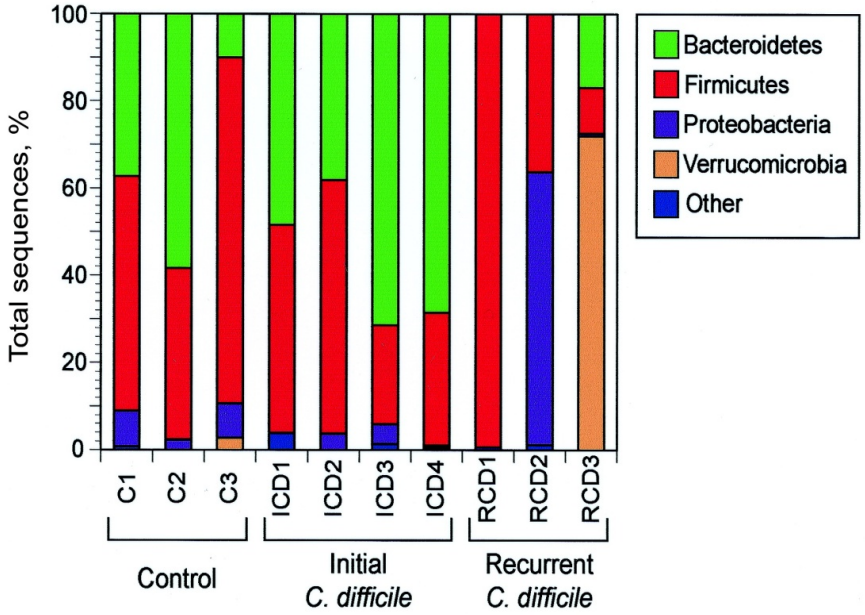


Clostridium difficile

Decreased microbial diversity



Patients with recurrent *C. difficile* have decreased phylogenetic richness



Bacteroidetes and *Firmicutes* are reduced in patients with recurrent *C. difficile* not in patients with just one episode of *C. difficile* infection

Chang, et al. J Infect Dis, 2008

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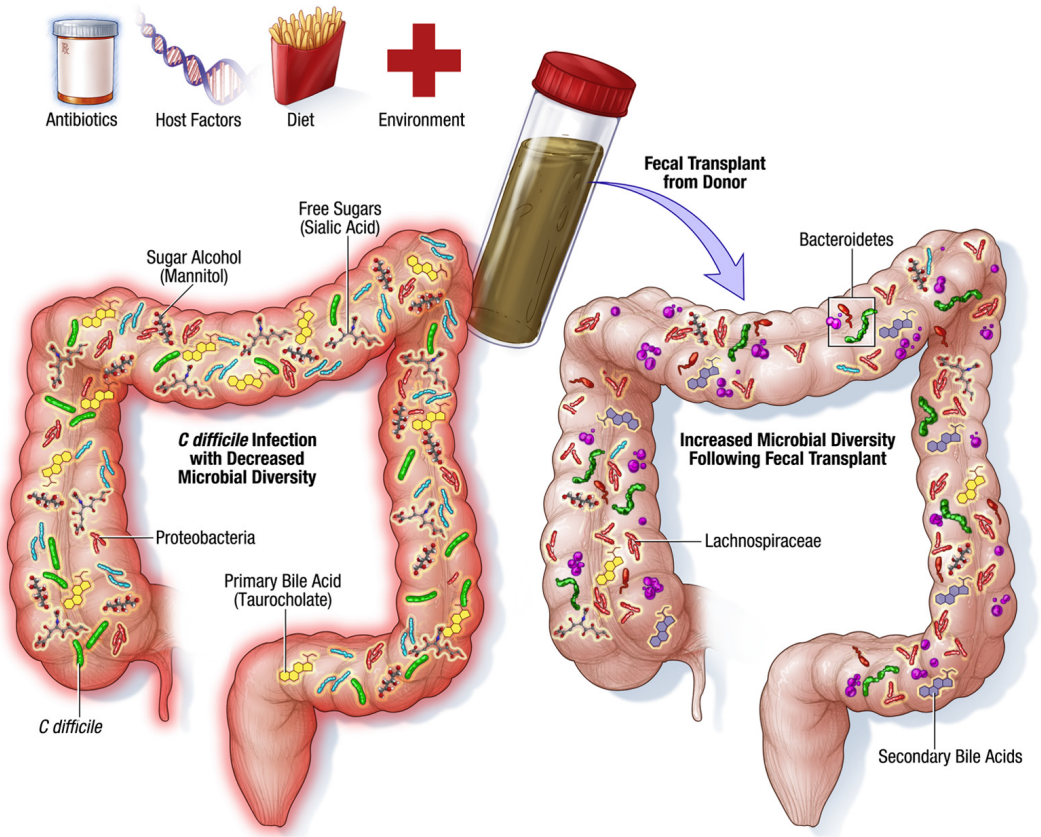
FMT Mechanism of Action



Change in microbial community structure:

- Restoration of microbial diversity
- Increase in phyla
  - Bacteroidetes
  - Firmicutes
- Increase in 2^0 bile acids

Kelly, et al. Gastroenterology, 2015

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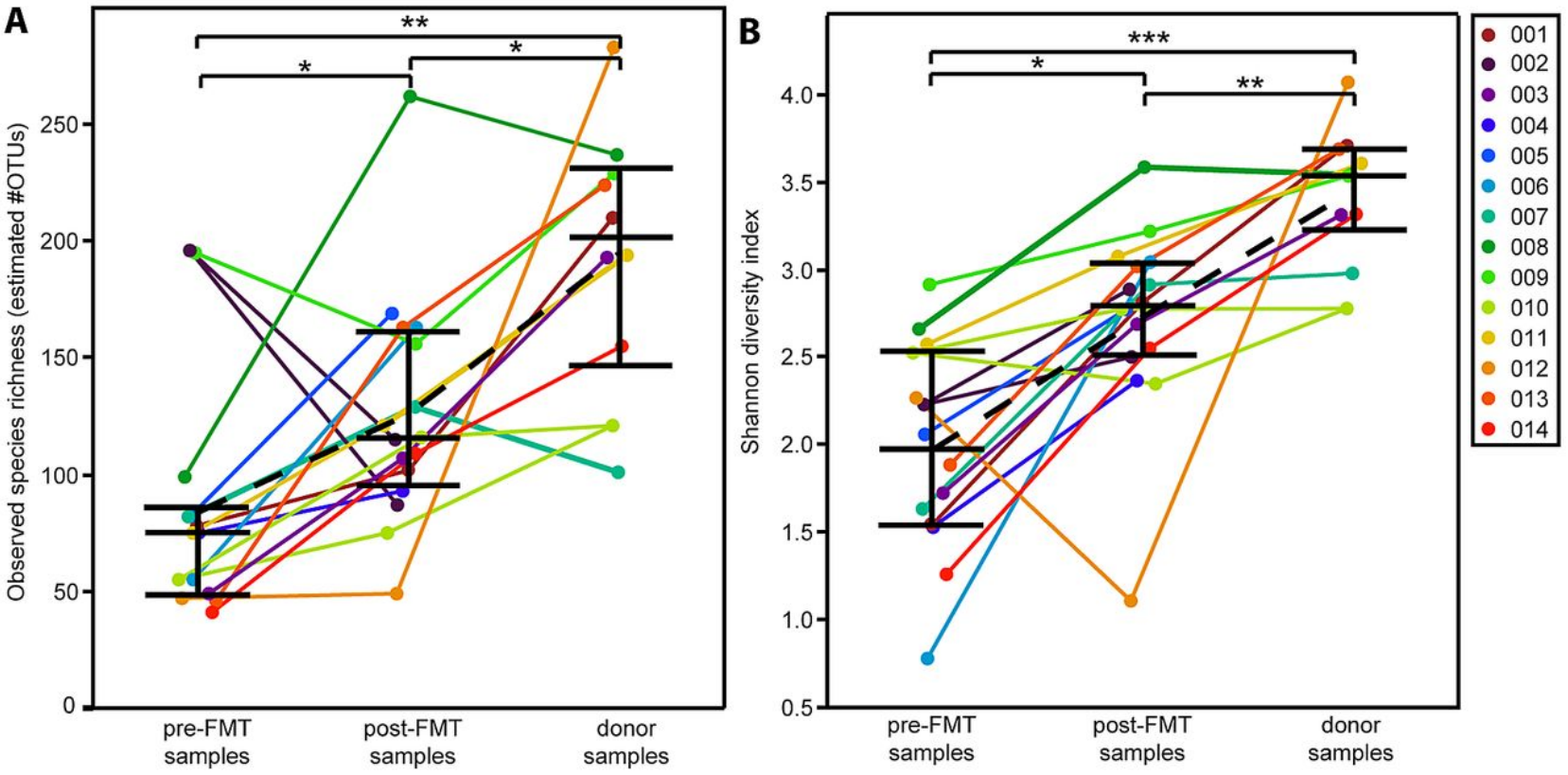
FMT Mechanism of Action



Seekatz, et al. mBio, 2014

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Recurrent *C. difficile* infection

FMT Efficacy Data Summary

- Multiple case-reports and case-series
- Meta-analyses & systematic reviews
- 6 clinical trials

Bottom-line: overall cure ≥90%

[1]Guo, et al. Aliment Pharmacol Ther, 2012
[2]Kassam, et al. Am J Gastroenterol, 2013
[3]Cammarota, et al. J Clin Gastroenterol, 2014
[4]Cammarota, et al. Aliment Pharmacol Ther, 2015
[5]Youngster, et al. JAMA, 2014
[6]van Nood, et al. NEJM, 2013
[7]Kelly, et al. Ann Int Med, 2016

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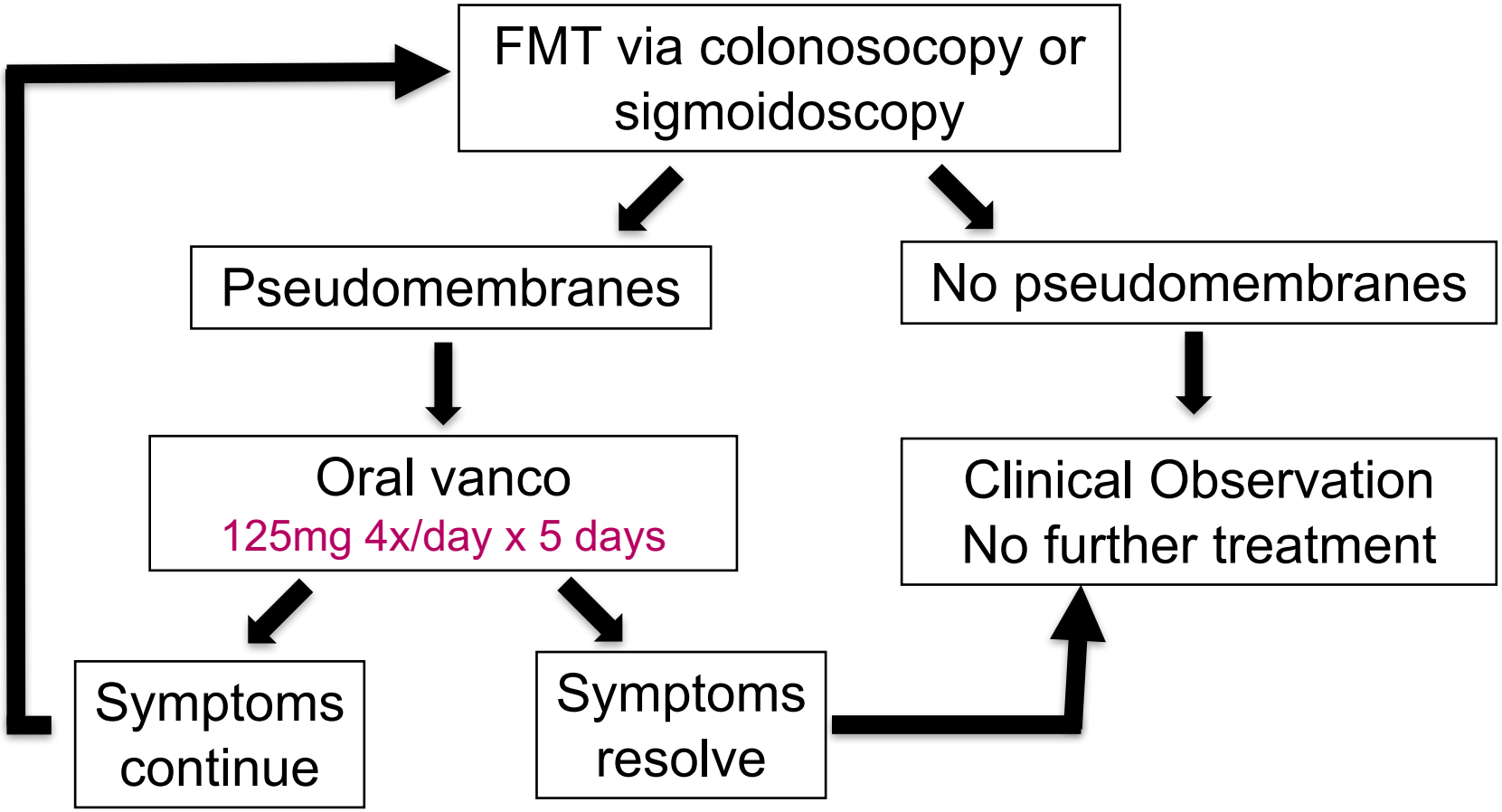
Severe-Complicated CDI



Fischer, et al. APT, 2015
Fischer, et al. Gut Microbes, 2017

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FMT Severe-complicated CDI

	Fischer, APT 2015	Fischer, Gut Microbes 2017
Study Design	Prospective cohort	
Number of Patients	29	57
Patient Characteristics	***Severe and/or severe-complicated CDI*** Refractory to PO +/- PR vanco, plus IV metronidazole	
FMT Treatment	***Sequential FMTs*** via colonoscopy +/- repeat FMT and continued oral vanco guided by clinical response and pseudomembranes	
Primary Outcome	Clinical cure at 30 days	
Overall Response	***93% (27/29)***	***91% (52/57)****
Response in Severe	100% (10/10)	100% (19/19)
Response in Severe-Comp	89% (17/19)	87% (33/38)
% of participants undergoing FMTs	1 FMT - 62% 2 FMTs - 31% ≥ 3 FMTs - 7%	1 FMT - 53% 2 FMTs - 31% ≥ 3 FMTs - 11%
Adverse Events	1 underwent colectomy 1 died CDI-related sepsis	No serious adverse events

** No difference between fresh and frozen stool; 94.7% survival at 1 month, 78.6% survival at 3 months*

FMT Guidelines, 2017

Disease State	ACG American College of Gastroenterology	IDSA/SHEA Infectious Diseases Society of America/Society Healthcare Epidemiology of America	ESCMID European Society of Clinical Microbiology and Infectious Diseases	WSES World Society of Emergency Surgery	ASID Australasian Society for Infectious Diseases
Initial Episode	No recommendations for FMT				
1st Recurrence	No recommendations for FMT				
Multiple Recurrences	If ≥3 recurrences		After 4d of vanco		After 3-5d of vanco or fidaxo
Severe	No recommendations for FMT				
Severe-Complicated	Consider FMT if no response in 48 hrs				After 3-5d of vanco or fidaxo

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FMT in Practice

- ≥3 episodes of mild/moderate CDI and failure to respond to antibiotic therapy
- ≥2 episodes of CDI resulting in hospitalization and significant morbidity
- Moderate CDI with no response to standard therapy for at least 1 week
- Severe (even fulminant) CDI with no response to standard therapy for 48 hours

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FDA Regulations and FMT Safety

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FDA Regulations

July 2013 – FDA announces stool is a drug/biologic

- Investigational New Drug (IND) application required
- FMT unavailable to the community physician

September 2013 – FDA liberalizes the restriction on FMT for *C. difficile* infection while maintaining discretionary regulation

- FMT available for CDI without an IND
- IND required for all other indications

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FMT Safety

Systematic-Review: AEs of FMT

- 7562 original articles reviewed, 50 included, 1089 patients
- **AE Incidence Rate (related or unrelated)**
  - All FMTs: 28.5%
  - EGD: 43.6%
  - Colonoscopic: 17.7%
- **Common AEs related to FMT**
  - Abdominal discomfort, flatulence, bloating, cramping
- **Serious AEs (related or unrelated)**
  - 9.2% of patients
  - Death (3.5%; 1 death related to FMT procedure)
  - Infection (2.5%)
  - Relapse of IBD (0.6%)

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Wang, et al. PLOS, 2016

Summary

- CDI results in increased morbidity and mortality
- Antibiotics are the mainstay of medical therapy
- FMT is highly successful for recurrent/refractory CDI
- FMT is promising for severe-complicated CDI
- Further studies are needed to assess efficacy and safety of FMT for severe-complicated CDI
- Adverse events need to be rigorously monitored

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Thank you

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