Diagnosis and Management of C. *difficile* Infections

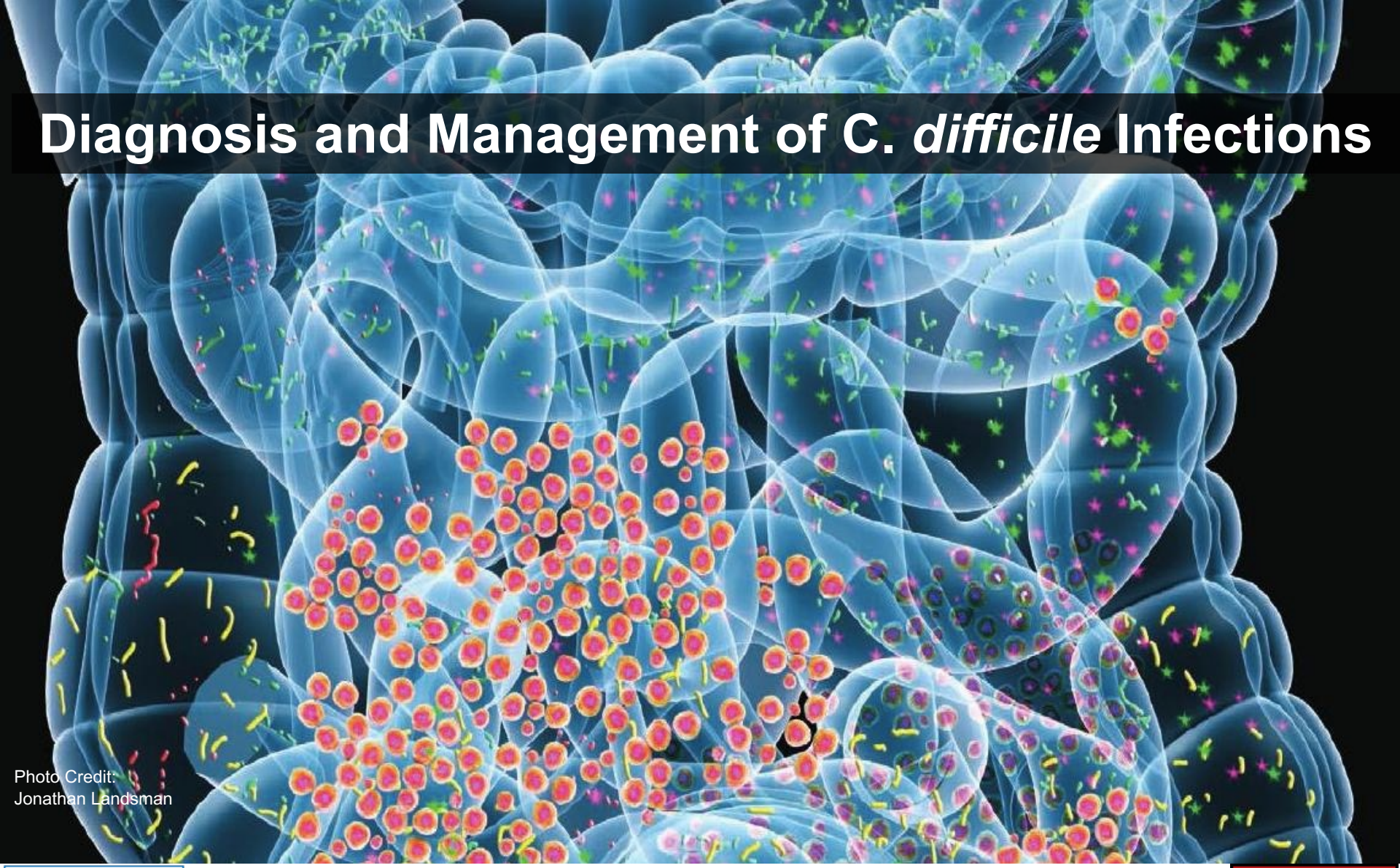


Photo Credit:
Jonathan Landsman

JESSICA R. ALLEGRETTI, MD, MPH
ASSOCIATE DIRECTOR, CROHN'S AND COLITIS CENTER
DIRECTOR, FECAL MICROBIOTA TRANSPLANT PROGRAM
DIVISION OF GASTROENTEROLGY, BRIGHAM AND WOMEN'S HOSPITAL
ASSISTANT PROFESSOR OR MEDICINE, HARVARD MEDICAL SCHOOL

Disclosures

- Consultant: Finch Therapeutics, Artugen, Servatus, Janssen, Pfizer, Takeda, Pandion, BMS, Baccain, Morphic
- Scientific Advisor Board: Iterative Scopes
- Research Support: Merck
- Unpaid Scientific Advisor to Openbiome

Clostridioides *difficile*: The Basics

- Anaerobic gram-positive, spore-forming, toxin-producing bacillus
- Spread via the fecal-oral route

- Two forms: spore and vegetative (toxin producing)

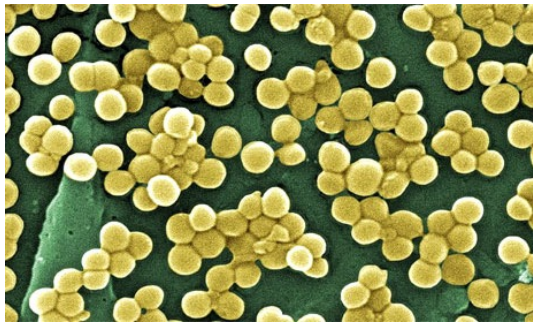
Toxins

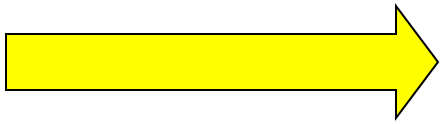
- Most disease causing strains produce two toxins: A and B
  - Once intracellular: inactivate regulatory proteins involved in cytoskeleton structure
  - Cell retraction and apoptosis

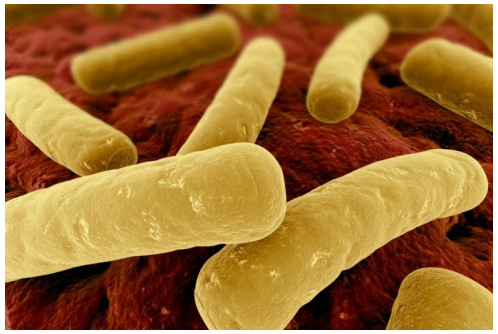
- More virulent strain (NAP1/BI/027) produces >20 fold the amount of toxin

The Scope of the Problem

- Most common cause of health-care-associated infection in the U.S.
- In 2011: estimated 476,400 cases US annually
- In 2017 down to 462,100
- Adjusting for PCR use – total decrease by 26%



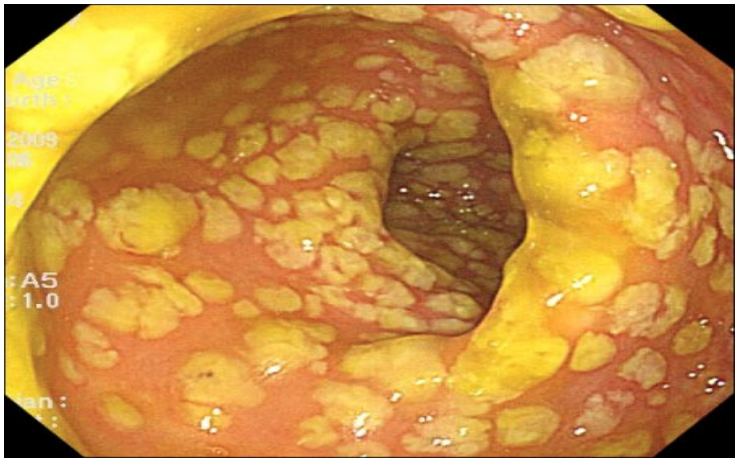


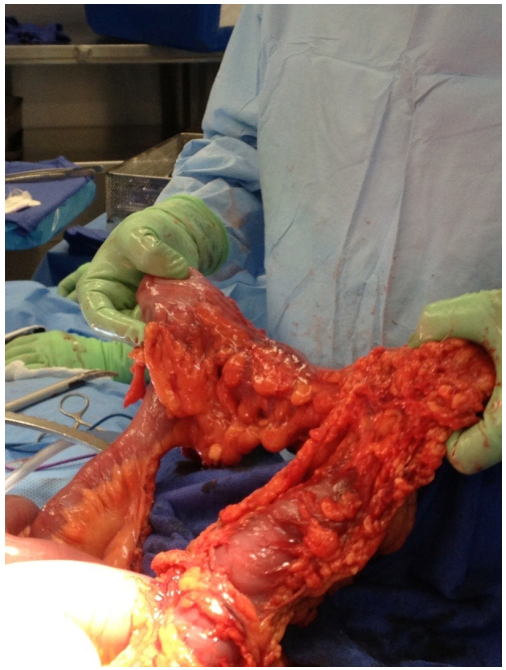


King RN. Pharmacotherapy 2011; Lessa FC. N Engl J Med 2015; Cohen SH. Inf Cont and Hosp Epidem 2010; Guh et al. NEJM 2020

Severe and Fulminant *C. difficile* infection

- Up to 8% of CDI cases
- Dramatically different phenotype
- Often refractory to maximum antibiotic therapy





Fulminant infection often requires surgery

- Total abdominal colectomy with end ileostomy procedure of choice
- 30-day perioperative mortality 19-57%
- Mean LOS: 45 days
- “Not good surgical candidates”

Fischer M. Gut Microbes 2016

- **The diagnosis of CDI is based upon:**
  - Presence of diarrhea, defined as a passage of 3 or more unformed stools in 24 or fewer consecutive hours
  - (Note: Severe CDI can lead to ileus and absence of bowel movements)
  - Positive stool testing for *C. difficile, or colonoscopic and/or histopathologic findings demonstrating pseudomembranous colitis*

CDI severity classification criteria: SHEA/IDSA/ACG/ESCMID

Severity	SHEA/IDSA (2018)	ACG (2021)	ESCMID (2014)
Severe	WBC ≥ 15,000/µl *or* Creatinine ≥ 1.5mg/dL	WBC ≥ 15,000/µl *or* Creatinine ≥ 1.5mg/dL	"one or more specific signs and symptoms of severe colitis or a complicated course of disease, with significant systemic toxin effects and shock, resulting in need for ICU admission, colectomy or death" Patient characteristics correlate with severe colitis: Fever ≥ 38.5 °C Shock Peritonitis Ileus WBC >15,000/µl Albumin < 3g/dl Creatinine ≥ 1.5 x baseline Pseudomembranous colitis Toxic megacolon (> 6 cm) Ascites
Fulminant	Hypotension or shock Ileus Megacolon	Hypotension or shock Ileus Megacolon	

Testing

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C. DIFFICILE ANTIGEN/TOXIN ASSAY - Final
  Reported: 24-Jul-14
  ANTIGEN:POSITIVE;    TOXIN:NEGATIVE
  RESULTS PENDING PCR ANALYSIS.

TOXIGENIC CLOSTRIDIUM DIFFICILE QUALITATIVE BY PCR
- Final     Reported: 24-Jul-14 11:54
  Reported: 24-Jul-14
  POSITIVE
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Antigen:

-GDH- glutamate dehydrogenase
-Enzyme produced by all c.diff isolates (toxic and nontoxic)
-First screen

Testing

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- Final Reported: 24-Jul-14 11:54
Reported: 24-Jul-14
POSITIVE

Toxin:

- ...ec... both toxin A... nd B
- ...nsitivity: ... Specific...: 99%
- ...h false neg... ra...

Testing

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C. DIFFICILE ANTIGEN/TOXIN ASSAY - Final
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PCR:

-Detects toxin A and B

-Confirmatory test

*colonization and not active infection

Testing

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PCR:

-Detects toxin A and B

-Confirmatory test

*colonization and not active infection

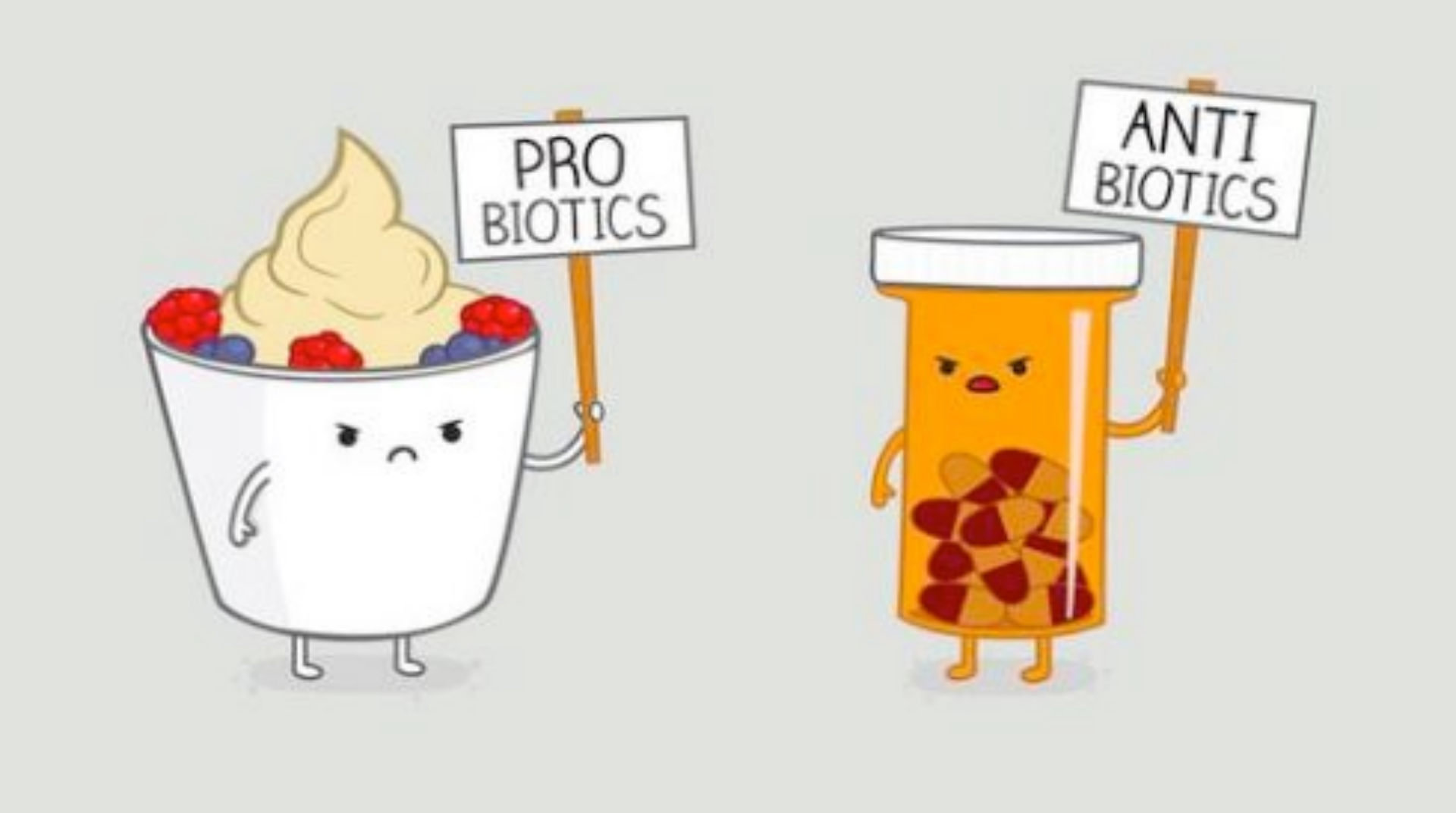
European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Guidelines

- No single commercial test can be used as a stand-alone

<u>Recommendations:</u>

- Two step approach (highly sensitive with reflex to highly specific test)
  - First: GDH or PCR testing.
  - Second: EIA for toxin A/B (high positive predictive value)

TREATMENT



IDSA 2018

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

McDonald et. Al CID 2018

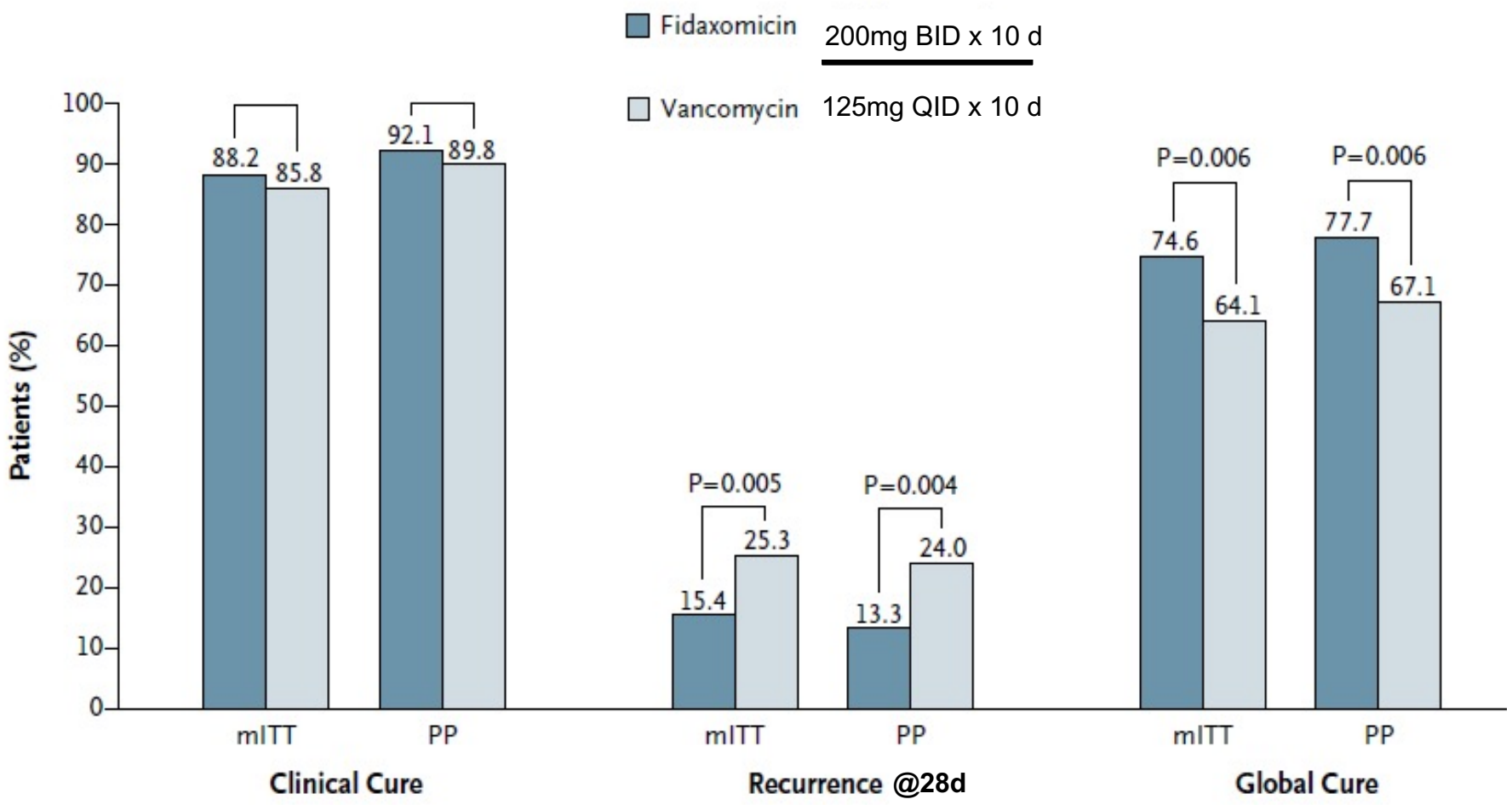
ACG 2021 C.*difficile* Guidelines

Treatment
4. We recommend that oral vancomycin 125 mg 4 times daily for 10 d be used to treat an initial episode of nonsevere CDI (strong recommendation, low quality of evidence).
5. We recommend that oral fidaxomicin 200 mg twice daily for 10 d be used for an initial episode of nonsevere CDI (strong recommendation, moderate quality of evidence).
6. Oral metronidazole 500 mg 3 times daily for 10 d may be considered for treatment of an initial nonsevere CDI in low-risk patients (strong recommendation/ moderate quality of evidence).
7. As initial therapy for severe CDI, we recommend vancomycin 125 mg 4 times a day for 10 d (strong recommendation, low quality of evidence).
8. As initial therapy for severe CDI, we recommend fidaxomicin 200 mg twice daily or 10 d (conditional recommendation, very low quality of evidence).
9. Patients with fulminant CDI should receive medical therapy that includes adequate volume resuscitation and treatment with 500 mg of oral vancomycin every 6 hr daily (strong recommendation, very low quality of evidence) for the first 48–72 hr. Combination therapy with parenteral metronidazole 500 mg every 8 hr can be considered (conditional recommendation, very low quality of evidence).
10. For patients with an ileus, the addition of vancomycin enemas (500 mg every 6 hr) may be beneficial (conditional recommendation, very low quality of evidence).
11. We suggest fecal microbiota transplantation (FMT) be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, particularly, when patients are deemed poor surgical candidates (strong recommendation, low quality of evidence).
12. We suggest tapering/pulsed dose vancomycin for patients experiencing a first recurrence after an initial course of fidaxomicin, vancomycin, or metronidazole (strong recommendation, very low quality of evidence).
13: We recommend fidaxomicin for patients experiencing a first recurrence after an initial course of vancomycin or metronidazole (conditional recommendation, moderate quality of evidence).

Fidaxomicin

- Trade Name: Dificid
- Non-systemic (minimally absorbed)
- Bactericidal
- Dose 200mg BID x 10 days

Fidoxamicin Vs Vancomycin Phase III



Bezlotoxumab

- Trade name: Zinplava
- Single IV Infusion
- A fully humanized monoclonal antibody that binds to C.difficile toxin B
- Indicated to prevent recurrence of CDI
- To be used with a course of antibiotics

Wilcox et al. NEJM 2017

Fecal Microbiota Transplantation

- Instillation of minimally manipulated microbial communities from stool of a healthy donor into a patient's GI tract.

- FMT is distinguished from a defined consortia of microorganisms, highlighting the degree of complexity and functionality of the microbiome.

- Can be considered both a "drug" and a "biologic or tissue"

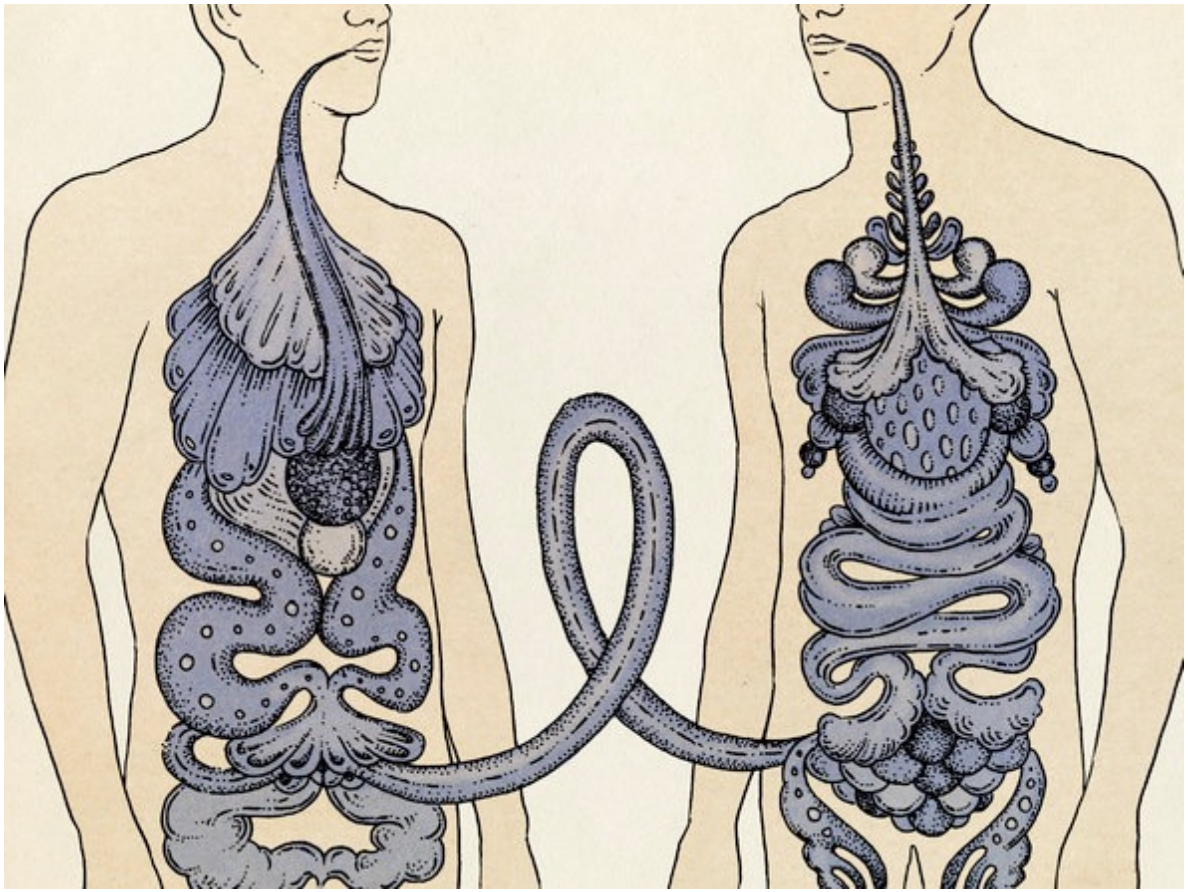
Regulations: US

- May use to treat *C. difficile* not responding to standard therapy
- No IND required

- Informed consent
  - State it is investigational
  - Discuss real and theoretical risks

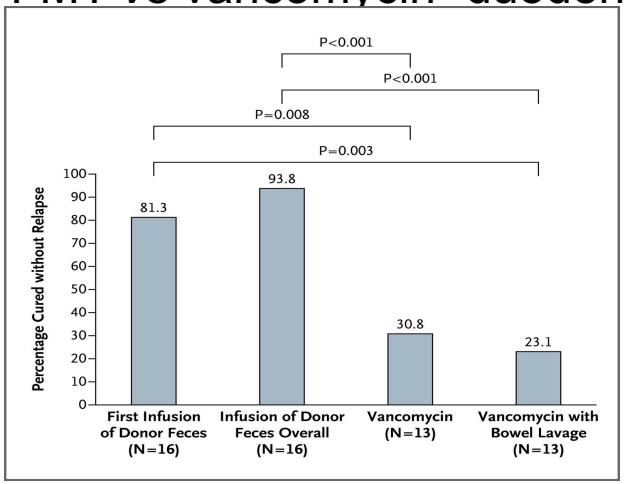
- Draft guidance March 2016
  - Would enforce IND requirement for stool banks

How Effective is FMT?



FMT: established role for multiply recurrent *C. difficile*

FMT *vs* vancomycin- duodenal infusion



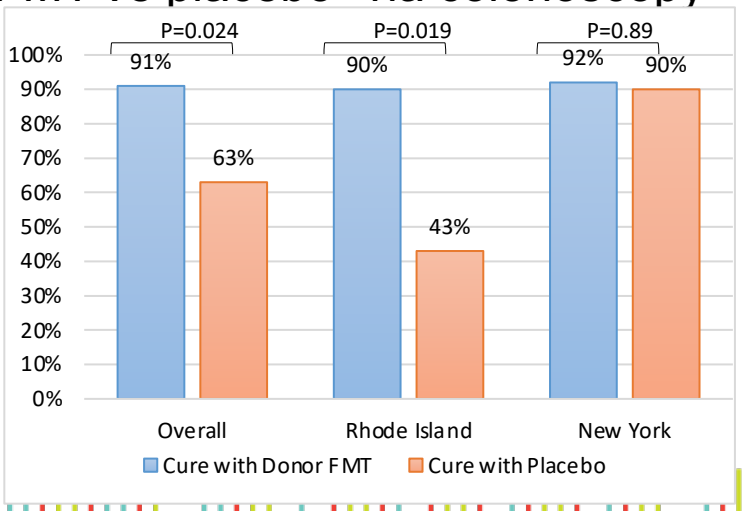
Van Nood 2013

Fresh *vs* Frozen FMT- enema

No. of FMTs	Per-Protocol Population	
	Frozen (n = 91)	Fresh (n = 87)
1	57 (62.7)	54 (62.1)
2	19 (83.5)	20 (85.1)
3-5	9 (93.4)	9 (95.4)
>5	2 (95.6)	1 (96.6)
Total	87/91 (95.6)	84/87 (96.6)

Lee 2016

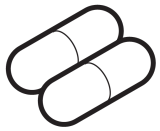
FMT *vs* placebo- via colonoscopy



Kelly 2016

Encapsulated FMT

- 70-94% cure rate
- Fresh (Louie 2013)
- Frozen (Youngster 2014)
- Microbial Emulsion Matrix (Allegretti/Openbiome 2018)
- Freeze-dried (Khoruts 2017)



Five D's of FMT: A Guide for appropriate FMT use

1. **Decision** – is FMT appropriate?
2. **Donor** – patient directed or universal? Fresh or frozen?
3. **Discussion** – informed consent.
4. **Delivery** – enema, colonoscopy/sigmoidoscopy, NG/NJ tube, capsules.
5. **Discharge** & follow up.

Allegretti JR et al. GIE 2017

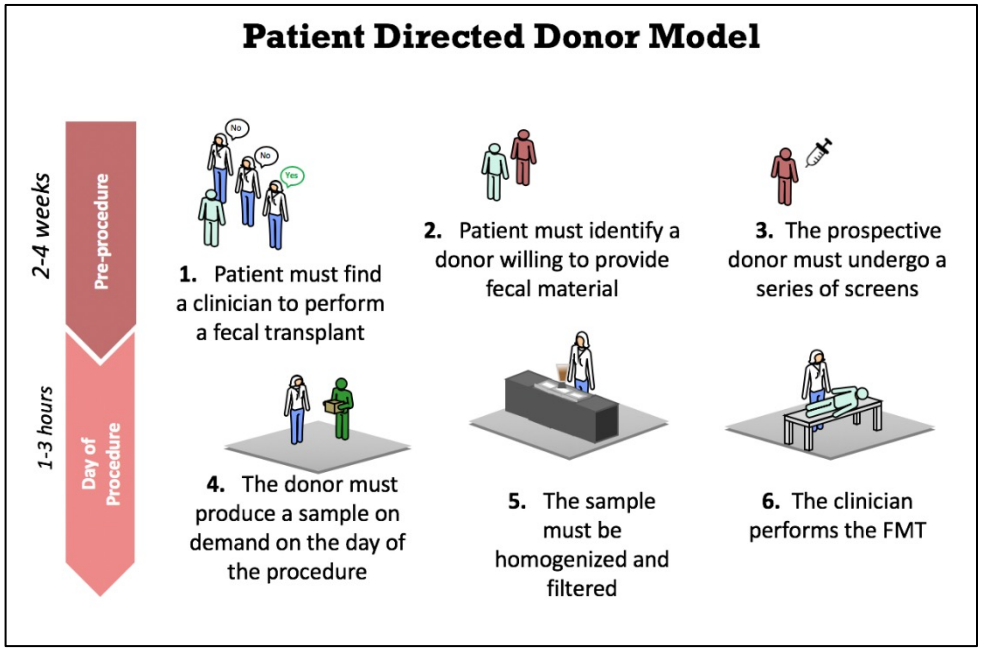
Step 1: Decision➔Patient Selection

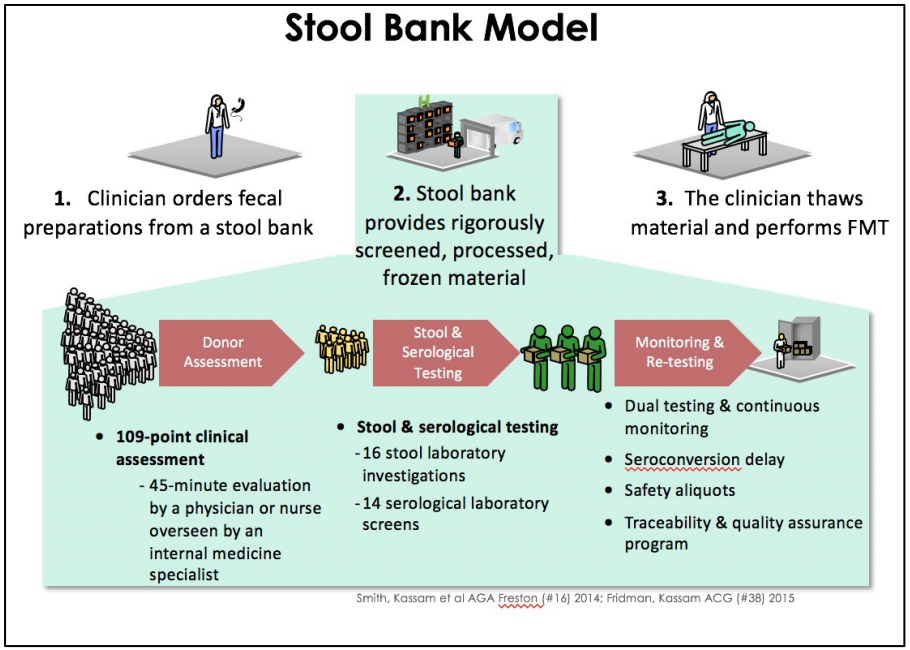
- **Recurrent CDI**
  - ≥ 3 episodes of CDI and failure of a 6-8 week vancomycin taper
  - ≥ 2 episodes of severe CDI resulting in hospitalization and significant morbidity

- **Fulminant CDI**
  - Dramatically different CDI phenotype
    - ICU admission for CDI
    - Hypotension
    - Fever ≥ 38.5°C
    - Ileus
    - Mental status changes
    - WBC >15 or <2
    - Lactate >2.2
    - End organ failure
  - Likely requires >1 FMT for severe and severe-complicated CDI with bridge vancomycin

Bakkan et al Clin Gastro Hep 2011
Surawicz et al Am J Gastro 2013
Fischer et al AP&T 2015

Step 2: Donor Selection





Pros:
- Patient comfort

Cons:
- Multiple tests
- Expensive
- Delays care
- Physician's time

Pros:
- Routinely tested
- healthy individual
- proven donor track
- Minimize cost

Cons:
- Billing
- Food allergies

COVID-19

Openbiome has implemented Sars-Cov-2 screening in asymptomatic donors with NP swabs

- Stool testing is also occurring on all samples
- Not reports of transmission of Sars-Cov-2 via FMT to date
- Material is now limited

Step 3: Discussion (Safety and Ethical Concerns)

Acute Concerns:

- bacterial, viral, parasitic infections
- acute allergic reactions

MDRO Transmission

- The FDA has recently reported two immunocompromised patients developing systemic infection with extended spectrum beta-lactamase producing (ESBL) Escherichia coli after FMT
  - One of whom died.

- The donor had not been tested for ESBL prior to the FMT (IND Approved Protocol)
  - but was confirmed as ESBL colonized subsequently.

- Scenarios such as this as emphasized the importance of meticulous attention to donor testing for potential pathogens, as supported by guidelines.

Other Infections of Concern

- EPEC and STEC
  - Stool is screened for: Enterohemorrhagic E. coli (EHEC) and Shiga-toxin producing *E. coli* (STEC) via enzyme immunoassay.
  - Enteropathogenic *E. coli* (EPEC) is not screened for (generally not considered a pathogen)
- 4 cases of STEC and 2 Cases of EPEC were reported post FMT
  - Self limiting diarrhea in all cases
- STEC and EPEC testing via PCR has already been implemented

Step 3: Discussion (Safety and Ethical Concerns)

Long-term concerns

- is it possible that we are predisposing the recipient to the diseases the donor will develop in his/her lifetime?
- Animal models suggests the microbiome may play a role in the pathogenesis of several human diseases.
  - Metabolic syndrome
  - Heart disease
  - Behavior

Step 4: Mode of delivery in Severe Disease

Nasogastric tube/ FMT capsules

- Simple
- No sedation
- Questionable efficacy in ileus
- Aspiration risk

Enema

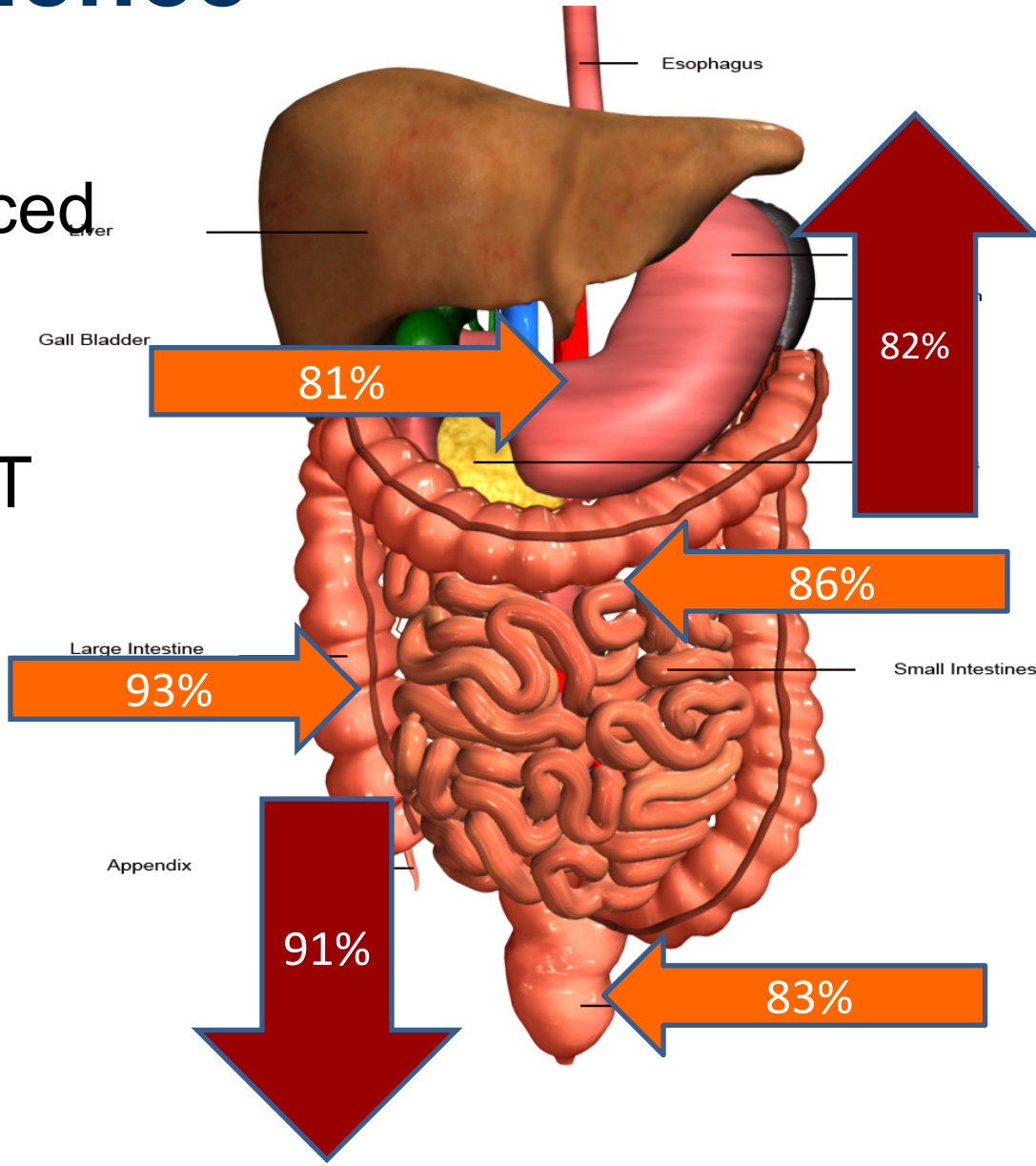
- Low cost
- No sedation
- No gastroenterologist needed
- Variable retainment
- Lack of visualization of mucosa

Colonoscopy

- Allows for visualization of mucosa
- Pseudomembranes important prognostic factors
- Can be safely performed even in toxic megacolon
- FMT delivery to cecum
- Expensive
- Requires expertise and sedation

Cumulative evidence

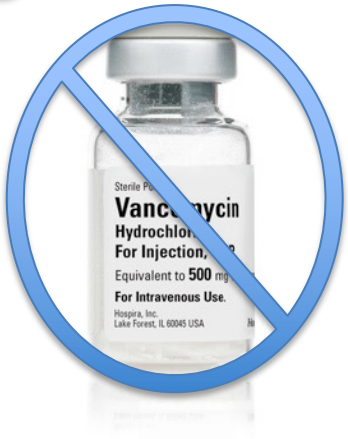
- 87%-89% experienced clinical resolution
- No adverse events associated with FMT reported



Cammarota G. J Clin Gastroenterol 2014
Kassam Z, Am J Gastroenterol 2013

Outpatient Discharge & Follow-Up

1 Antibiotics



Do **not** resume vancomycin after FMT for recurrent CDI

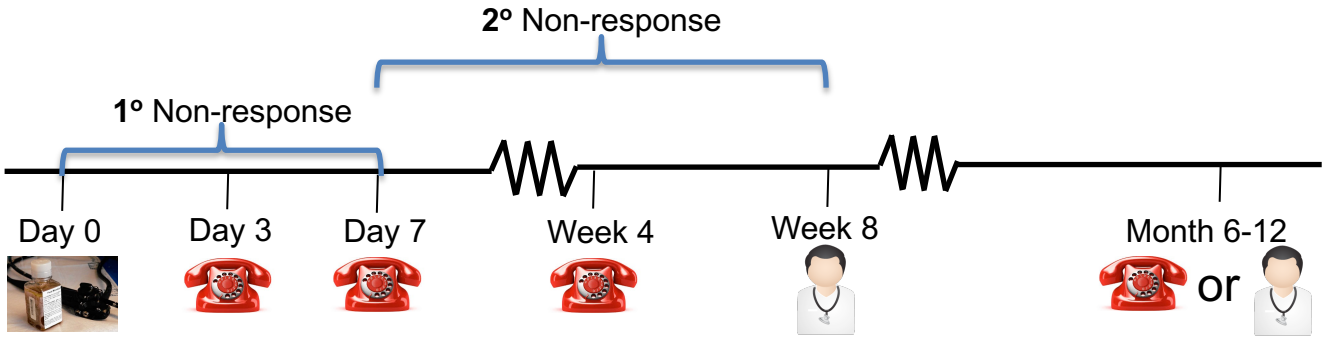
2 Testing

Do **not** "test for cure"

3 Patient Education

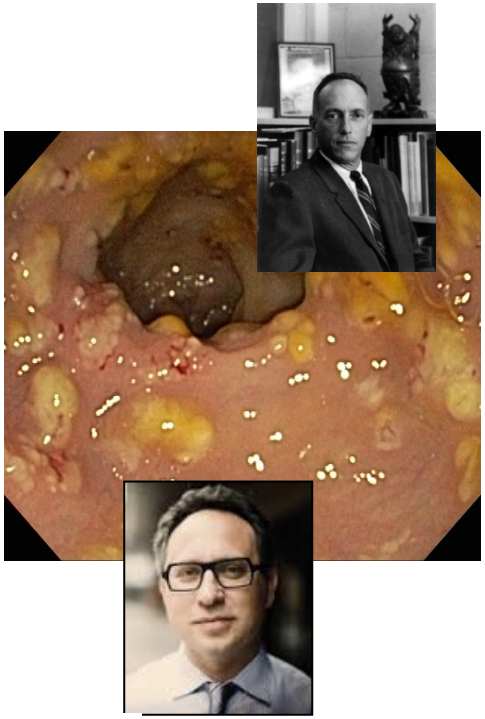
- ✓ Clean high-touch surface areas
- ✓ Antibiotic stewardship

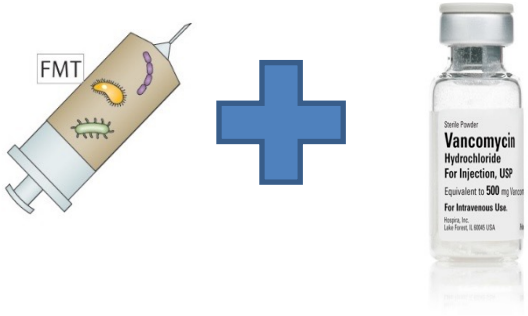
4 Follow-Up Cadence: Adverse Events & Non-response



Evolution of FMT in severe and fulminant CDI

- 2008: few case reports - dramatic results
- Retrospective case series with single FMT in severe CDI
  - 88% success in 17 patients via colonoscopy
  - 79% success in 14 patients with NG tube
- Weingarden and Khoruts in fulminant CDI
  - Four patients with dramatic but unsustained response to single FMT
  - Single FMT is insufficient
  - Re-initiation of anti-CDI antibiotic and repeat FMT needed

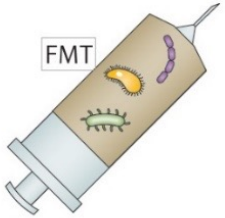


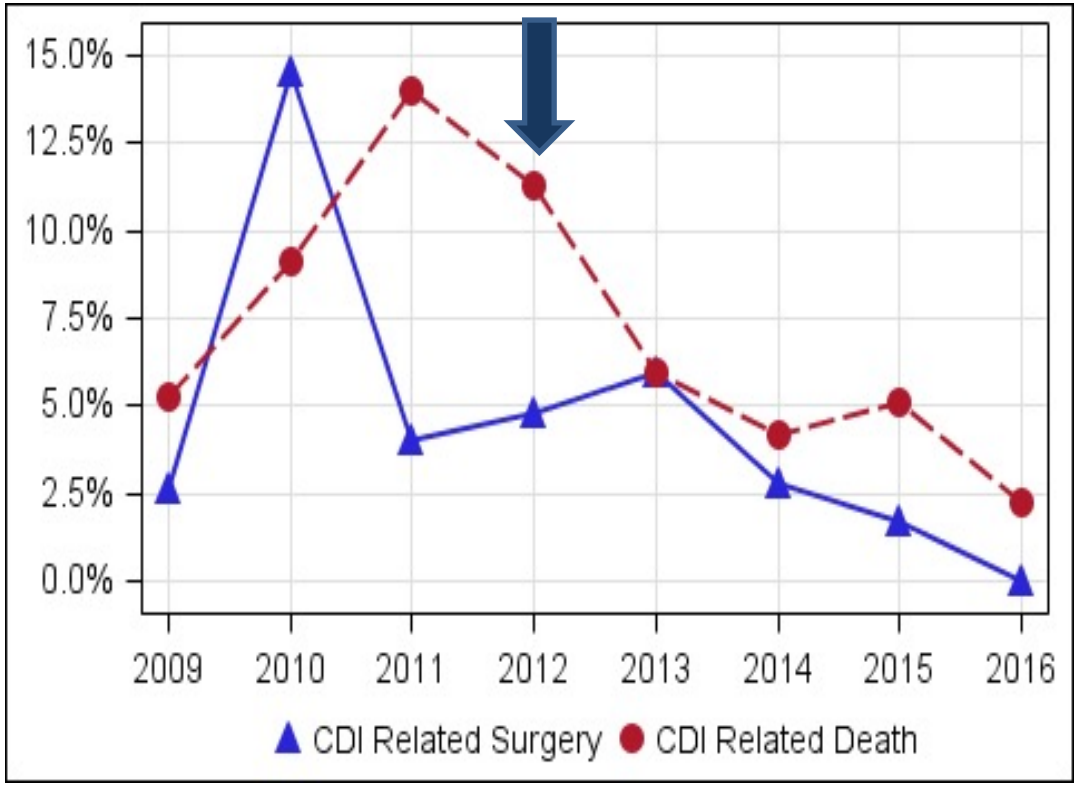


Eiseman. Surgery 1958, You. Ann Intern Med 2008, Aroniadis. JCG 2015, Zainah. 2015 Dig Dis Sci., Weingarden. CGH 2013.

Impact of inpatient FMT program

- All CDI-related admissions 4 years before (N=1,237) and after inpatient FMT program (N=1,589)
- N=429 severe or severe/complicated CDI
- 118 patient received FMT
- CDI-related death decreased from 1.7% to 0.6% (p=0.007)
- CDI-related colectomy decreased from 1.1% to 0.4% (P=0.018)
- LOS decreased from 9 (IQR: 5-18) to 8 (IQR: 4-17) (P=0.01)

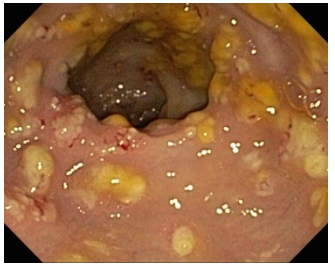




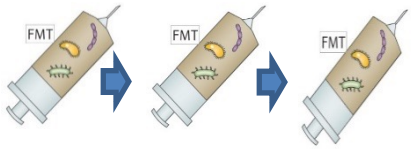
Cheng. ACG 2017

FMT: evolving role for Severe/ Fulminant CDI

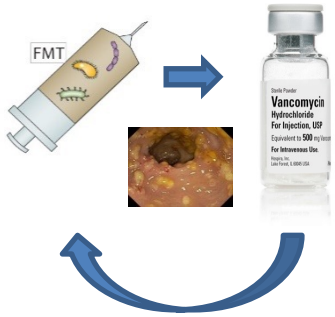
- Dramatically different phenotype
- Unsustained response to single FMT
- Repeat FMT is often needed for cure



- FMTs in rapid cycles (q3 days) (Cammarota trial)
  - 100% cured (5/5)
  - On average # 3 FMTs given



- FMT plus selected use of vancomycin (IU protocol)
  - 91% cure (52/57)
  - On average # 1.5 FMTs given



Weingarden. CGH 2013, Cammarota AP&T 2015., Fischer AP&T, Fischer Gut Microbes 2016

FMT plus selected use of vancomycin for severe and severe-complicated CDI

Predictors of repeat FMT

Odds of repeat FMT

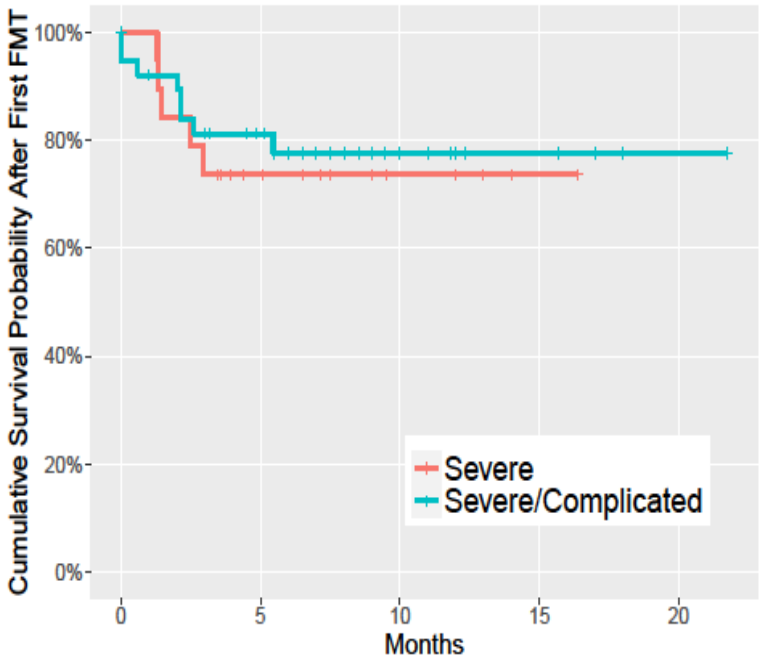
- higher WBC
- lower albumin
- longer ICU stay
- > 6 fold with pseudomembranes
- > 3-fold with systemic antibiotic use

Safety

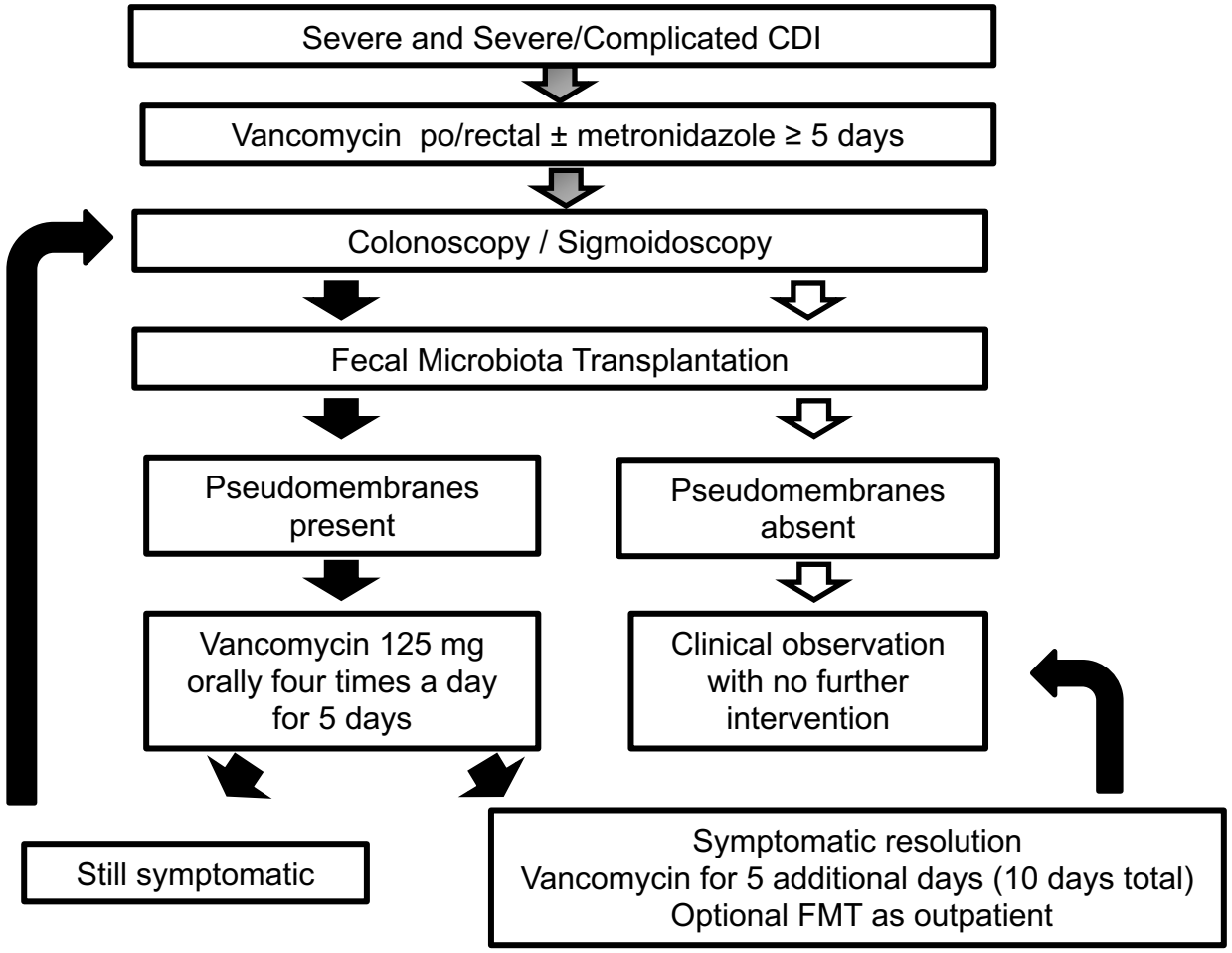
- No FMT related SAEs

Survival

- 95% at 1 month
- 78% at 3 months



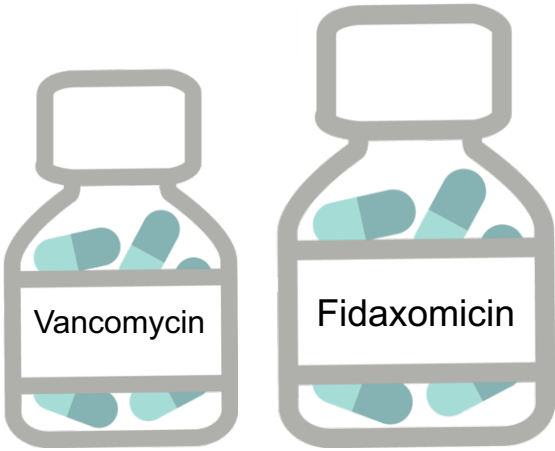
Fischer M. Gut Microbes 2016



Fischer Gut Microbes 2016

Role of anti-CDI antibiotics in fulminant CDI

- Hypothesis
  - C. difficile burden is too high
  - Single FMT is insufficient for cure
    - restores microbial scaffolding to enable response to anti-CDI antibiotic
- Choice of anti-CDI antibiotic
  - Vancomycin cheaper (dictated by hospital policy)
  - Fidaxomicin is a more desirable choice
    - Narrower antimicrobial spectrum



Pecere. AP&T. 2015

Unanswered questions

- Role of anti-CDI antimicrobial therapy *vs.* repeat FMT in rapid cycles
  - Type of anti-CDI antimicrobial agent
  - Optimal length of anti-CDI antibiotic therapy between FMTs
- Mode of delivery
  - ➢ colonoscopy
  - ➢ enema
- Role of bowel prep
- Role of pseudomembranes as prognostic markers
  - ➢ disease severity
  - ➢ response to therapy
- Timing of discharge from hospital

FMT in Fulminant CDI

- A promising treatment- guideline supported
- Sequential FMTs ± anti-CDI antibiotic needed
- High cure rate, favorable risk profile
- Simple logistics using banked, frozen stool
- Should be considered prior to colectomy
- May work for “too ill for surgery” patients
- Microbiome profiling needed
- RCT would be helpful (hindered by ethical considerations)

Key Take Home Points

- Incidence of CDI is increasing at an alarming rate
- Vancomycin is now first line for both severe and non-severe first episode CDI
- FMT is an effective therapy for severe CDI infections and should be offered if maximum medical therapy (including PR vanco) fails,
- More then 1 FMT is often needed
- Many unanswered questions remain!